Hair glucocorticoids are associated with childhood adversity, depressive symptoms and reduced global and lobar grey matter in Generation Scotland

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INTRODUCTION

Major depressive disorder (MDD) is the leading cause of disability worldwide [1] and affects ~6% of the adult population globally per year [2]. Exposures to psychosocial stress and stressful circumstances are consistently implicated in the aetiology of MDD and are associated with onset, severity, remission, and antidepressant response [3, 4]. Early-life stress in particular is one of the largest environmental risk factors for depression [5], and the association between childhood adversity and subsequent psychopathology has been linked to dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis [6–10]. However, precise mechanisms in MDD are unclear since previous findings are inconsistent with substantial variability in effect sizes across studies [11–16]. This is potentially due to differing approaches to the measurement of the highly phasic/variable HPA system, which is predominantly measured using cross-sectional measures of glucocorticoids in blood, saliva or spot urine samples. These acute measures demonstrate strong diurnal effects and both inter- and intra-individual fluctuations in response to environmental factors and are therefore temporally unstable [17]. Further, the structural neural correlates of prolonged glucocorticoid exposure in the context of MDD and in relation to early-life stress remains unclear.

Glucocorticoids are the liposoluble downstream effectors of the HPA-axis and can readily cross the blood–brain barrier. Murine models indicate that long-term excess glucocorticoid exposure suppresses neurogenesis, decreases dendritic branching and inhibits synaptogenesis, most notably in the hippocampus [18–20]. Previous human studies of glucocorticoid effects on the brain have typically
relied on acute cross-sectional measures from saliva, blood, or urine. Although findings should be interpreted cautiously due to the short timeframe and variability of these measures, these studies to some extent indicate that elevated levels of cortisol are associated with general global brain atrophy [21, 22]. One study of urinary markers also found that elevated glucocorticoid levels at baseline predicted subsequent brain atrophy and cognitive decline over the following 6 years [23]. Further, individuals with Cushing’s syndrome, characterised by long-term hypercortisolaeoma, have been consistently shown to have structural brain abnormalities, as well as a high prevalence of cognitive deficits and low mood/depression [24–26].

Previous studies of glucocorticoid associations with brain structure in the context of MDD are however inconsistent, not only because of the prevailing use of temporally unstable serum/saliva measures, but they have also typically focused on one imaging modality (structural T1 weighted imaging), single regions of interest (e.g. the hippocampus), and with relatively small sample sizes (N < 50) [27–30]. Since there are no previous studies of long-term glucocorticoid exposure with both global/regional brain morphology and white matter microstructure phenotypes, there is a clear need for research that examines neuroarchitecture more broadly, and with measures that capture chronic glucocorticoid associations.

Hair glucocorticoid measures have been shown to provide a more temporally stable measure of exposure over several weeks compared to phasic blood/saliva measures [31–34]. However, there have been no prior studies of the association between hair glucocorticoids, structural neuroimaging phenotypes and depression. Furthermore, cortisone, the inert metabolite of cortisol, which is more prevalent in hair [35], has not been investigated in relation to brain imaging phenotypes, and may be a biologically relevant marker in the investigation of longer-term HPA-axis activity. Cortisone is activated to cortisol by 11β-hydroxysteroid dehydrogenase (11β-HSD) type 1 in target organs including the brain, liver, adipose tissue and vasculature. In contrast, 11β-HSD type 2 inactivates cortisol to cortisone, predominantly in the kidney, colon and salivary/sweat glands. Measuring both steroids in hair gives a more comprehensive measure of total glucocorticoid exposure over time.

In the current study, we report a large-scale investigation of hair glucocorticoid associations with brain structure and MDD in a large community-based sample (N = 993) from a cohort of deeply phenotyped individuals (Generation Scotland) in mid-life. Previous work in this cohort has found that depression case/control status is associated with reduced total grey matter volumes, however, the degree to which HPA-axis activity plays a role in this association is currently unclear [36]. We sought to characterise structural neural correlates of HPA-axis dysregulation and associations with early-life adversity, current-life stress and depressive symptomatology. We utilised hair glucocorticoid measures of active cortisol, its inert metabolite cortisone and their total as markers of cumulative HPA-axis activity over the preceding weeks and months. In terms of neuroimaging, we investigated 190 structural neuroimaging-derived phenotypes using an a priori unbiased approach to characterise brain structure associations, including T1 and diffusion tensor imaging (DTI) measures. We investigated hair glucocorticoid associations with (i) MDD case/control status and depressive symptoms, (ii) childhood adversity and current-life stress and (iii) structural neuroimaging-derived phenotypes from the two imaging modalities.

Given the evidence from salivary/serum glucocorticoid measures described above, we hypothesised that increased hair cortisol, cortisone and their total would be related to MDD status and to increased measures of depressive symptoms, along with childhood adversity. We further hypothesised that increased glucocorticoids in hair would be associated with decreased global cortical volumes, regionally decreased hippocampal volumes and decreased global white matter microstructure integrity, in line with previous research.

**MATERIALS AND METHODS**

**Participants**

Participants in this study were recruited through Generation Scotland and included ~1000 individuals who were re-contacted in 2015–2019 for further assessment of mental health and brain imaging. Full details of the recruitment and demographics of this cohort are published elsewhere [36–38]. Demographics of the current sample are included in Table 1. In the current study, N = 993 individuals were included in symptom analyses, N = 894 individuals had T1 imaging data and N = 864 also had DTI data.

Ethical approval was formally obtained from the NHS Tayside committee on research (reference 14/SS/0039), and all participants provided written informed consent [37].

**Depression status and symptoms**

We measured both the lifetime incidence of MDD (case/control status) and current depression symptoms and symptom severity. MDD case/control status was ascertained using the research version of the Structured Clinical Interview for DSM disorders (SCID) [39] and diagnostic criteria were based on the ‘Diagnostic and Statistical Manual of Mental Disorders’ (DSM-IV-TR). Using this definition, the sample had N = 317 MDD cases and N = 676 controls.

To assess depression symptoms, the ‘Quick Inventory of Depressive Symptomatology’ (QIDS) [40] was employed to assess both total current symptoms and symptom severity.

**Measures of early and current-life stress**

Early-life stress was measured in terms of childhood trauma which was assessed using the ‘Childhood Trauma Questionnaire’ (CTQ), a retrospective 28-item questionnaire that assesses three areas of abuse (emotional, physical, and sexual) and two areas of neglect (emotional and physical) [41]. A total CTQ summary score was calculated as well as total scores for each subscale, with higher scores representing higher reported trauma [37].

Recent life stress was measured using a brief life events questionnaire: the ‘List of Threatening Experiences’ (LTE) [42], a self-report measure consisting of 12 questions regarding common and life-threatening events in the 6 months preceding the assessment. Where a participant has experienced one of these life events, a follow-up question required rating the threat from 3 (very bad), 2 (moderately bad) to 1 (not too bad) [43]. A total sum score of the LTE was calculated for analysis purposes.

**Hair glucocorticoid measurement**

Hair samples were collected from the posterior vertex region of the head as close to the scalp as possible [37]. Cortisol (F) and cortisone (E) concentrations were measured by LC–MS/MS, at the Technische

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**Table 1.** Participant demographics.

| Variable                  | Unit          | Cases (N = 317) | Controls (N = 676) | P-value |
|---------------------------|---------------|----------------|--------------------|---------|
| Agea (mean, SD)           | Years         | 57.4 (10.1)    | 60.8 (9.8)         | <0.01   |
| Sexb                      | Males (N)     | 72             | 265                | <0.01   |
|                           | Females (N)   | 245            | 411                |         |
| Study site                | Aberdeen      | 122            | 361                | <0.01   |
|                           | Dundee        | 195            | 315                |         |
| Hair processing batchb    | Batch 1       | 228            | 506                | 0.367   |
|                           | Batch 2       | 89             | 170                |         |
| Total QIDS scorea         | Mean (SD)     | 7.04 (4.9)     | 3.6 (2.3)          | <0.01   |

*aWilcoxon t-test.  
*bChi-squared test.  
*cCalculated by SCID diagnosis.
Statistical analyses

Hair cortisol, cortisone and their total were log-transformed and outliers ± 3 standard deviations from the mean were removed for statistical analyses. All analyses were conducted using R (version 3.2.3). For all global and lobar measures and CTQ/LTE/MDM measures, a generalised linear model was applied (function ‘glm’ in R package ‘stats’). For all bilateral imaging-derived phenotypes (T1 and DTI), both sides of the brain were included in mixed-effect linear models (function ‘lme’ in R package ‘nlme’ correcting for hemisphere as a within-subject variable for each participant and one individual per family with the highest random number was included in subsequent analyses, excluding all other family members. The unrelated dataset comprised \( N = 665 \) unrelated individuals with T1 data and \( N = 640 \) with DTI data.

RESULTS

Demographics

Demographics and descriptive statistics of the key variables are presented in Table 1. Hair cortisol and cortisone were also positively correlated (\( r = 0.66, P < 0.001 \)).

Hair glucocorticoid associations with measures of depression

We tested the associations between the three glucocorticoid measures and measures of depression (case/control status, total QIDS scores and QIDS severity; Fig. 1 and Supplementary Table 1). Although there were no FDR-significant associations with hair cortisol, increased hair cortisone concentrations were significantly associated with MDD case–control status (\( \beta = 0.115, P_{FDR} = 0.002 \)), total QIDS scores (\( \beta = 0.089, P_{FDR} = 0.014 \)), and QIDS depression severity (\( \beta = 0.071, P_{FDR} = 0.038 \)). There were no FDR-significant
associations between total glucocorticoid (F + E) concentrations and any measure of depression.

Hair glucocorticoid associations with stress measures

We tested the associations between the three glucocorticoid measures with early-life adversity using total CTQ scores and the six subscales of the questionnaire (Supplementary Table 1). While we found no associations with hair cortisol, increased hair cortisone concentrations were significantly associated with total CTQ scores ($\beta = 0.083, P = 0.017$) and with two subscales of the CTQ: higher reported total emotional abuse ($\beta = 0.087, P_{FDR} = 0.034$) and total physical neglect ($\beta = 0.090, P_{FDR} = 0.034$). Total hair glucocorticoids (F + E) were also significantly associated with total CTQ scores ($\beta = 0.076, P = 0.040$) but not with any of the individual subscales. None of the hair glucocorticoid measures were significantly associated with recent life stress (as measured by total LTE scores).

Hair glucocorticoid associations with global and lobar measures of brain structure

Increased hair cortisol concentrations were significantly associated with reduced global grey matter volumes ($\beta = -0.057, P = 0.003$; Fig. 2) and reduced global cortical volumes ($\beta = -0.104, P = 0.0007$; Supplementary Table 2). This global loss was also reflected in regional reductions where higher hair cortisol was significantly associated with reduced cortical volumes in...
Hair glucocorticoid associations with regional brain structures
We tested the associations of hair glucocorticoids with 34 cortical regions (volume, thickness and surface area measures) and 8 subcortical volumes and found that increased hair cortisol was significantly associated with reduced volume of the temporal pole ($\beta = -0.096, P_{FDR} = 0.049$; Supplementary Table 3) and also demonstrated consistently negative effect sizes for the 34 cortical measures although these did not reach corrected levels of significance (Fig. 3). We also found that increased hair cortisone concentrations were significantly associated with reduced volume of the nucleus accumbens ($\beta = -0.075, P_{FDR} = 0.044$; Fig. 4 and Supplementary Fig. 1, Supplementary Tables 4, 6). The measure of total hair glucocorticoids ($F + E$) was associated with reduced volume of the pars orbitalis ($\beta = -0.089, P_{FDR} = 0.0497$; Supplementary Fig. 2 and Supplementary Table 5). Both of these latter findings survived controlling for multiple comparisons.

Hair glucocorticoid associations with white matter integrity
There were no significant associations after FDR correction between hair glucocorticoids and any measure of white matter integrity including global measures (Supplementary Tables 7–9).

Relatedness analyses
All of the hair cortisol and total hair glucocorticoid ($F + E$) associations with global and lobar brain measures remained significant in the sample of unrelated participants (Supplementary Tables 10–17). For hair cortisone, the association with global cortical volume remained significant whereas the association with the nucleus accumbens did not, however, the effect size remained in the same direction and of a similar magnitude ($\beta_{\text{unrelated}} = -0.06$ versus $\beta_{\text{related}} = -0.075$). The total hair glucocorticoid association with the pars orbitalis also remained significant in the unrelated sample.

DISCUSSION
We report the findings from a comprehensive and large-scale, multimodal study with in-depth phenotypic data investigating hair glucocorticoid associations with brain morphology, measures of depressive psychopathology, and early/late life stress. Hair glucocorticoids were significantly associated with measures of depression, specific types of childhood trauma scores, but not with measures of current-life stress. In terms of brain morphology, hair glucocorticoids were associated with global reductions, along with regional volumetric loss in frontal, temporal and cingulate cortices, with some evidence for the involvement of reward-associated regions, but not with decreased hippocampal volumes, or with deficits in structural connectivity. This study provides important evidence in support of widely held hypotheses suggesting links between early adversity, disrupted HPA-axis functioning, altered brain morphology and depression, and lays essential foundations for future work to address causation and potential interventions.

Our findings expand on previous studies of acute salivary/serum measures of cortisol and MDD associations by utilising a hair measure of cumulative/integrated long-term glucocorticoid levels, and also additionally considering cortisone and total hair glucocorticoid associations [11–15]. Using these broader
longer-term markers of HPA-axis activity, we found elevated levels of hair cortisone were significantly associated with three measures of depression: lifetime case/control status, total current depressive symptom scores and depression severity. The results, therefore, indicate that HPA-axis activity, as measured by hair cortisone, has a robust association with depression in terms of both current symptoms and lifetime incidence.

In addition, we also report that hair cortisone was associated with early-life stress, specifically in terms of childhood physical neglect and emotional abuse. Several previous studies have found that childhood adversity alters stress-reactivity in adulthood [48–53], with increased responses in individuals with depression [54]. One meta-analysis of 28 studies including N = 3397 individuals found that childhood adversity is also significantly related to hair cortisol concentrations and this association is moderated by the type and timing of the adversity experienced [55]. Animal work has also shown that early-life adversity/prenatal stress elicits changes in HPA-axis functioning that persists into adulthood (developmental programming), including HPA-axis hyperactivity and glucocorticoid/insulin resistance [56–58] and the frequent comorbidity between early-life adversity and MDD may be linked to HPA-axis dysregulation [59]. We build on this preclinical work in humans to show that chronically elevated glucocorticoids were specifically associated with early-life stress, but not contemporaneous stress, and were further specifically associated with childhood physical neglect and emotional abuse, as well as current and lifetime MDD. This finding further demonstrates the importance of the type and timing of adversity experienced with potential long-term consequences for HPA-axis functioning and wellbeing.

We further extend this work to also study associations with brain imaging phenotypes. To our knowledge, this is the first large-scale neuroimaging study of hair glucocorticoid associations with both T1 MRI and white matter microstructural integrity data in adults. We found higher concentrations of hair glucocorticoids were significantly associated with reductions in total grey matter and global cortical volumes. Increased hair cortisol concentrations were further associated with volumetric loss in the frontal/temporal lobes and cingulate regions. These areas are important for cognition and emotion regulation, and volumetric loss in these areas may underlie associations with MDD which is characterised by cognitive impairment and dysregulated emotional processing [60]. Preclinical work has shown that excess glucocorticoid exposure is associated with grey matter damage and that brain regions with higher numbers of glucocorticoid receptors are more vulnerable to these noxious effects including regions such as the cingulate described here [61–63]. Furthermore, animal models indicate that chronic glucocorticoid exposure is associated with changes in dendritic morphology, decreased neurogenesis/synaptogenesis and decreased plasticity, which may be indicative of the pathophysiological mechanisms underlying the grey matter loss seen in the current study [19, 64–67]. Taken together, these novel findings implicate chronically elevated glucocorticoids as having deleterious associations with brain structure which may potentially underlie associations with psychopathology, although formal tests of directionality are required.

In terms of regional findings, we also report associations between increased hair glucocorticoids and reduced volume of the nucleus accumbens and pars orbitalis (lateral/orbitofrontal cortex). Since these regions are central to reward processing, these findings suggest that elevated glucocorticoids are associated with structural alterations of reward neurocircuitry, which is also a key feature of MDD. This is consistent with previous studies which link chronic stress to altered reward processing by the attenuation of reward sensitivity, increasing vulnerability to anhedonia and psychopathology [68–71]. Animal work has also shown that

**Fig. 4** Significance plot for cortisol, cortisone and total glucocorticoid associations with regional structural imaging phenotypes. **A** Cortisol, **B** cortisone, and **C** total glucocorticoid. The x-axes represent structural imaging phenotypes, and the y-axes represent the −log10 of uncorrected p-values between the measure and the imaging phenotype corrected for covariates. Each dot represents one imaging phenotype, and the colours indicate their categories. The dashed lines indicate the p-value threshold of 0.05 and the diamonds represent phenotypes that survive FDR correction. The hippocampus (not significant) is marked in brackets for reference to previous studies.
glucocorticoid-receptor antagonists inhibit normal reward processing and that glucocorticoid neurotransmission plays a key role in reward-related behaviours [72, 73]. Future work should aim to replicate these associations in larger samples and further explore the importance of disrupted reward processing in the context of HPA-axis activity and early adversity in the aetiology of MDD.

Notably, we report no association between elevated glucocorticoids and hippocampal volumes, in contrast to previous findings [22, 27]. This may be due to our ‘non-ROI’ type approach, or to differing methods of measurement of HPA-axis activity. Hair measures may for example capture a distinct aspect of HPA-axis biology in relation to integrated long-term glucocorticoid secretion that may be specific to these imaging findings. We also note that we report differing patterns of associations dependent on whether we examine the active or the inactive metabolite. Hair cortisol was associated with clinical features and early-life adversity, while hair cortisols/total hair glucocorticoids were primarily associated with neural features. Cortisol and cortisone are interconverted by two tissue-specific intracellular isozymes of 11β-HSD. Both glucocorticoids circulate at nanomolar levels in the blood. Whilst some have postulated that hair cortisol:cortisone reflects 11β-HSD in the hair follicle, there is little evidence of significant expression of either isozyme in this tissue. Thus, we consider it more probable that the specific hair glucocorticoid levels here reflect the kinetics of accumulation of cortisol and cortisone from the blood into the growing hair root.

In terms of limitations, our study was comprised of community-based, relatively well participants. Our findings may not, therefore, reflect associations of hair glucocorticoid measures in individuals with more severe forms of MDD but may be more widely generalisable to the population. The main findings of this sample were also conducted in a related sample, however, the additional analyses in the unrelated sample replicated the main findings of this paper, lending confidence to these findings. A further limitation is that we cannot exclude the possibility of biases in the retrospective self-report measures of childhood adversity in our sample and this should be considered when interpreting findings. Longitudinal research investigating childhood adversity, glucocorticoid trajectories and MDD would be able to disentangle these relationships further. In addition, given the association identified here between hair cortisol and MDD, future research in terms of causal directionality is clearly important foundations for future mechanistic studies to explore formal causal relationships between specific types of early adversity, prolonged glucocorticoid exposure, changes in brain morphology and subsequent psychopathology in order to develop novel and efficacious interventions.

**CODE AVAILABILITY**

The code of the statistical analyses is available from the corresponding author upon request.

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AUTHOR CONTRIBUTIONS

Analysed the data and drafted the manuscript: C.G. Supervision of analyses: H.C.W., A.M.M. and J.C. Preparation of data: A.S., M.A.H., X.S., M.C.B., E.L.H., J.D.S., G.D.W., A.-L.S., A.C. and R.M.R. Additional manuscript editing: H.C.W. All authors critically revised the manuscript and approved the final version.

COMPETING INTERESTS

The authors declare no competing interests.

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C. Green et al.