

Hair glucocorticoids and resting-state frontal lobe oxygenation: Findings from The Irish Longitudinal Study on Ageing

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ABSTRACT

Cerebral blood flow and oxygenation are crucial for maintaining healthy brain structure and function, with hypoperfusion and hypometabolism associated with neurodegenerative and neuropsychiatric conditions. Chronic stress and elevated cortisol have also been associated with cognitive decline, poor mental health and peripheral vascular and cerebrovascular changes. It is plausible that glucocorticoids could alter brain structure and function through increased vulnerability to hypoperfusion and reduced oxygenation. The aim of the current study was to investigate the association between hair glucocorticoids (GCs) and frontal lobe oxygenation using near-infrared spectroscopy (NIRS) in a population sample of 1078 older adults. Data from Wave 3 of The Irish Longitudinal Study of Ageing was analysed. Hair samples were taken for the analysis of glucocorticoids and NIRS was used to measure frontal lobe oxygenation. After both minimal and full adjustment for covariates, hair cortisol and the cortisol-to-cortisone ratio were associated with lower Tissue Saturation Index (TSI; cortisol: $B = -0.37$, $CI -0.60$ to -0.14 , $p = .002$; ratio: $B = -0.43$, $CI -0.70$ to -0.16 , $p = .002$). Cortisone was not significantly associated with TSI ($B = -0.17$, $CI -0.55$ to $.21$, $p = .388$). The finding of an inverse relationship between frontal lobe oxygenation and GCs as assessed over a period of months may indicate that reduced oxygenation is one pathway through which chronically elevated GCs affect brain health and function. However, no causality can be inferred from the current data and prospective studies are required to interrogate this.

1. Introduction

Adequate cerebral blood flow (CBF) and oxygenation is required for normal brain function. The metabolic activity of the brain is reliant on sufficient blood flow to supply the necessary oxygen, and reduced oxygenation is associated with impairment in function. CBF decreases with age (Schultz et al., 1999) and can lead to an insufficient supply of the nutrients necessary for optimal metabolic function (Camandola and Mattson, 2017) and, if prolonged, to brain atrophy. Neuroimaging studies have revealed hypometabolism to be an early indicator of functional brain changes during aging (Mosconi et al., 2008), with largest declines evident in the frontal cortex (Kuhl et al., 1984). In Alzheimer's disease, evidence suggests that hypoperfusion and hypometabolism may be central to the etiology of the disease and may manifest by as much as decades before significant cognitive decline is detectable (Yew et al., 2017).

Chronic, elevated psychosocial stress is associated with altered cognitive function and increased susceptibility to depression and

dementia (Marin et al., 2011). The autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis are central to the physiological stress response, exerting a myriad of effects on the body that are designed to maintain homeostasis and promote adaptation in the face of threat (Sapolsky et al., 2000). However, prolonged or persistent activation of these systems can lead to eventual dysregulation and consequent maladaptive physiological and behavioural changes, operating across immune, metabolic and cardiovascular systems (McEwen, 1998). Chronic stress leads to an increased risk of cerebrovascular events linked to reduced cerebral perfusion, i.e. stroke and transient ischaemic attack (Everson-Rose et al., 2014). Notably, chronic stress is also associated with elevated vascular risk in the periphery, and, in tandem with the autonomic nervous system, neuroendocrine changes seem to play a role. For example, higher glucocorticoids (GCs), namely cortisol – the primary end-product of HPA axis activation in humans – have been associated with atherosclerosis in carotid (Dekker et al., 2008) and coronary arteries (Hamer et al., 2010) in large cohort studies. Recently, the measurement of cortisol in hair has come to the fore as a novel

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biomarker of psychosocial stress. It reflects exposure to cortisol over a period of weeks-months and has high test-retest reliability (Stalder et al., 2012), supporting its use as an indicator of long-term cortisol levels. Furthermore, there is mounting evidence that elevated hair cortisol predicts the development of cardiovascular disease and is associated with cardiometabolic risk factors (Iob and Steptoe, 2019).

Certain regions of the brain are particularly vulnerable to the adverse effects of prolonged increases (or conversely, marked decreases) in cortisol levels. The frontal lobe, and in particular the prefrontal cortex (PFC), is rich in GC receptors and a key region of interest with respect to the regulation of both the HPA axis and autonomic nervous system, projecting to key subcortical regions such as the hippocampus and amygdala involved in the perception of a stressor and initiation of a stress response (McEwen and Morrison, 2013). Prolonged elevation of glucocorticoids can have neurotoxic effects in these key brain regions (for a comprehensive review see Lupien et al., 2018). In animal models, chronic stress causes structural change in the medial PFC, including dendritic shortening and reduction in dendritic spine density (Bloss et al., 2010), and aging seems to render neurons more vulnerable to shrinkage and, crucially, less able to recover after a stressor (McEwen and Morrison, 2013; Bloss et al., 2010). Elevated cortisol in adulthood has also been shown to interfere with PFC function, for example, impairing working memory in older adults (Lupien et al., 1999), and cortisol increases following psychosocial stress are associated with deficits in flexible, goal-directed behaviours typically ascribed to the frontal lobes (Plessow et al., 2012).

The frontal lobe is also particularly vulnerable to neuronal damage arising from hypoperfusion, and the consequent decrease in oxygen supply (Payabvash et al., 2011). Whether diminished CBF and hence oxygenation might be one possible mechanism exacerbating or even driving some stress-induced changes in frontal lobe structure and function over time is not clear, however recent evidence supports this hypothesis. Reductions in frontal perfusion and metabolism have been observed in depression and post-traumatic stress disorder (Briggs et al., 2019; Im et al., 2016), both clinical conditions associated with HPA axis dysfunction (de Kloet et al., 2006; Pariante and Lightman, 2008). In healthy adults, resting blood flow in the anterior cingulate cortex was shown to be inversely correlated with salivary cortisol levels (Hodkinson et al., 2014). Neurovascular coupling (NVC), the process by which regional blood flow and metabolic support are dynamically regulated to match neural activity, is disrupted by chronic (Longden et al., 2014) and acute psychological stress and the resultant neuroendocrine changes (Elbau et al., 2018). Impairment of NVC thus provides another plausible mechanism through which prolonged stress could alter cerebral metabolism and structural integrity of vulnerable regions, leading to disruption of function and increased susceptibility to neuropsychiatric and neurodegenerative conditions. Taken together, these lines of evidence suggest that prolonged elevation of GC levels could plausibly influence resting-state cerebral perfusion and thus oxygen supply to regions of the brain such as the frontal cortex which exhibit both a high GC receptor density and increased relative vulnerability to hypoperfusion. To the best of our knowledge there have been no studies of the relationship between long-term GC secretion and resting cerebral oxygenation in humans. The aim of the current study was to investigate the association between hair GCs (cortisol and its inactive metabolite cortisone) and frontal lobe oxygenation using near-infrared spectroscopy (NIRS) in a population sample of older adults. NIRS is a non-invasive technique based on the principles of absorption of light and the modified Beer-Lambert law, measuring continuous changes in oxygenated and deoxygenated haemoglobin in the local microvasculature. It is portable and has been validated against other imaging methodologies such as TCD, MRI and CT (Taussky et al., 2012), and is an alternative method to TCD and MRI for assessing cerebral hemodynamics. Its ease of use and relative low-cost compared with other imaging modalities make it accessible and applicable to epidemiological studies.

2. Methods

2.1. Participants and design

Data from Wave 3 of The Irish Longitudinal Study on Ageing (TILDA) was analysed. TILDA is a nationally representative prospective cohort study of community-dwelling adults aged 50 and older, living in the Republic of Ireland. The study began in 2009 (Wave 1) and participants are revisited every two years. Wave 3 data was collected in 2014. Participants were recruited through a two-stage clustered, sampling design stratified by geographic region and household. There are three main modes of data collection within TILDA: 1) a computer assisted personal interview (CAPI) carried out in the respondent's home; 2) a self-completion questionnaire (SCQ); and 3) a health assessment, administered by trained nurses either in a health centre or during a home visit (for full details see Donoghue et al., 2018).

Ethical approval was obtained from the Research Ethics Committee at Trinity College Dublin, and all respondents provided written informed consent prior to participation in the study. All experimental procedures adhered to the Declaration of Helsinki.

2.2. Hair GC measurement

Hair samples were collected during the health assessment. The sample was cut as close to the scalp as possible and the proximal 3 cm was taken to approximate growth over the previous 3-month period (Wenig, 2000). Steroid hormone analysis was carried out on samples with a minimum weight of 7.5 mg by Dresden LabService GmbH at the Technische Universität Dresden, Germany. Cortisol and cortisone were analysed (as part of a hormone panel) by high performance liquid chromatography tandem mass spectrometry (LC-MS/MS) as detailed by Gao et al. (Gao et al., 2013). Information on additional factors that could unduly influence hair hormone concentrations was gathered by means of an ancillary questionnaire, administered to participants at the time of hair sampling. Participants were asked about washing and hair treatment, use of steroid containing medications and any medical conditions that would affect GC levels. The cortisol/cortisone ratio in hair (R_{hcc}) was further calculated. The ratio provides a measure of cortisol metabolism and primarily reflects the actions of the enzymes 11- β hydroxysteroid dehydrogenase Type 1 (11- β HSD 1) and Type 11 (11- β HSD 2) which regulate the activation of GC in a tissue-specific manner and modulate cortisol turnover (Weber et al., 2000).

2.3. Cerebral oxygenation measurement using NIRS and data processing

Resting-state cerebral oxygenation was measured during the health assessment by trained nursing staff. Participants lay supine for 5 min in a quiet room kept at a temperature of 21–23 °C. Cerebral oxygenation was measured continuously at 50 Hz using the Portalite (Artinis Medical Systems, Zetten, Netherlands) NIRS device. A single probe was placed on the forehead, corresponding approximately to the FP1 position in the international 10–20 electrode placement system (Jasper, 1958). A black headband was placed over the device to block out ambient light. Multiple transmitters (using nominal wavelengths of 760 nm and 850 nm) facilitated spatially resolved spectroscopy (SRS) which determined absolute values of tissue saturation index (TSI). TSI equals serum concentration levels of haemoglobin (O2Hb) expressed as a percentage of combined O2Hb and deoxygenated haemoglobin (HHb), i.e. $O2Hb/(O2Hb+HHb)*100$. Data was downsampled to 5 Hz and the average of the final minute was used for analysis as described in Newman et al. (2020).

2.4. Statistical analysis

We excluded one individual with Addison's disease because of the impact of this condition on the HPA axis. We also excluded one

individual with a doctor's diagnosis of dementia, and four individuals with Parkinson's disease because of the distinct impact that these conditions may have on regional cerebral blood flow. Anyone taking corticosteroid medications or hormone replacement therapy was also excluded for the above reason ($n = 200$). Finally, we screened and removed any outliers (individuals with values ± 3 SD above or below the mean) on TSI or hair GCs. Fig. 1 provides a detailed breakdown of how the analytic sample was created. The final sample for complete case analysis was $N = 1078$.

Cortisol and cortisone were heavily right-skewed and were log transformed prior to analysis. The following potential confounders were considered a priori for inclusion in regression models: age, sex, education, height, waist-hip ratio, smoking status (current, previous, lifetime non-smoker), problematic drinking as assessed by the CAGE questionnaire (Ewing, 1984), self-reported history of stroke, diabetes total number of cardiovascular conditions, hypertension, antihypertensive medication use, antidepressant medication use and total number of prescription medications.

The cross-sectional association between hair GCs and the TSI (dependent variable) was investigated using linear models, by regressing TSI on log-transformed cortisol, cortisone and the ratio of cortisol/cortisone, in separate models. Models were first adjusted for age and sex only and subsequently for the remaining covariates. In addition to the linear terms, a quadratic term for cortisol and cortisone was also tested to investigate the possibility of an inverted U-shaped relationship between GC levels and TSI. The robustness of the model results to further control for depressive symptoms (regardless of medication use) as measured by the 8-item Center for Epidemiological Studies Depression (CES-D) scale (Radloff, 1977), and momentary anxiety as assessed by the 6-item Spielberger State Anxiety Inventory (Marteau and Bekker, 1992), was checked by way of a sensitivity analysis. All analyses were performed using Stata 15 (StataCorp, College Station, TX).

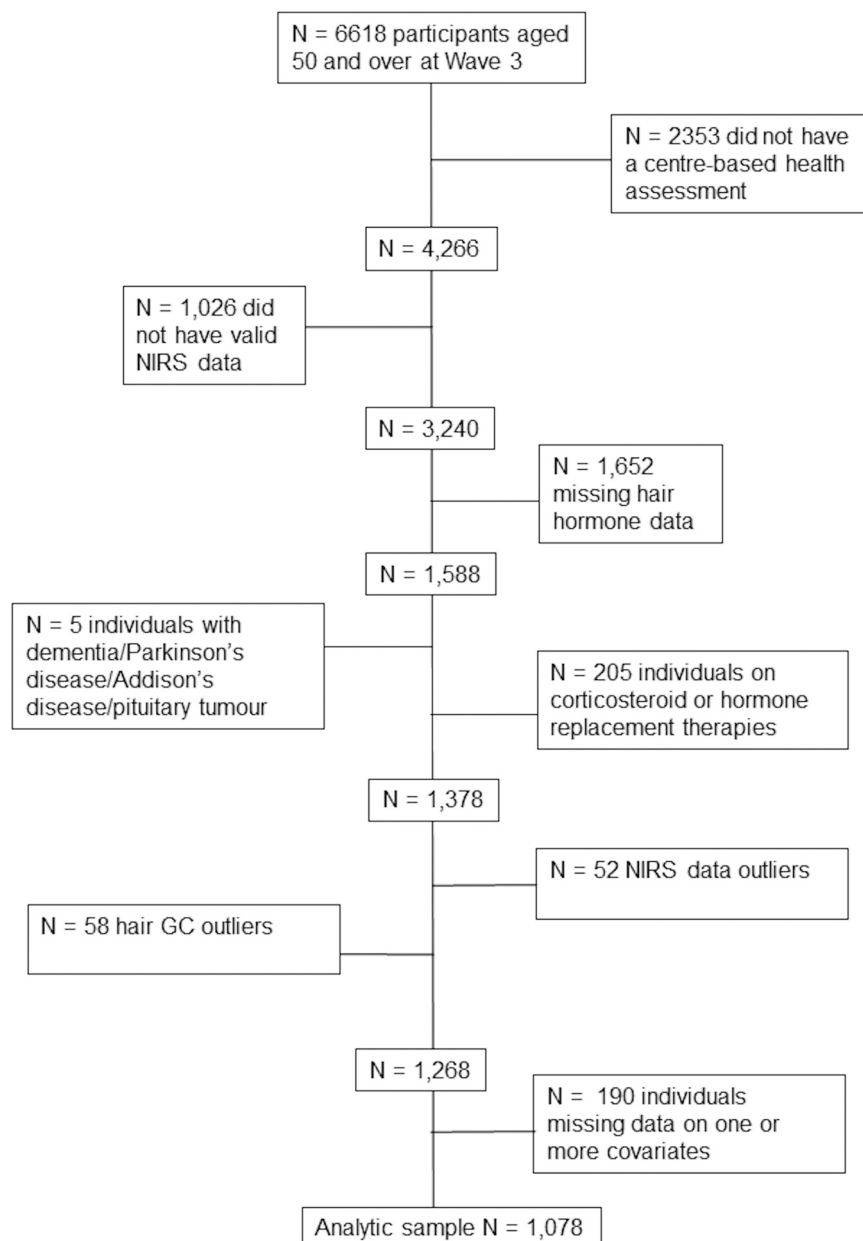


Fig. 1. Flow chart detailing how the analytic sample was created.

3. Results

3.1. Participant characteristics

The comparison of individuals in the analytic sample and non-responders/those excluded from analysis revealed a number of differences on demographic and health-related variables (Table 1). Participants in the analytic sample were younger (mean age = 64 years versus 67 years for those not included). They were more likely to be female, and to have attained tertiary level education. They also differed on a number of health indicators. Participants were less likely to have any cardiovascular conditions or to be current smokers. They were also less likely to be taking antihypertensive medications, had a smaller waist-hip ratio and were more physically active than the excluded individuals.

3.2. Bivariate associations between TSI and variables of interest

Mean TSI for the sample was 74.0% (SD= 4.4%), and values were normally distributed (a figure showing the distribution is included as Supplementary Data). TSI was inversely associated with log transformed cortisol ($r = -0.11, p < .001$), and the R_{hcc} ($r = 0.09, p = .003$), but the association with cortisone was not significant ($r = -0.05, p = .128$). TSI was inversely correlated with age ($r = -0.07, p = .015$) and waist-hip-ratio ($r = -0.06, p = .060$). TSI decreased with increasing number of cardiovascular conditions ($p = .033$), and with antihypertensive ($p = .021$) and general medication usage ($p < .001$). TSI was also marginally lower in individuals with diabetes ($p = .075$), current smokers ($p = .079$) and problem drinkers ($p = .055$; note: group means and standard deviations are included as Supplementary Data). All of the

Table 1
Characteristics of individuals included and excluded from analysis.

	Included (n = 1078)	Excluded (n = 5540)	P value
Age (mean $\pm$ SD)	64.5 (8.0)	67.4 (9.6)	<0.001
Sex (female) %	75	52	<0.001
Education %			
None/primary	14	29	
Secondary	39	39	
Tertiary/higher	47	32	<0.001
Cardiovascular (CV) conditions ^a %			
None	40	36	
One	35	35	
Two or more	25	29	=0.009
Other chronic conditions ^b (non-CV) %			
None	43	40	
One	35	33	
Two or more	22	27	=0.04
Smoking %			
Never	50	44	
Past	41	42	
Current	9	14	<0.001
Use of antihypertensives %	35	46	<0.001
Problem drinking %	11	13	0.296
Physical activity %			
Low	35	41	
Moderate	40	33	
High	25	26	<0.001
Polypharmacy (5 + medications) %	17	28	<0.001
Waist-hip ratio (mean $\pm$ SD)	0.88 (0.08)	0.91 (0.09)	<0.001

Note:
The p value in the final column (0.04) is the relevant level of significance.
^a Hypertension, angina, heart attack, heart failure, stroke, transient ischaemic attack, high cholesterol, heart murmur and irregular heart rhythm.
^b Lung disease, asthma, arthritis, osteoporosis, cancer, Parkinson's disease, substance addiction, ulcer, liver disease, thyroid disease, kidney disease, anaemia.

above variables were also associated with hair GC concentrations with the exception of problem drinking, and thus this variable was not considered as a covariate in the subsequent regression analysis. TSI was not associated with any of the other potential covariates of interest (p 's > 0.10).

3.3. Multivariable regression analysis

In the first model, adjusted for age and sex only, higher hair cortisol was associated with lower TSI ($B = -0.39, CI -0.62$ to $-0.16, p < .001$). A larger R_{hcc} was also significantly associated with lower TSI ($B = -0.44, CI -0.71$ to $-0.16, p = .002$). However, the association between cortisone alone and TSI was not significant ($B = -0.19, CI -0.57$ to $0.19, p = .324$). Further adjustment in model 2 for number of cardiovascular conditions, diabetes, systolic blood pressure, waist-hip ratio, antihypertensive use, smoking status and total number of medications, made very little difference to the coefficients (cortisol: $B = -0.37, CI -0.60$ to $-0.14, p = .002$; R_{hcc} : $B = -0.43, CI -0.70$ to $-0.16, p = .002$; cortisone: $B = -0.17, CI -0.55$ to $0.21, p = .388$). Fig. 2 shows the relationship between TSI and standardized values of cortisol and R_{hcc} , adjusting for covariates. The inclusion of a quadratic term to test a possible inverted U-shaped relationship between GCs and TSI revealed no evidence of such an association.

A sensitivity analysis further controlling for depressive symptoms and state anxiety, as assessed during the health assessment and prior to the NIRS recording, made little difference to the results (cortisol: $B =$

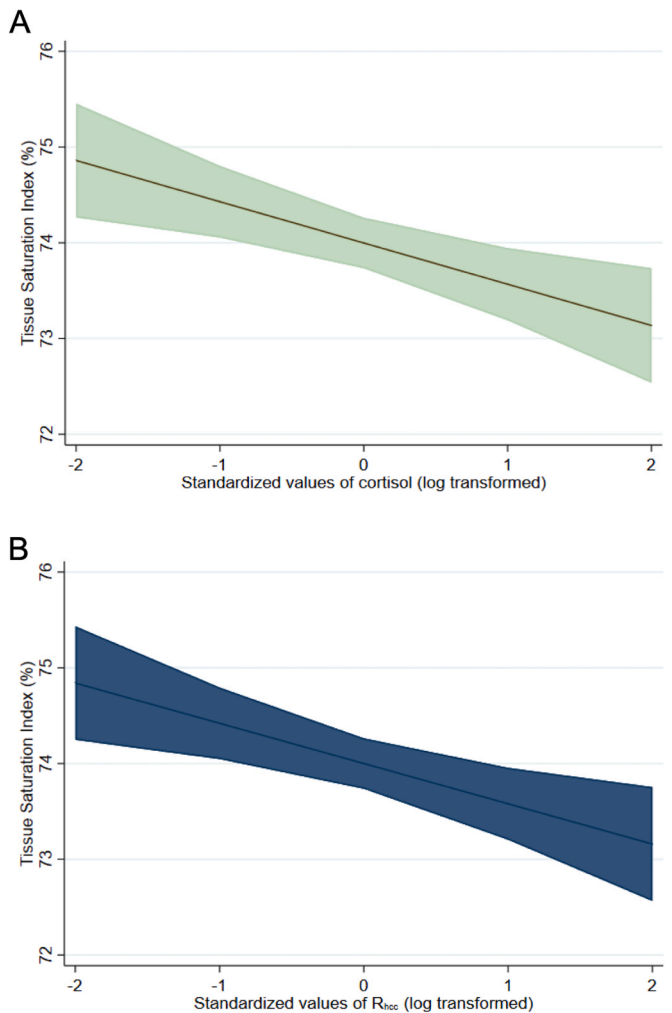


Fig. 2. The estimated marginal mean Tissue Saturation Index by standard deviation of A) cortisol and B) cortisol/cortisone ratio (R_{hcc}).

-0.36 , CI -0.60 to -0.14 , $p = .002$; R_{hcc} : $B = -0.42$, CI -0.70 to -0.15 , $p = .002$; cortisone: $B = -0.16$, CI -0.54 to $.22$, $p = .403$).

4. Discussion

This study investigated the relationship between hair cortisol, cortisone, ratio of the two and frontal cerebral oxygenation as assessed by NIRS, in a large population-based sample of older adults. We found that higher cortisol concentrations and a higher R_{hcc} were both associated with lower resting-state oxygenation, and this association remained even after adjustment for covariates, including cardiovascular conditions, recent depressive symptoms and current anxiety levels at the time of NIRS measurement.

This is one of very few studies to investigate cerebral oxygenation with resting NIRS in a non-clinical, aging cohort and the first to show a relationship between stress hormones present in scalp hair and frontal lobe oxygenation levels. The difference in TSI between individuals with low cortisol and a low ratio of cortisol-to-cortisone, versus high (-2 SD to $+2$ SD above the mean), was almost 2%. While these values reflect the very lower and upper ends of the observed GC distribution, these individuals come from a community-dwelling aging population with extreme outliers removed. The magnitude of the associated decrease in TSI, while not large, represents the independent effect after adjustment for confounders, and is likely to be meaningful for brain health given that a 4% difference in resting cerebral oxygenation was previously observed between individuals with amnesic mild cognitive impairment (MCI) and a control group (Tarumi et al., 2014).

Another somewhat novel aspect of this study concerns the investigation of cortisone and the R_{hcc} in addition to cortisol, providing a more detailed picture of GC action over a prolonged period of time (Zhang et al., 2018). The R_{hcc} has been the subject of little investigation in studies of GCs to-date. This represents the ratio of cortisol/cortisone and is taken as an index of integrated activity of the two 11- β HSD subtypes across the various organs and tissues. Whereas the Type 2 enzyme inactivates cortisol by converting it to cortisone, Type 1 acts primarily as a reductase, regenerating cortisol from inactive cortisone, thereby increasing biological activity. The tissue specificity of the two enzyme subtypes notable, with Type 1 predominant in the brain (particularly the hippocampus, prefrontal cortex and cerebellum), liver, adipose tissue and vasculature, and Type 2 in the kidney, colon, salivary gland, adrenal cortex and placenta (Weber et al., 2000). Variations in 11- β HSD enzymatic activity have been associated with cardiovascular risk factors including hypertension and obesity (Walker, 2007). Furthermore, an elevated ratio of cortisol/cortisone (or of their metabolites) measured has been noted in under conditions of stress (Plenis et al., 2011). Interestingly a higher ratio predicted a decline in cognitive processing speed over 6 years in older men independently of cortisol levels (MacLulich et al., 2012). Inflammatory stress upregulates 11- β HSD 1 activity in the brain and activity of this enzyme is also elevated in the hippocampus and cortex with aging (Wyrwoll et al., 2011). These findings have generated interest in the inhibition of 11- β HSD 1 as a potential therapeutic target in metabolic disorder (Walker, 2007) and more recently, in cognitive impairment (MacLulich et al., 2012; Sandeep et al., 2004). Our finding that a higher R_{hcc} is associated with lower frontal oxygenation is interesting and relevant in this context and, taken with the aforementioned observations, suggests the need for further research into the regulation of GC production and metabolism at the pre-receptor level, and its possible role in brain aging.

While evidence that elevated GCs directly alter cerebral oxygenation at rest has thus far been lacking, empirical research demonstrates that repeated activation of the HPA axis can compromise both peripheral cardiovascular and cerebrovascular health (Burrage et al., 2018). Sapolsky and colleagues have demonstrated the ability of GCs to increase the susceptibility of neurons to death following hypoxia-ischaemia, as part of a phenomenon they term 'endangerment'. High levels of GCs can inhibit glucose uptake and utilisation throughout the brain (Sapolsky,

1999) and chronic elevation of cortisol increases inflammation (Herriot et al., 2017). In addition, GCs inhibit angiogenesis, reducing the recovery of damaged or ischaemic tissue (Burrage et al., 2018). GC receptor activation increases oxidative stress and reduces oxidative damage repair (Sapolsky, 1999). One consequence of these physiological changes in response to chronic stress and aberrant cortisol signalling is endothelial dysfunction (Poitras and Pyke, 2013). Endothelial cells are crucial in the regulation of vascular tone and vascular homeostasis in the brain as well as the periphery, and the regulation of cerebral blood flow and consequently oxygenation is reliant on healthy vascular endothelial cells (Toda, 2012). Impaired endothelial function might have implications for brain health via subtle reductions in cerebral oxygen supply (Sabayan et al., 2014). For example, markers of endothelial dysfunction have been associated with impaired cognitive functioning and endothelial function declines with increasing age (Toda, 2012). It is possible that elevated GC secretion may exacerbate this decline. GCs decrease the potent vasodilator nitric oxide by inhibiting endothelial nitric oxide synthase and chronic psychosocial stress in a variety of different contexts has also been shown to compromise endothelial function (see Toda and Nakanishi-Toda, 2011 for a review). By reducing endothelial function or cell turnover, raised GCs might lead to a reduction in the density of the cerebrovascular network (Ekstrand et al., 2008).

Consistent with evidence that compromised cerebrovascular health increases the risk of both Alzheimer's disease and vascular dementia (Yew et al., 2017), reduced cerebral oxygenation as assessed using NIRS has recently been observed in individuals with mild cognitive impairment (MCI), considered to be a preclinical stage of dementia and one which has also been associated with changes in GC signalling. Liu and colleagues observed reduced oxygenation at rest and decreased neurovascular coupling in MCI compared with a control group, in the absence of differences in grey or white matter volumes (Liu et al., 2014). Tarumi and colleagues also observed reduced cerebral oxygenation at rest using NIRS in MCI patients, and oxygenation level was associated with cognitive performance measured later in the same month (Tarumi et al., 2014). Thus, NIRS can reveal reductions in cerebral oxygenation even in prodromal or preclinical neurodegenerative states, lending further support to the notion that reduced oxygenation may be implicated in disease aetiology, rather than simply being the result of tissue atrophy.

Reduced frontal perfusion, in particular, has been noted in depressed individuals following autonomic nervous system challenge using NIRS (Briggs et al., 2019). It has been hypothesised that reduced frontal blood flow and oxygenation could lead to an increase in white matter hyperintensities and consequent impairment of function (Briggs et al., 2019). In the current study adjusting for concurrent depressive symptoms did not attenuate the associations observed, suggesting that increased cortisol levels in those with a higher burden of depressive symptoms does not explain the results. Nonetheless it would be of interest to investigate whether the association between GC and reduced oxygenation predicts any change in depressive symptoms or in cognitive function over time.

We must also acknowledge several limitations. This is a cross-sectional study and thus no causal relationship can be inferred from the current data. It may be the case that structural brain changes associated with high and prolonged GC exposure may explain reductions in regional oxygenation, or that the association may be bi-directional. These data only provide a snapshot of the relationship between these variables at one stage of the life-course. It is plausible that the association observed may be the result of adverse early life exposures during critical periods (pre- or postnatally or in later childhood) which could act to alter neuronal structure and function, the cerebral microvasculature and the development of the HPA axis and receptor density within discrete brain regions. Thus cross-talk between these interrelated physiological systems may be programmed early in development, accounting for the observed patterns of association, and linking an adverse early environment to reduced biological function or reserve in later life. The individuals in the current analyses represent a sub-sample of all

TILDA participants and differed slightly across certain health and demographic characteristics from the parent sample, those included being less likely to suffer from chronic health conditions and having higher education levels. Notably, women were over-represented in our sample, due to the requirement for a minimum amount of hair for GC analysis. For these reasons we cannot generalise our findings to the entire population of adults aged 50 and over in Ireland.

The NIRS measurement was limited to a single channel for practicality (FP1 position). The frontal cortex is particularly vulnerable to age-related neurodegenerative processes and age-associated hypometabolism (Kuhl et al., 1984) making it an area of particular interest in relation to age- and disease related changes in haemodynamics. However we cannot extrapolate from the current results to other areas of the brain, where associations with haemodynamics may differ.

The use of spatially resolved spectroscopy in the NIRS measurement of TSI greatly minimises any extracerebral influences (Ferrari and Quaresima, 2012); however, it is possible that some may remain.

Finally, the potential exists for the association between GCs and oxygenation to be the consequence of residual confounding; however, we consider this unlikely as many potential confounders were investigated in the current study.

5. Conclusions

In summary, we observed an inverse association between hair cortisol levels, the ratio of cortisol-to-cortisone and frontal lobe oxygenation, as measured by resting state NIRS in a sample of over one thousand adults aged 50 and over from TILDA. Older adults with chronically higher GCs may be vulnerable to reduced cerebral oxygenation, with potential negative consequences for brain health, including an increased risk of neurodegenerative disease and depression. However, these hypotheses remain to be tested with prospective data.

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Declarations of interest

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.psyneuen.2020.105107](https://doi.org/10.1016/j.psyneuen.2020.105107).

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