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Brain white matter integrity and cortisol in older men: the Lothian Birth Cohort 1936☆

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ABSTRACT

Elevated glucocorticoid (GC) levels are hypothesized to be deleterious to some brain regions, including white matter (WM). Older age is accompanied by increased between-participant variation in GC levels, yet relationships between WM integrity and cortisol levels in older humans are underexplored. Moreover, it is unclear whether GC-WM associations might be general or pathway specific. We analyzed relationships between salivary cortisol (diurnal and reactive) and general measures of brain WM hyperintensity (WMH) volume, fractional anisotropy (g_{FA}), and mean diffusivity (g_{MD}) in 90 males, aged 73 years. Significant associations were predominantly found between cortisol measures and WMHs and g_{MD} but not g_{FA}. Higher cortisol at the start of a mild cognitive stressor was associated with higher WMH and g_{MD}. Higher cortisol at the end was associated with greater WMHs. A constant or increasing cortisol level during cognitive testing was associated with lower g_{MD}. Tract-specific bases of these associations implicated anterior thalamic radiation, uncinate, and arcuate and inferior longitudinal fasciculi. The cognitive sequelae of these relationships, above other covariates, are a priority for future study.

1. Introduction

Glucocorticoids (GCs; cortisol in humans) are produced via activation of the hypothalamic-pituitary-adrenal (HPA) axis in response to stress. They also exhibit a diurnal rhythm, with high levels in the morning which decline during the day. Sustained chronic exposure to high GCs through stress or exogenous administration has deleterious effects on brain structure and function in animals (McEwen and Gianaros, 2010). A similar effect is observed in Cushing disease in humans, a disease whose hallmark is chronically elevated cortisol (Patil et al., 2007). In some animals and humans, aging is accompanied by flatter diurnal slopes, lower GC levels on waking (Heaney et al., 2010), and increased GC levels in reaction to stress (Otte et al., 2005). A flatter cortisol slope is considered to represent HPA axis dysregulation, whereby the negative feedback loop fails to reduce cortisol levels either in line with the normal diurnal pattern, or following cortisol elevation in response to an environmental catalyst (Herman et al., 2003). Aging and GC levels are hypothesized to interact in complex ways dependent on cell type; some such interactions may affect the brain adversely and contribute to cognitive decline (Landfield et al., 2007; Sapolsky et al., 1986). However, research examining the cerebral correlates of these complex age-GC interactions has mainly focused on cortical and subcortical loci that comprise the GC regulatory network. Little empirical research has examined how GCs might relate to the integrity of white matter (WM) tracts, some of which connect these regions. Moreover, studies investigating the neurostructural correlates of GCs in older age tend not to consider both diurnal and reactive measures together.

HPA axis activity is modulated by a complex network of regions including the hippocampus, amygdala, and prefrontal cortex (Ulrich-Lai and Herman, 2009). These regions appear particularly

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sensitive to the detrimental effects of excess GCs. Prolonged exposure to repeated instances of restraint stress or exogenous steroids in animals results in reduced synaptic and dendritic complexity in the hippocampus and medial prefrontal cortex (reviewed in McEwen and Gianaros, 2010). In older humans, reduced anterior cingulate volume (MacLullich et al., 2006) and thinner lateral frontal cortex (Kremen et al., 2010) are associated with markers of HPA axis dysregulation. However, models of the brain network(s) that influence HPA axis regulation (Dedovic et al., 2009) have underplayed the role of WM integrity, and studies of GC effects on WM are scarce. WM is essential in facilitating efficient information transfer between cerebral regions (Filley, 2010) and plays a central role in the body's response to environmental and homeostatic challenge (Ulrich-Lai and Herman, 2009). Poorer integrity of this connectivity via any mechanism could therefore also lead to impaired operation of GC regulation and impaired cognition, just as it would for relevant cortical and subcortical sites.

The theoretical importance of WM in HPA axis control in aging and disease is supported when considering that elevated GC levels impair axonal sprouting in response to insult. Following experimental lesions in rodents, WM repair by axonal sprouting was significantly reduced in a dose-dependent manner by exposure to a glucocorticoid receptor agonist compared with controls (Scheff and Cotman, 1982; Scheff and DeKosky, 1983). Increased exposure to GCs pre-lesion led to less axonal sprouting than when GCs were administered only post-lesion (Scheff and Dekosky, 1989). Moreover, GCs and stress inhibit the proliferation of astrocytes and oligodendrocytes in animal models (Rajkowska and Miguel-Hidalgo, 2007). Higher GC levels might result in a reduced repair response to accumulated damage via any route and affect the maintenance of axonal myelination. This could also lead to further impairment of HPA axis regulation as information transfer becomes compromised, impairing GC regulation and further impairing reparative responses to subsequent WM insult (Sapolsky et al., 1986).

Measures of the magnitude of water molecule diffusion (mean diffusivity; MD) and its directional coherence (fractional anisotropy; FA) obtained from diffusion tensor magnetic resonance imaging (DT-MRI) allow an estimate of WM microstructure. More tightly packed fiber bundles characteristically exhibit higher FA and lower MD, and comparison of these DT-MRI biomarkers and postmortem histopathology suggests that FA and MD are reliable indices of reduced axonal integrity, demyelination, and accumulation of extracellular fluid in frontotemporal dementia (Larsson et al., 2004), multiple sclerosis (Schmierer et al., 2007), and older age (Kochunov et al., 2007; Sullivan and Pfefferbaum, 2007). Using DT-MRI, tractography can measure the 3-dimensional structure and integrity of major axonal fiber bundles, providing generally good concordance with WM fibers identified postmortem (Catani and Thiebaut de Schotten, 2008; Klein et al., 2010; Wakana et al., 2004). Additionally, WMHs are a common feature of the aging brain, observable on T_2 and fluid-attenuated inversion recovery (FLAIR)-weighted MRI (Longstreth et al., 2000; Schmidt et al., 2011). The total WM hyperintensity (WMH) load can therefore be quantitatively assessed by measuring the total volume of WMHs and offers a neuroradiologically complementary metric of WM integrity to the diffusion-based measures discussed previously. Using both approaches, we are able to estimate WM integrity both at the level of major connective fiber pathways and at the level of aggregate brain-wide volume of visible age-related WM deterioration.

Few studies have examined the association between indices of HPA axis activity and brain WM integrity measured using DT-MRI. Increased MD, indicating lower WM structural integrity, measured in callosal, uncinate, and cingulum bundles was associated with higher observational rating of behavioral stress reactivity but not directly with 12 hours urinary cortisol in rhesus monkeys (Willette et al., 2012). In humans, one study reported an inverse relationship between evening cortisol levels and a measure of periventricular WM integrity using a region of interest approach in small healthy sample (n = 23, mean age = 43.9, SD = 11.6 years; Macritchie et al., 2013). Given that the hippocampus, amygdala, and prefrontal cortex have been centrally implicated in supra-HPA axis regulation (Dedovic et al., 2009; Ulrich-Lai and Herman, 2009) findings that associate specific fiber integrity with indices of HPA axis dysregulation are partially commensurate with the underlying neuroanatomy. For example, the uncinate fasciculus arises lateral to the hippocampus and amygdala, connecting entorhinal cortex with prefrontal cortex. The cingulum bundle runs from the parahippocampal gyrus and uncus of the temporal lobe and runs superior to the corpus callosum into the frontal lobes. Similarly, the anterior thalamic radiation (ATR) is a major efferent pathway between the prefrontal cortex (PFC) and thalamus; the anterior thalamic nucleus receives afferents from the hippocampus and anterior projections extend predominantly to the cingulate cortex and lateral PFC (Catani and Thiebaut de Schotten, 2008; Nolte and Angevine, 1995). Consequently, the ATR, uncinate, and cingulum bundles are plausible candidates to examine the hypothesis of tissue specific relationships with cortisol levels among older humans.

In summary, elevated GCs and flatter slopes in aging are possible contributors to brain and cognitive aging, and this might be partly because of the effects on WM integrity. General WM integrity is significantly associated with processing speed, which in turn is strongly associated with higher general cognitive ability in older age (Penke et al., 2012). Thus, disruption of information transfer by WM damage in older age could partially explain impairments to both cognitive ability and GC regulation. However, it is unclear whether the hypothesized interactions between aging and cortisol are differentially expressed among the brain's various long-range WM tracts, and also across various measures of the complex cortisol profile, whose characteristics do not show a unidirectional change with increasing age. The limited animal and human data are relatively underpowered and have not explicitly addressed cortisol-WM relationships in aging nor have they examined the contribution of both reactive and diurnal GC levels. We therefore measured the total volume of WMHs, the water diffusion characteristics of 7 major long-range WM tracts and both diurnal and reactive cortisol levels in a group of 90 healthy older men. We hypothesized that higher reactive cortisol levels and flatter slopes (between sampling points on the same occasion) would correlate with lower WM integrity, as indicated by higher WMH volume, lower FA, and higher MD.

2. Methods

2.1. Participants

Ninety male participants from the Lothian Birth Cohort 1936 (LBC1936) participated in this study. Details of this cohort have been described previously (Deary et al., 2007, 2012). All participants who scored <11 on the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) were not taking antidepressant or GC medication, made no self-report of stroke, had no history of serious neurologic event such as large brain infarcts, meningiomas, frontal or temporal cysts, or extensive siderosis, frontal infarcts (all MRI scans were examined by a consultant neuroradiologist, Joanna M. Wardlaw) were free from a diagnosis of neurodegenerative disorders, and scored 24 or above on the Mini-Mental State Examination (MMSE; Folstein et al., 1975). Participants were of mean age 73.30 (SD 0.37) years at MRI scanning. Salivary cortisol sampling took place just over 1 year after MRI acquisition (mean 431.42 days, SD 103.62). Written informed consent was obtained from each participant and the study was conducted in compliance with departmental guidelines on