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Does white matter structure or hippocampal volume mediate associations between cortisol and cognitive ageing?

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ABSTRACT

Elevated glucocorticoid (GC) levels putatively damage specific brain regions, which in turn may accelerate cognitive ageing. However, many studies are cross-sectional or have relatively short follow-up periods, making it difficult to relate GCs directly to changes in cognitive ability with increasing age. Moreover, studies combining endocrine, MRI and cognitive variables are scarce, measurement methods vary considerably, and formal tests of the underlying causal hypothesis (cortisol → brain → cognition) are absent. In this study, 90 men, aged 73 years, provided measures of fluid intelligence, processing speed and memory, diurnal and reactive salivary cortisol and two measures of white matter (WM) structure (WM hyperintensity volume from structural MRI and mean diffusivity averaged across 12 major tracts from diffusion tensor MRI), hippocampal volume, and also cognitive ability at age 11. We tested whether negative relationships between cognitive ageing differences (over more than 60 years) and salivary cortisol were significantly mediated by WM and hippocampal volume. Significant associations between reactive cortisol at 73 and cognitive ageing differences between 11 and 73 ($r = -.28$ to $-.36$, $p < .05$) were partially mediated by both WM structural measures, but not hippocampal volume. Cortisol-WM relationships were modest, as was the degree to which WM structure attenuated cortisol–cognition associations (<15%). These data support the hypothesis that GCs contribute to cognitive ageing differences from childhood to the early 70s, partly via brain WM structure.

1. Introduction

Exposure to elevated glucocorticoid (GC) levels is hypothesised to have deleterious effects on brain structure (or specific regions or tissue types thereof), which negatively affect cognitive function (Landfield et al., 2007; Sapolsky et al., 1986). GCs (cortisol in humans) exhibit a complex diurnal pattern and also a phasic response to psychological and physical challenge. Increasing age is associated with altered diurnal and reactive profiles of GCs (cortisol in humans; Heaney et al., 2010; Otte et al., 2005) as well as average declines in brain structure and cognitive function. Several studies using moderate-to-large sample sizes suggest that impairments in domains of processing speed, memory and global cognition are associated with higher diurnal and reactive cortisol measures in older adults ($97 \leq n \leq 1154$; Comijs et al., 2010; Gerritsen et al., 2009; Kuningas et al., 2007; Lee et al., 2007; MacLullich et al., 2005). Separately, other studies suggest that cognitive ageing may be mediated via brain structure (discussed below), yet, studies with all three types of data—cortisol, brain structure, and cognition—are rare, and no formal tests of mediation have been undertaken to directly test this central three-component hypothesis. Synthesis of findings is hampered by the variety of cognitive measures employed, and diurnal and reactive cortisol (e.g. in response to a psychological stressor) are seldom reported together. The absence of information about prior cognitive ability in the majority of previous studies also makes cross-sectional analyses of GCs, brain and behaviour difficult to interpret because the overarching causal

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hypothesis posits a change of cognition over time, dependent upon GC levels.

With respect to possible mediators of cortisol-cognition relationships, the hippocampus is one putative neural substrate of these effects. The initial hypothesis of GC-induced hippocampal cell death has been moderated by evidence of reversible dendritic atrophy in the rodent hippocampus (Conrad, 2009; McEwen and Gianaros, 2010) and GC-induced impairments in memory tasks (Dachir et al., 1993; Sousa et al., 2000). However, evidence of significant associations between cortisol levels and hippocampal volume among healthy older humans is limited. Lupien et al. (1998) reported that 11 individuals with increasing 24 h cortisol over 5 years had decreasing hippocampal volumes and concomitant declines in memory. Subsequent studies in larger samples report no significant relationship between cortisol and hippocampal measures in non-pathological ageing (Coluccia et al., 2008; Gold et al., 2005; Kremen et al., 2010a; MacLullich et al., 2005, 2006, 2012).

There is also evidence that the brain's white matter (WM) may be susceptible to elevated GC effects. WM is significant because of its relationship with cognitive ability (Filley, 2010; Penke et al., 2012) and because it supports efficient information transfer between brain regions involved in supra-HPA axis regulation (Ulrich-Lai and Herman, 2009). There is evidence that elevated GCs alter cerebral white matter microstructure. In rodents, administering a GC receptor agonist following brain lesion impaired axonal sprouting in a dose-dependent manner when compared to controls (Scheff and Cotman, 1982; Scheff and DeKosky, 1983). Elevated GCs and stress inhibit the proliferation of astrocytes and oligodendrocytes (Alonso, 2000; Miyata et al., 2011; Rajkowska and Miguel-Hidalgo, 2007), suggesting that GCs may play a role in hindering oligodendrocyte-mediated axonal remyelination. In humans, Cushings syndrome patients reportedly exhibit widespread loss of white matter integrity and predominant demyelination (Pires et al., 2015), and these differences persist many years after remission (van der Werff et al., 2014). In healthy older adults, higher evening cortisol was associated with lower estimates of periventricular WM structure (Macritchie et al., 2013). In the same older males as in the present study, we reported that elevated reactive cortisol at the start or end of cognitive testing was associated with lower WM structural estimates (Cox et al., 2015). In the current study, we therefore, expand the analyses to report novel associations between cortisol and cognitive ability, and also novel associations between cortisol and hippocampal volume. We then use mediation analysis to test the hypothesis that these cortisol–brain associations might have ramifications for cognitive ageing differences.

In summary, cross-sectional bivariate analyses have been the mainstay of studies which test the hypothesis that elevated cortisol has deleterious effects on the brain and cognitive functioning. Yet there remain no attempts to test whether cortisol–cognition relationships are mediated by poorer brain structure. This may be due to a lack of studies that collect all three requisite domains of data, or to the file-drawer effect in previous studies with all three types of data (i.e. no significant 3-way associations—required for mediation analysis—were found). This, in turn, may be due to the focus on hippocampal measures whereas, in fact, other brain indices (such as WM measures) might be just as – or more – pertinent to cognitive performance among healthy older individuals. Finally, inferring whether cortisol affects cognitive decline in old age requires knowledge of how a subject is performing now, relative to their prior ability. This information is absent in many existing GC studies which use cross-sectional cognitive indices, and longitudinal cognitive data are few, spanning only 6 years or less. In the current study, we examine a group of 90 older males who have provided both diurnal and reactive salivary cortisol measures, hippocampal volume and measures of white matter structure measured at age 73 years, and cognitive ability scores obtained at ages 11 and 73 years. The association between childhood and older-age cognitive ability measured in this way typically ranges between .60 to .70 (reviewed in Deary, 2014), indicating that intelligence between youth and old age is remarkably stable throughout the lifecourse. Importantly, however, the association is not perfect, allowing investigations into which factors might be related to cognitive ageing differences. In this instance, these data afford a rare opportunity to test the hypothesis that elevated cortisol levels are associated with negative cognitive change (over more than 60 years) via negative relationships between cortisol and hippocampal volume or WM structure.

2. Material and methods

2.1. Participants

The participants were 90 older community-dwelling males from the Lothian Birth Cohort 1936 (LBC1936). The members of this cohort were born in 1936 and sat a valid IQ-type test (Moray House Test No. 12; MHT) at school in Scotland in June 1947 at an average age of 11 years. At around 70 years of age, 1091 surviving, healthy, community-dwelling residents in the Edinburgh and Lothians area, most of whom had taken this test in 1947, were recruited as the LBC1936 and underwent a series of cognitive and physical tests (Deary et al., 2007). Three years later, 866 returned for a second follow-up wave of cognitive testing and an MRI brain scan (Deary et al., 2012; Wardlaw et al., 2011).

From this second wave of LBC1936 testing, male participants were selected on the following criteria: a score of 24 out of 30 or greater on the MMSE (Folstein et al., 1975), a score less than 11 out of 21 on the depression facet of the Hospital Anxiety and Depression Scale (Snaith, 2003), a complete MRI scan, not taking any antidepressant or glucocorticoid medication, free from diagnosis of neurodegenerative disorders and no history of serious neurological event (brain scans were examined by a consultant neuroradiologist; JMW). Of 118 potential participants, 90 agreed to take part. These participants were of mean age 73.10 (SD 0.40) years when they sat a battery of cognitive tests (see Section 2.3). At MRI scanning, they had a mean age of 73.30 (SD 0.37) years. They were invited to attend an appointment in a novel (for them) location (Department of Psychology, University of Edinburgh) to attend a cognitive testing session during which salivary cortisol was collected at the start and end of the testing session; diurnal salivary cortisol was sampled on waking and at 10pm on a separate weekday (see Section 2.2). Salivary cortisol sampling took place just over one 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 participant testing and the Declaration of Helsinki. Ethical approval was gained from NHS Lothian Research Ethics Committee (NREC:07/MRE10/58) and the Philosophy, Psychology and Language Sciences Research Ethics Committee at the University of Edinburgh.

2.2. Cortisol

Salivette devices (Sarstedt, Numbrecht, Germany) were used and samples stored at −80 °C following collection. Assays were carried out by Dresden LabService GmbH in accordance with a Material Transfer Agreement. All measures are reported in nmol/l. Reactive cortisol was measured at the start and end of a cognitive testing appointment (referred to as START and END, respectively; Cox et al., 2015). Efforts were made to normalise the testing time for each participant, which took take place three hours following waking