



Cognitive ability across the life course and cortisol levels in older age

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ABSTRACT

Elevated cortisol levels have been hypothesized to contribute to cognitive aging, but study findings are inconsistent. In the present study, we examined the association between salivary cortisol in older age and cognitive ability across the life course. We used data from 370 members of the 36-Day Sample of the Scottish Mental Survey 1947, who underwent cognitive testing at age 11 years and were then followed up at around age 78 years, completing further cognitive tests and providing diurnal salivary cortisol samples. We hypothesized that higher cortisol levels would be associated with lower cognitive ability in older age and greater cognitive decline from childhood to older age but also lower childhood cognitive ability. Few of the tested associations were significant, and of those that were, most suggested a positive relationship between cortisol and cognitive ability. Only 1 cognitive measure showed any sign of cortisol-related impairment. However, after correcting for multiple comparisons, no results remained significant. These findings suggest that cortisol may not play an important role in cognitive aging across the life course.

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1. Introduction

The glucocorticoid hormone cortisol is important in coordinating adaptive responses to stressful events, but prolonged elevated levels may also be harmful (Landfield et al., 2007; Sapolsky, 1996). Administration of high doses of glucocorticoids has been shown to produce transient cognitive deficits (Kirschbaum et al., 1996; Newcomer et al., 1994), and patients with diseases characterized by elevated cortisol levels, such as Cushing's syndrome, also show impairments in cognition (Belanoff et al., 2001; Forget et al., 2000; Mauri et al., 1993), as well as brain atrophy, particularly in the hippocampus (Toffanin et al., 2011). A number of studies have reported relationships between higher daytime salivary cortisol levels and lower cognitive ability in non-pathological samples (Gaysina et al., 2014; Geoffroy et al., 2012; Stawski et al., 2011). More chronic associations between cortisol

and cognition may be due to the adverse effects of sustained high levels of glucocorticoids on neurons (Abraham et al., 2001; Sapolsky, 1996), including those involved in regulation of the hypothalamic-pituitary-adrenal (HPA) axis. According to the glucocorticoid cascade hypothesis by Sapolsky et al. (1986), excess glucocorticoids can ultimately impair the ability of the HPA axis to downregulate cortisol after a stress response, thus further increasing cortisol levels and leading to accumulating adverse effects. This may explain, in part, the cognitive deficits associated with mental disorders whose etiology may involve stress, such as depression (Hinkelmann et al., 2009; Rubinow et al., 1984). Huang et al. (2009) also observed modest correlations (around $r = 0.2$) between elevated basal plasma cortisol levels, hippocampal atrophy, and cognitive decline in 172 Alzheimer's patients, consistent with the glucocorticoid cascade hypothesis.

Chronic exposure to elevated cortisol levels may also play an important role in cognitive aging (Belanoff et al., 2001; Landfield et al., 2007), whereby neurodegeneration and hypersecretion of glucocorticoids might continuously exacerbate one another, producing cognitive decline even in normal aging (Sapolsky et al., 1986). Several studies have provided evidence to support this. For

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example, Lee et al. (2007) observed that higher overall (mean and area under the curve) salivary cortisol was associated with poorer performance in a range of cognitive domains among 967 participants aged 50–70 years. Similarly, Comijs et al. (2010) observed that higher daytime serum concentrations of cortisol related to impairments in memory and processing speed among 1154 older participants, aged 65–88 years. Others have found similar results in smaller samples (Beluche et al., 2010; Lara et al., 2013; Lupien et al., 1994; MacLulich et al., 2005; $N = 19$ –197). Importantly, O'Brien et al. (1994) demonstrated that aging-related cognitive deficits were associated with impaired cortisol suppression, following administration of dexamethasone, providing clearer evidence in support of the glucocorticoid cascade hypothesis of cognitive aging. A number of studies have focused on the hippocampus, which participates in regulation of the HPA axis, and is also involved in memory. Several studies have associated higher cortisol levels with greater hippocampal atrophy and reduced hippocampal activation (Lupien et al., 1998; McAuley et al., 2009), as well as poorer performance on hippocampus-dependent memory tests (Lupien et al., 1998; Segerstrom et al., 2016). More recently, in another sample, Cox et al. (2015) formally tested the role of neurodegeneration in the association between cortisol and cognitive decline across the life course, observing that white matter microstructural measures mediated the relationship—at least for reactive cortisol measures—also supporting the hypothesis. However, looking at aging-related changes in hippocampal morphology and microstructure, Cox et al. (2017) were unable to conclude that cortisol is an important mediator.

It is unclear if cortisol levels are sufficiently high in non-pathological aging to have a detectable deleterious effect, and results do not always support an association between excess cortisol and cognitive decline. For example, in a large study of 3229 middle- to old-age participants, Singh-Manoux et al. (2014) found no evidence of an association between diurnal salivary cortisol levels and cognitive decline over around 5 years. Other studies have even shown that cortisol facilitates memory consolidation (McGaugh and Rozendaal, 2002) and can be neuroprotective (Abraham et al., 2001), thereby ameliorating brain aging (Patel and Finch, 2002). In a study of 1226 older people, Potvin et al. (2013) observed an association between higher morning salivary cortisol levels and cognitive impairment among participants with a history of anxiety or depression, but the opposite relationship in those with no such history. In another recent study of 4244 older people, Geerlings et al. (2015) found that, while higher evening cortisol levels were associated with smaller total brain volume and poorer cognitive functioning, higher morning levels were associated with greater white matter volume, faster processing speed, and executive functioning. Other recent studies suggest that dysregulation of diurnal cortisol secretion (Johar et al., 2015), reduced variability in levels (Dijckmans et al., 2017), or blunted cortisol responses to stress (Almela et al., 2014) may be more important than overall elevation of levels in mediating cognitive aging. In addition, Franz et al. (2011) observed that lower early-adulthood cognitive ability predicted higher later-adulthood cortisol levels (in salivary samples taken over 3 days), rather than the other way around, which may indicate a different mechanistic relationship between cortisol and cognition across the life course. As these mixed findings suggest, the relationships between various cortisol characteristics and cognitive ability in older age are complex and not yet fully understood.

With the present study, we aimed to shed further light on the association between cortisol and cognitive aging. We made use of data from 396 members of the 36-Day Sample, a group of Scottish people born in 1936, who were assessed on intelligence at around age 11 years, and provided salivary cortisol samples and

contemporaneous cognitive scores at around age 78 years. These data allowed us to make several important contributions to the field: (1) all participants were of the same age, removing the important potential confounding effect of age, (2) we were able to examine the relationship between cognitive ability in youth, and cortisol levels ~67 years later, and (3) we were able to examine associations between cortisol levels in older age and relative change in cognitive ability across most of the life course. In accordance with the hypothesis that higher cortisol levels contribute to neurocognitive decline in aging, we expected to observe associations between higher older-age cortisol levels—whether at specific times of day or overall—and lower contemporaneous cognitive ability at age 78 years, as well as greater cognitive decline from age 11 to 78 years.

However, we also assessed relations between these cognitive measures and other derived measures of the diurnal cortisol profile, testing the hypothesis that dysregulation and blunted responses play a more important role. Furthermore, given previous findings that intelligence predicts later cortisol levels, we explored the hypothesis that cortisol levels are influenced by cognitive ability (rather than the other way around), by testing associations between childhood IQ and cortisol measures. Higher childhood intelligence could be associated with the use of better coping mechanisms in response to stress throughout life, the cumulative benefits of which could lead to lower cortisol levels in older age, in line with the findings by Franz et al. (2011). Finally, considering that cortisol levels and cognitive ability may each influence the other and that there may be a complex relationship between them throughout life, we explored whether the degree of cortisol's impact on older-age cognitive ability is determined by prior cognitive ability, by testing for interactions between childhood IQ and cortisol measures.

2. Material and methods

2.1. Participants

On June 4, 1947, almost all children born in 1936 and attending school in Scotland ($N = 70,805$) completed the second Scottish Mental Survey (SMS1947; Scottish Council for Research in Education; SCRE, 1949). Shortly afterward, a representative sample of the cohort (including those absent from school on the day of the SMS1947; $N = 7380$) completed a short sociological schedule (MacPherson, 1958). As participants were selected according to their dates of birth being on one of the first 3 days of the month (i.e., 36 days throughout the year), they were known as the “36-Day Sample.” Within this sample, the “6-Day Sample” (born on the first day of the 6 even-numbered months; $N = 1208$) was also studied in greater depth over the following 16 years (Maxwell, 1969).

In 2012, the 6-Day Sample and, in 2013, the remainder of the 36-Day Sample (or “30-Day Sample”) were traced through the United Kingdom National Health Service Central Register (Brett and Deary, 2014). Those who were still alive, and resident in Scotland, England, or Wales ($N = 2977$) were invited to participate in a follow-up study. Those who agreed to participate completed a detailed questionnaire booklet ($N = 722$), physical testing ($N = 423$), and a telephone interview ($N = 365$; Deary and Brett, 2015). Physical testing included providing 3 (waking, waking + 45 minutes, and evening) salivary cortisol samples, and a range of cognitive tests were administered during the telephone interview (several weeks later, avoiding any potential effects of test anxiety on sampled cortisol levels). For the present study, we selected participants who provided viable cortisol samples—157 (81 female) from the 6-Day Sample and 239 (95 female) from the 30-Day Sample.

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