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No evidence of a longitudinal association between diurnal cortisol patterns and cognition☆

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ABSTRACT

We examined the effect of salivary cortisol on cognitive performance and decline in 3229 adults (79% men), mean age 61 years. Six saliva samples over the day along with a cognition test battery were administered twice in 5 years. In fully-adjusted cross-sectional analyses from 2002 to 2004, higher waking cortisol was associated with higher reasoning score ($\beta = 0.08$, 95% confidence interval: 0.01, 0.15) but this finding was not replicated using data from 2007 to 2009. Over the mean 5 years follow-up there was decline in all cognitive tests but this decline did not vary as a function of cortisol levels; the exception was among APOE e4 carriers where a flatter diurnal slope and higher bedtime cortisol were associated with faster decline in verbal fluency. Changes in cortisol measures between 2002/2004 and 2007/2009 or chronically elevated levels were not associated with cognitive performance in 2007/2009. These results, based on a large sample of community-dwelling adults suggest that variability in hypothalamic-pituitary-adrenal function is not a strong contributor to cognitive aging.

1. Introduction

Cortisol is a glucocorticoid hormone, regulated via the hypothalamic-pituitary-adrenal (HPA) axis. Dysregulation of this axis is hypothesized to impair cognitive function, in particular memory and learning processes (Sapolsky et al., 1986, 2000). Much of the evidence for this view comes from animal models where glucocorticoid receptors have been found in the rodent hippocampus (Jacobson and Sapolsky, 1991; McEwen et al., 1986), and elevated glucocorticoid levels shown to be associated with spatial memory impairments and neuronal loss in the hippocampus (Issa et al., 1990; Montaron et al., 2006). Small experimental studies in humans show short term elevations in cortisol improve consolidation of memories (Abercrombie et al., 2003; Buchanan and Lovallo, 2001; Kuhlmann and Wolf, 2006). However, sustained elevations in cortisol may be toxic to brain cells, as in Cushing disease (Starkman et al., 1992) and contribute to risk of dementia. Dementia patients show higher cortisol levels (Elgh et al., 2006; Hartmann et al., 1997) but no disturbance in the diurnal rhythm (Hartmann et al., 1997). Neuroimaging data show plasma cortisol to be correlated with beta amyloid, a hallmark of Alzheimer's disease (Toledo et al., 2012). However, given the long preclinical phase of dementia (Braak and Del, 2011; Jack et al., 2010) it is unclear whether HPA dysregulation is a cause, correlate, or consequence of dementia. Evidence of an association between elevated cortisol levels and accelerated cognitive decline would support an etiological role for cortisol.

There is some evidence, mostly from studies of limited size on elderly persons (Lupien et al., 1994, 1998) that memory is the domain specifically affected by higher cortisol levels. While glucocorticoid receptors are localized to the rodent hippocampus (Jacobson and Sapolsky, 1991; McEwen et al., 1986), they are widely present in primate brains (Sanchez et al., 2000), making it important to consider the association of cortisol with a wide range of cognitive domains. The measurement of cortisol is not straightforward, salivary cortisol over the day is seen to better measure HPA axis function compared with plasma or urinary cortisol (Kirschbaum and Hellhammer, 1989, 1994; Vining et al., 1983). In this article, we examined the association of salivary cortisol,

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assessed with 6 samples over the day, and cognitive decline over a 5-year period in a large cohort of middle-aged community-dwelling adults. Since APOE e4 is a risk factor for both cognitive decline before the age of 60 years (Caselli et al., 2009) and dementia (Corder et al., 1993) and is hypothesized to modify cortisol's association with cognitive function (Lee et al., 2008), we also conducted analyses stratified by APOE ε4 status. We used tests of memory, reasoning, and verbal fluency in the analysis.

2. Methods

2.1. Participants

The Whitehall II study is an ongoing study of men and women, originally employed by the British civil service. The target population was all London-based office staff, aged 35–55 years at study inception. A total of 10,308 persons (6895 men and 3413 women), response rate 73%, were recruited to the study in 1985–1988 (Marmot and Brunner, 2005). Since the baseline medical examination, follow-up examinations have taken place approximately every 5 years: 1991/1993 (n = 8815); 1997/1999 (n = 7870); 2002/2004 (n = 6967), and 2007/2009 (n = 6761). Ethical approval for the Whitehall II study was obtained from the University College London Medical School committee on the ethics of human research; all participants provided written informed consent.

2.2. Assessment of cortisol, 2002/2004 and 2007/2009

Cortisol data collection was initiated part way through the 2002/2004 wave and repeated in 2007/2009. Instructions were given in a face-to-face interview where participants were requested to provide 6 saliva samples using salivettes over the course of a normal weekday at waking, +30 minutes, +2.5 hours, +8 hours, +12 hours, and bedtime. The intention was to study diurnal rhythm, characterized by high levels upon waking, a further increase—peaking at about 30–40 minutes (the cortisol awakening response, CAR) and subsequent decline over the remainder of the day (Kirschbaum and Hellhammer, 1989). Participants were instructed not to brush their teeth or eat or drink for 15 minutes before sample collection. A booklet was used for participants to record information on the day of sampling including date of collection, wake time, and time each sample was taken. The salivettes and booklet were returned in a prepaid envelope by post. Salivettes were centrifuged at 3000 rpm for 5 minutes, resulting in a clear supernatant of low viscosity. Salivary cortisol levels were measured using a commercial immunoassay with chemiluminescence detection (CLIA; IBLHamburg, Hamburg, Germany). The lower concentration limit of this assay was 0.44 nmol/liter; intra and interassay coefficients of variance were below 8%.

2.3. Cognitive function, 2002/2004 and 2007/2009

The cognitive test battery was chosen to provide a comprehensive assessment of cognitive function while being appropriate, with respect to ceiling effects, for this population composed of individuals younger than in most studies on cognitive aging. The tests had high test–retest reliability, range 0.60–0.89, assessed on 556 participants within 3 months of having taken the test in 2002/2004.

Short-term verbal memory was assessed with a free recall test. Participants were presented a list of 20 one or 2 syllable words at 2 seconds intervals and were then asked to recall in writing, within 2 minutes, as many words as possible, in any order.

The Alice Heim 4-I is composed of a series of 65 verbal and mathematical reasoning items of increasing difficulty (Heim, 1970). It tests inductive reasoning, measuring the ability to identify patterns and infer principles and rules. Participants had 10 minutes to do this section.

Verbal fluency (Borkowski et al., 1967), phonemic, and semantic tests were combined for the purposes of the analysis. Participants were asked to recall in writing as many words beginning with "S" (phonemic fluency) and as many animal names (semantic fluency) as they could. One minute was allowed for each test; the observed range on these tests was 0–35.

2.4. Covariates

Demographic measures included age, sex, ethnicity (white, non-white), and education, defined as the highest qualification on leaving full-time education and categorized as lower secondary school or less, higher secondary school (usually achieved at the age of 18 years) and university or higher degree. Other covariates in the analyses were seasonality (using 21 March, June, September, and December as cutoffs); depressive symptoms using the 20-item Center for Epidemiologic Studies Depression Scale; (Radloff, 1997) stress on the day of cortisol sampling using questions on whether the participant had experienced a stressful event and, if yes, response to how stressful this was on a 5 point Likert-scale; cardiovascular risk using the Framingham general cardiovascular disease risk score which includes age, sex, systolic blood pressure, treatment for hypertension, high density lipoprotein cholesterol, total cholesterol, smoking, and diabetes (D'Agostino et al., 2008); coronary heart disease and stroke identified using linkage to national hospital records, diabetes mellitus determined by fasting glucose ≥7.0 mmol/L, a 2-hour postload glucose ≥11.1 mmol/L, reported doctor-diagnosed diabetes, or use of diabetes medication; and medication to treat cardiovascular risk factors and depression.

For the sensitivity analysis, we assessed APOE genotype. Two TaqMan assays (Rs429358 and Rs7412, Assay-On-Demand, Applied Biosystems) were used and run on a 7900HT analyzer (Applied Biosystems), and genotypes indicated by the Sequence Detection Software version 2.0 (Applied Biosystems). Participants were categorized as APOE ε4 carriers for those with at least 1 ε4 allele.

2.5. Statistical analysis

All analyses were conducted using STATA 12. Participant characteristics were described using percentages, or mean (standard deviation, SD) when appropriate, as a function of sex. Five parameters were used to operationalize diurnal cortisol patterns in the analysis: (1) waking cortisol, the first measure of the day; (2) CAR, cortisol awakening response calculated by subtracting cortisol measured at time 1 (waking) from cortisol measured at time 2 (+30 minutes); (3) diurnal slope to reflect the decline in cortisol levels over the day, calculated by regressing logarithmically transformed cortisol values (excluding cortisol at time 2 so that slope across the day is not unduly biased by CAR) against sample time using a hierarchical linear model (random slope and intercept) where measurement occasion was a level 1 identifier and person a level 2 identifier, lower (more negative) slopes indicate a more rapid decline in cortisol levels, whereas slope values closer to zero reflect flatter diurnal rhythms; (4) bedtime cortisol, the last measure of the day; and (5) mean cortisol over the day, using the area under the curve (Pruessner et al., 2003), this measure was derived using the trapezoid formula and then divided by the time between the first and the last measure of the day for each person to yield mean hourly cortisol.

All 5 measures were categorized into tertiles; we also ran analyses using continuous scores, modeled as an increment of 1 standard deviation after log transforming the values which showed a skewed distribution (waking and bedtime cortisol). Linear