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Hypothalamic—pituitary—adrenal axis activity in older persons with and without a depressive disorder

D. Rhebergen[a,*,1], N.C.M. Korten[b,1], B.W.J.H. Penninx[a], M.L. Stek[a], R.C. van der Mast[c], R. Oude Voshaar[d,e], H.C. Comijs[a]

[a] *GGZ inGeest/Department of Psychiatry and the EMGO+ Institute for Health and Care Research, VU University Medical Center, Amsterdam, The Netherlands*
[b] *Department of Epidemiology and Biostatistics and the EMGO+ Institute for Health and Care Research, VU University Medical Center, Amsterdam, The Netherlands*
[c] *Department of Psychiatry, Leiden University Medical Center, The Netherlands*
[d] *University Center of Psychiatry & Interdisciplinary Center of Psychiatric Epidemiology, University Medical Center Groningen, The University of Groningen, Groningen, The Netherlands*
[e] *Department of Psychiatry, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands*

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Summary
Background: Altered functioning of the hypothalamic—pituitary—adrenal axis (HPA-axis) has been associated with depression, but findings have been inconsistent. Among older depressed persons, both hyperactivity and hypo-activity of the HPA-axis were demonstrated. However, most studies were population-based studies, with single cortisol measurements, lacking insight into diurnal patterns of HPA-axis functioning. We aim to provide insight into functioning of the HPA-axis, assessed by various salivary cortisol samples, in depressed older adults and non-depressed controls.
Methods: Data were derived from the Netherlands Study of Depression in Older Persons. Cortisol levels of older persons without a lifetime diagnosis of depression and/or anxiety ($n = 109$) were compared with older persons with a 6-month major depression diagnosis ($n = 311$). ANCOVA analyses and random coefficient analysis on the four morning cortisol samples were performed. A possible U-shaped association between cortisol and depression status was examined.

* Corresponding author at: Department of Psychiatry, VU University Medical Center Amsterdam, A.J. Ernststraat 1187, 1081 HL Amsterdam, The Netherlands. Tel.: +31 20 7885659; fax: +31 20 7885664.
E-mail address: d.rhebergen@ggzingeest.nl (D. Rhebergen).
[1] These two authors contributed equally to the manuscript.

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Results: Depressed older persons showed higher morning cortisol levels at awakening (T1) and a less dynamic awakening response compared to non-depressed older persons. Dexamethasone suppression did not differ across groups. No U-shaped association between HPA-axis activity and depression was observed.
Conclusion: We demonstrated a hypercortisolemic state and a diminished ability to respond to the stress of awakening among depressed older persons. Previously it was shown, that hypercortisolemic states may indicate a lifelong biological vulnerability for depression. Our findings expand on previous literature by demonstrating that in older persons the HPA-axis may become less responsive to stress, culminating in a further dysregulation of the diurnal cortisol-rhythm, superimposed on — possibly lifelong — hypercortisolemic states.

1. Introduction

Since the 1960s, the hypothalamic—pituitary—adrenal axis (HPA-axis) has been regarded as a central pathophysiological process involved in depression, even though study findings have not always been consistent. Most studies to date have been performed in adults, but there are several studies available that have been conducted among older persons. Heaney et al. (2010) observed a lower cortisol awakening response (CAR) in older depressed persons compared to younger depressed persons, but no differences between older persons with and without depression were found. In contrast, other studies observed hypercortisolemia in depressed older persons compared to non-depressed older persons (Balardin et al., 2011; Kohler et al., 2010; O'Brien et al., 2004) whereas hypocortisolemia in depressed older persons has also been found (Morrison et al., 2000; Oldehinkel et al., 2001). A recent meta-analysis demonstrated that depression in older persons is associated with diurnal elevations in cortisol as compared to non-depressed older persons (Belvederi Murri et al., 2014).

Moreover, debates on possible non-linear associations between cortisol levels and depression are ongoing. Both Bremmer et al. (2007) and Penninx et al. (2007) demonstrated that depression was associated with both higher and lower cortisol levels in older persons, as compared to non-depressed older persons. It was hypothesized that hypercortisolism might be a sign of a dysregulated stress-response, whereas hypocortisolism might be a sign of exhaustion of the HPA-axis that is associated with frailty (Penninx et al., 2007). Thus far, these issues remain to be settled since most studies on HPA-axis functioning in depressed older persons had limited sample sizes or were derived from population-based studies, lacking a formal depression diagnosis. Finally, due to difficulties to obtain repeated measurements in general population studies, many studies obtained only one cortisol measure, e.g. total cortisol level in urine, thereby limiting a comprehensive insight into the diurnal pattern of cortisol (Miller et al., 2007).

The Netherlands Study of Depression in Older Persons (NESDO) provides an opportunity to study HPA-axis functioning in older persons with and without a formally diagnosed clinical depressive disorder, a sufficient sample size, repeated cortisol measurements, and information on putative confounding variables. The aim of the current study is to examine diurnal salivary cortisol levels according to the cortisol awakening response (CAR), evening cortisol level as well as cortisol level after dexamethasone ingestion, in depressed and non-depressed older persons. In addition, the presence of non-linearity is explored, by examining whether both hypo- and hypercortisolemia are associated with depression.

2. Methods

2.1. Study sample

Data were derived from the baseline assessment (April 2007 to September 2010) of the Netherlands Study of Depression in Older Persons (NESDO; http://nesdo.amstad.nl). NESDO was designed to investigate in a prospective design the course of late-life depression and its comorbidities in detail. In short, respondents, aged 60 years or older, were recruited from five regions in the Netherlands. Depressed persons were recruited from both mental health care institutes and general practitioners in order to include persons with current late-life depression in various developmental and severity stages. Non-depressed persons were recruited from general practices and were included when no lifetime diagnosis of depression was present. Exclusion criteria for both groups were a primary clinical diagnosis of dementia, psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe addiction disorder, a Mini Mental State Examination-score (MMSE) below 18 (out of 30 points), and insufficient command of the Dutch language. The final study population consisted of 378 currently depressed and 132 non-depressed persons aged 60—93 years ($n = 510$). Depression included a 6-month diagnosis of major depressive disorder (MDD) (95%) and/or 6-month dysthymic disorder (26.5%), or minor depression (two to four depressive symptoms lasting at least two weeks, 5.0%) according to DSM-IV-R criteria. The ethical review boards of all participating study sites approved the NESDO study protocol and written informed consent was obtained. The method of recruitment was extensively described elsewhere (Comijs et al., 2011).

For the present study, older persons without a lifetime depression diagnosis, or lifetime diagnosis of any anxiety disorder (panic disorder, agoraphobia, social phobia or generalized anxiety disorder) and a total score below 14 on the Inventory of Depressive Symptomatology ($n = 117$) were compared with older persons with a 6-month diagnosis of MDD ($n = 359$). Persons with only dysthymia ($n = 6$) or minor depression ($n = 13$) were excluded. Data cleaning was