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The predictive value of cortisol levels on 2-year course of depression in older persons

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ABSTRACT

Background: Depressive disorders in older persons are associated with an altered functioning of the Hypothalamic–Pituitary–Adrenal (HPA)-axis. In adults, a lower cortisol awakening response is a predictor of a worse prognosis of depression, but to date longitudinal studies in older depressed persons are lacking. We hypothesised that a lower cortisol awakening response is also associated with poorer course of depression in later life.

Methods: Data were derived from the Netherlands Study of Depression in Older Persons (NESDO). Participants with a 6-month Major Depressive Disorder (MDD), who provided 2-year follow-up data, were included ($n = 246$). Logistic regression analyses were conducted to examine the association between diurnal cortisol levels and depressive status at 2-year follow-up.

Results: Both lower (OR = 3.54; 95% CI = 1.59–7.89) and higher evening cortisol levels (OR = 2.41; 95% CI = 1.09–5.35) at baseline were associated with poorer prognosis of MDD. Low dexamethasone suppression was associated with poorer course (OR = 2.37; 95% CI = 1.09–5.16), but failed to reach significance after additional adjustment for severity and chronicity of MDD (OR = 1.98; 95% CI = 0.89–4.42). Cortisol awakening response was not significantly associated with course. Since smoking has a great impact on cortisol levels, we conducted post-hoc analyses including non-smokers only, indicating that lower evening cortisol levels (OR = 2.83, 95% CI = 1.31–6.13) predicted unfavourable course.

Conclusions: This first longitudinal study on cortisol and prognosis of depression in older persons demonstrates that in particular lower evening cortisol levels may predict poorer course in MDD. This finding may have clinical implications. Evening cortisol values may serve as a marker to identify persons at risk for an unfavourable course.

1. Introduction

Late-life major depressive disorder (MDD) is a debilitating disease, with prevalence rates varying between 0.9% to 9.4% among older community-dwelling persons, and up to 42% among persons living in institutions (Djernes, 2006). Furthermore, about ten percent of the persons in this age group are suffering from minor depression (Beekman et al., 1999). The prognosis of late-life depression is poor as compared to depressions among younger adults. It was demonstrated that chronicity or recurrence of depression affects one-third of depressed older adults (Cole, 1999). Comijs et al. (2015) have recently shown an even more unfavourable prognosis in a large cohort of depressed elderly. They demonstrated that almost half (48.4%) of the depressed persons in this cohort were still suffering from depression at 2-year follow-up. Early onset of depression, higher severity, co-morbid dysthymia and/or physical chronic diseases alongside older age were identified as predictors of poorer course (Beekman et al., 2001; Comijs et al., 2015; Licht-Strunk et al., 2007). In addition to clinical predictors, previous research aimed to disentangle the pathophysiological processes involved in depression and their contribution to the course of depression.

Since decades, the central role of the Hypothalamic–Pituitary–Adrenal (HPA)-axis in the pathogenesis of depression was acknowledged (e.g. Gibbons and McHugh, 1962). However, the majority of studies on cortisol and depression in older persons had a cross-sectional design, limiting insight into the association between HPA-axis functioning and course trajectories of depressive disorders. Some studies focused on the association between cortisol and the onset of depression or depressive symptoms later in life (e.g. Nabeta et al., 2014; Chinthapalli,

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2014; Geoffroy et al., 2013), however studies on the predictive value of HPA-axis functioning on the course of current depressive disorders in older persons are lacking. Likewise, the majority of studies on adults examine the impact of HPA-axis functioning on either onset or recurrence of depression (Bockting et al., 2012; Lok et al., 2012; Hardeveld et al., 2015; Dedovic and Ngiam, 2015; Vrshek-Schallhorn et al., 2013). One study examined the association between cortisol and course trajectories of both depression and anxiety disorders in an adult population (aged 18–65 years). It demonstrated that a lower cortisol awakening response was associated with an unfavourable course of illness (Vreeburg et al., 2013). Finally, it has been suggested that an impaired signaling pathway via corticosteroid-activated mineralocorticoid and glucocorticoid receptors would lead to an impaired negative feedback regulation of the HPA system. This could cause high levels of cortisol, which in turn may be associated with unfavorable course of depression (Schüle et al., 2009). Hence, the Dexamethasone Suppression test (DST) was propagated as a putative predictor for course of depressive disorders (e.g. Schweitzer et al., 1987; Charles et al., 1989). However, since then, results from research on its predictive value were inconclusive, and research among older persons is lacking.

Although Bremmer et al. (2007) and Penninx et al. (2007) demonstrated a U-shaped association with both lower cortisol levels and higher cortisol levels being associated with depression in a cross-sectional population based study, a recent meta-analysis (Belvederi Murri et al., 2014) and our own findings (Rhebergen et al., 2015) could not replicate this. Nevertheless, when studying the predictive value of cortisol on the course of depression in older persons, one needs to take a possible U-shape into account, since neglect of this non-linear association may potentially mask underlying associations.

The Netherlands Study of Depression in Older Persons (NESDO) gives us the opportunity to investigate the association between cortisol and longitudinal course of late-life depressive disorders. The aim of this study is to examine the predictive value of cortisol on the 2-year course of depression in older persons, aged 60–93 years. To address the issue of a putative non-linear association, cortisol measures will be divided into tertiles, including lower, average or higher cortisol levels. We hypothesize that lower cortisol levels, a lower awakening response and lower Dexamethasone Suppression ratio may predict an unfavourable course trajectory of depressive disorders in older persons, as compared to average or higher cortisol levels or Dexamethasone Suppression ratio.

2. Methods

2.1. Study sample

Data were obtained from the Netherlands Study of Depression in Older Persons (NESDO; Comijs et al., 2011; http://nesdo.amstad.nl). NESDO is a longitudinal cohort of 378 currently depressed persons and 132 persons without a lifetime depression diagnosis aged 60–93 years ($n = 510$). Respondents were recruited from five different regions in the Netherlands. Both patients from mental health care institutes and patients from general practitioners participated, enabling inclusion of both healthy control persons and persons with different variants and stages of depressive disorders. Exclusion criteria for both the control group and depressed persons were (1) Mini-Mental State Examination (MMSE)-score below 18 or a current clinical dementia diagnosis; (2) some co-morbid psychiatric disorders, including psychotic disorder, obsessive compulsive disorder, bipolar disorder or severe addiction disorder and (3) insufficient mastery of the Dutch language. The study protocol has been approved by the Ethical Boards of the several participating medical centres and written informed consent from the study participants was obtained. A more detailed description of the methods of recruitment has been described by Comijs et al. (2011). In NESDO, baseline and 2-year follow-up measurements were obtained by face-to-face interviews. In addition, at 6-month intervals the course of depression and its predictors is followed up by means of a postal assessment.

In the present study persons were included if they had a 6-month prevalence rate diagnosis of Major Depressive Disorder (MDD) at baseline ($n = 378$), if they provided data during 2-year follow up (75.4% ($n = 285$)), and if they had at least one reliable cortisol measure available at baseline (86.3%) leaving a final study population of $n = 246$. Attrition analyses revealed that persons who were excluded from analyses ($n = 132$) did not differ in sex, depression severity, and smoking status from the included persons, but they had lower levels of education and a higher average age ($p < 0.05$) than the included persons.

2.2. Measurements

2.2.1. Psychopathology

Psychopathology was assessed, both at baseline and at 2-year follow-up, with the Composite International Diagnostic Interview (CIDI) (WHO version 2.1; life-time version). The CIDI is a structured clinical interview that was designed for use in research settings and has a high validity and reliability (Wittchen et al., 1991; Wittchen, 1994). Remitter status was defined as the absence (remitters) or presence (non-remitters) of a 6-month MDD diagnosis at 2-year follow-up.

2.2.2. Salivary cortisol

Respondents were instructed to collect six salivary cortisol samples at home on two consecutive days shortly after the baseline interview, and not to eat, not to drink tea and/or coffee or brush their teeth within 15 min before sampling. In addition, respondents should not have dental work done in the 24 h before sampling. Saliva samples were obtained using Salivettes (Sarstedt, Germany). Five samples were taken at the time of awakening, 30 min after awakening, 45 min after awakening, an hour after awakening and at ten o' clock p.m. (sampling times are named T1–T5 respectively). The sixth sample (T6) was taken the next morning at awakening after dexamethasone ingestion of 0.5 mg the night before (directly after T5). Respondents restored the Salivettes in a tube and labelled the tubes with date and time, and they were asked to return all six saliva samples to the research centre by post. In the research centre, Salivettes were centrifuged at $2000 \times g$ for ten minutes, aliquoted and stored at $-20\,^{\circ}C$. Cortisol analysis was performed by competitive electrochemiluminescence immunoassay (E170 Roche, Switzerland). The functional detection limit was 2.5 nmol/l and the intra- and inter-assay variability coefficients in the measuring range were less than 10%. A random selection of 23 assays were repeated if cortisol levels were high (>60 nmol/L); 19 samples remained high after reassessment, and the mean of the values was used. Three high values became lower after reassessment and were reassessed for a second time. All three remained low, and the mean of the two low values was used (see also Rhebergen et al., 2015).

Cortisol measures were assumed reliable if they fulfilled three criteria. First, the value should not be more than two standard deviations from the mean. Second, the time protocol for sampling should not be exceeded by more than five minutes. Third, corticosteroid use would serve as an exclusion criterion; however none of the persons were using corticosteroids. Several cortisol measures were calculated, including the Area Under the Curve with respect to the ground (AUCg), the Area Under the Curve with respect to the increase (AUCi), evening cortisol and the dexamethasone suppres-