Journal of Psychosomatic Research 95 (2017) 19–25

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

Loneliness in older adults is associated with diminished cortisol output

N. Schutter [a,*], T.J. Holwerda [a], M.L. Stek [b], J.J.M. Dekker [c,d], D. Rhebergen [b], H.C. Comijs [b]

[a] Arkin Mental Health Care, Department of Geriatric Psychiatry, Nieuwe Kerkstraat 156, 1018 VM Amsterdam, The Netherlands
[b] GGZ InGeest, Department of Psychiatry, Amsterdam Public Health Research Institute, VU University Medical Center Amsterdam, The Netherlands
[c] Department of Psychology, VU University Amsterdam, Amsterdam, The Netherlands
[d] Department of Clinical Research, Arkin Mental Health Care, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 18 July 2016
Received in revised form 30 January 2017
Accepted 2 February 2017
Available online xxxx

Keywords:
Loneliness
Depression
Cortisol
Older adults

ABSTRACT

Objective: Loneliness in older adults has been associated with increased mortality and health problems. One of the assumed underlying mechanisms is dysregulation of the hypothalamic-pituitary-adrenocortical axis (HPA–axis). The purpose of this study was to investigate whether loneliness in older adults is associated with HPA-axis dysregulation and whether this association differs between depressed and non-depressed persons.
Methods: Cross-sectional data of 426 lonely and non-lonely older adults in the Netherlands Study of Depression in Older Persons (NESDO) were used. Linear regression analyses and multinominal logistic regression analyses were performed to examine the association between loneliness and morning cortisol, cortisol awakening response, diurnal slope and dexamethasone suppression ratio. In all analyses, confounders were introduced. In order to examine whether the association between loneliness and cortisol measures is different in depressed versus non-depressed persons, an interaction term for loneliness x depression diagnosis was tested.
Results: Cortisol output in the first hour after awakening and dexamethasone suppression ratio was lower in lonely participants. There were no significant interactions between loneliness and depression diagnosis in the association with the cortisol measures.
Conclusion: This study is the first to investigate the association between the HPA–axis and loneliness in a large group of older adults aged 60–93 years. We found lower cortisol output in the first hour after awakening and lower dexamethasone suppression ratio in lonely older depressed and non–depressed adults. Whether diminished cortisol output is the underlying mechanism that leads to health problems in lonely older adults is an interesting object for further study.

1. Introduction

Loneliness is one of the main indicators of social well-being in all age categories [1]. It is described as a situation that occurs from a lack of quality relationships and is considered to be an expression of negative feelings of missing relationships in contrast with the actual absence of relationships [1]. Loneliness in older adults has been associated with increased mortality and a wide range of health problems such as less sleep, depression, decreased cognitive functioning over time and age-related increases in systolic blood pressure [2–7]. Previous studies have investigated the mechanisms through which loneliness affects health. One of the assumed underlying mechanisms is dysregulation of the hypothalamic-pituitary-adrenocortical axis (HPA-axis) [3,8–10].

The HPA-axis is a hormonal response system that can be activated by a broad array of mental and physical stressors [11,12]. Cortisol output usually shows a diurnal rhythm, with the highest levels in the early morning and lowest levels in the evening [13]. Cortisol levels are high upon waking, show a substantial increase in the 30–45 min after waking (called the cortisol awakening response or CAR) and decline over the remainder of the day (diurnal slope) [14,15]. These different features of cortisol levels can be influenced by a variety of sociodemographic variables and health indicators, such as sex, age, smoking and cardiovascular disease [14,16]. Additionally, chronic or severe stress may lead to dysregulation of the HPA-axis [13]. For instance, Heim et al. described several studies that have found that chronic stress, such as found in Post Traumatic Stress Disorder (PTSD), may lead to decreased urinary cortisol secretion and to low cortisol levels in plasma or saliva samples [17]. Yehuda [18] in her overview of HPA-axis alterations in PTSD concluded that PTSD patients show evidence of a highly sensitized HPA-axis with decreased basal cortisol levels and increased negative feedback. Seedat et al. found that 'intimate partner violence' encompassing physical and sexual abuse frequently in the context of emotional abuse, leads to decreased mean plasma cortisol levels [19].

Loneliness is considered a chronic source of stress [20]. Various researchers have studied the effects of loneliness on the HPA- axis, mostly in middle-aged adults. They found that loneliness is associated with a higher cortisol awakening response (CAR) [8,10]. In adolescents and

* Corresponding author.
E-mail address: natasja.schutter@mentrum.nl (N. Schutter).

http://dx.doi.org/10.1016/j.jpsychores.2017.02.002
0022-3999/

young adults, loneliness has been found to be associated with flattening of the diurnal cortisol rhythm, but not with changes in CAR [21,22]. However, Doane and Adam did find that prior day increases in loneliness predicted a greater cortisol awakening response the following morning. Elevated mean salivary cortisol levels across the course of a day were found in undergraduate students who were chronically lonely [23]. These outcomes in middle-aged (higher cortisol awakening response) and younger adults (flatter cortisol rhythm) suggest that there is a possible age-related difference in the effects of chronic loneliness on HPA-axis activity. Thus far, the effect of loneliness on the HPA-axis in older adults has not yet been extensively investigated. The only study that included older adults is the one by Adam et al. [8], who included older adults up to 68 years old.

Next, loneliness has been found to be a significant risk factor for depressive symptoms in a group of adults aged 54 years and older [4]. Loneliness and depression have strong reciprocal influences in middle-aged and older adults [4]. In depression, a fairly consistent biological finding is an altered activity of the HPA-axis, such as higher basal cortisol levels in the morning and high post-dexamethasone levels [24]. The dexamethasone suppression test examines the function of the negative feedback loop: dexamethasone, a synthetic glucocorticoid, decreases cortisol levels by acting on the pituitary [25]. With adequate feedback, cortisol levels are suppressed after dexamethasone intake. In depression, this negative feedback decreases, leading to higher post-dexamethasone cortisol levels (non-suppression). Depression in older adults is also associated with changes in cortisol output. Rhebergen et al. [26] found higher morning cortisol levels and lower AUCi (area under the curve with respect to the increase) in depressed older patients. Lower AUCi signifies a decreased ability to respond dynamically to the stress of awakening, thus indicating a less dynamic cortisol awakening response [26]. Belvederi Murri et al. [24] found a high degree of dysregulation of HPA-axis activity, with higher basal cortisol levels in older depressed patients compared to younger ones during all phases of the diurnal cycle and high post-dexamethasone cortisol levels in plasma. These findings possibly indicate a specific pattern of dysregulation of HPA-axis activity in geriatric depression.

Since loneliness and depression are strongly associated, and depression is associated with HPA-axis dysregulation, the effect of depression has to be taken into account when studying the association between loneliness and the HPA-axis. The aim of our study is to investigate whether loneliness in older adults is associated with dysregulation of the HPA-axis. Based on previous research in middle-aged and older adults [8,10,24,26], we hypothesize that loneliness is associated with higher cortisol awakening response and that the effects of loneliness on HPA-axis functioning are more pronounced in depressed participants.

2. Methods

2.1. Study sample

Study participants were derived from the Netherlands Study of Depression in Older Persons (NESDO), a large cohort ($N = 510$) study designed to investigate in a prospective design the course of late-life depression and comorbidities. Detailed information on the NESDO design, recruitment and methods is described elsewhere [27]. In short, respondents were recruited from general practitioners and mental health institutions. Non-depressed participants were recruited from general practices and were included when there was no lifetime diagnosis of depression. General exclusion criteria were: a primary clinical diagnosis of dementia or other severe psychiatric disorder, a Mini-Mental State Examination-score (MMSE) [28] below 18 (out of a maximum of 30 points) indicating severe cognitive impairment, and not being fluent in the Dutch language. The final study population consisted of 378 depressed and 132 non-depressed persons aged 60 through 93 years ($n = 510$). A diagnosis of depression included a 6-month diagnosis of a Major Depressive Disorder (MDD) (95% of depressed persons) and/or a 6-month dysthymic disorder (26.5% of depressed persons), or a minor depression (5% of depressed persons) according to DSM-IV-TR criteria [29]. The ethical review boards of participating study sites approved of the research protocol and all respondents provided written informed consent.

For the present study, an exclusion criterion would be the use of corticosteroid medication, as corticosteroid use would influence cortisol levels. However, none of the participants used corticosteroids. Persons with at least one cortisol measure were included. Since 84 persons had missing values on all the cortisol measures, the final study population consisted of 426 participants [26].

2.2. Measurements

2.2.1. Psychopathology

Psychopathology was assessed with the Composite International Diagnostic Interview (CIDI; WHO version 2.1; life-time version). The CIDI is a structured clinical interview that is designed for assessing mental disorders according to the definitions of ICD-10 and DSM-II-R, to be used in research settings, and has a high validity and reliability [30–32]. Due to its high degree of standardization of symptom questions, it improves consistency of symptom assessment and reliability of diagnostic decision and can be administered reliably by non-clinicians after a relatively brief training [32].

2.2.2. Cortisol

Cortisol levels were obtained through saliva sampling. Respondents were instructed to collect saliva samples at home on two consecutive days shortly after the interview at baseline. For each sample, participants were instructed to refrain from eating, drinking or brushing teeth within 15 min before sampling. No dental work up to 24 h prior to sampling was allowed [26]. Six saliva samples were taken: at the time of awakening (T1), 30 minute post-awakening (T2), 45 min post-awakening (T3), 60 minute post-awakening (T4) and at 22:00 h (T5). Furthermore, dexamethasone suppression was measured by sampling the next morning at awakening (T6) after dexamethasone ingestion of 0.5 mg the night before (directly after T5). The Dexamethasone Suppression Test (DST) is a measure of HPA-axis regulation and normally shows a decrease of morning cortisol concentrations due to inhibition of adrenocorticotropic hormone (ACTH) secretion after ingestion of dexamethasone the night before [25,33]. The salivettes were stored in the refrigerator in a tube labeled with date and time. After collecting all six samples, the participants were asked to return the samples by regular mail to the research center. After receipt, salivettes were centrifuged at 2000*g* for 10 min, aliquoted and stored at −80 °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 <10% [26].

2.2.2.1. Cortisol awakening response (CAR). From the four saliva samples taken within 1 h after awakening (T1 through T4), the areas under the curve with respect to the increase (AUCi) and with respect to the ground (AUCg) were calculated using Pruessner's formulas [34]. The AUCg is an estimate of the total cortisol secretion over the first hour after awakening, whereas the AUCi represents the dynamics of the cortisol awakening response (CAR), more related to the sensitivity of the system, emphasizing changes over time after awakening (see also [26]). AUCi and AUCg could be calculated for all persons from whom all four morning cortisol samples were available (AUCg: $n = 369$; AUCi: $n = 371$). For area under the curve (AUC) analyses, at least three samples had to be available [15,26,35]. For those with one missing cortisol value ($n = 53$), the missing value was imputed using linear regression analyses including information on the three available cortisol levels, sex, age, awakening time and smoking status (see also [26]).