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The relationship between loneliness and cognition in healthy older men and women: The role of cortisol

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ABSTRACT

Loneliness has been associated with an increased risk of cognitive decline and dementia in older people, as well as a dysregulation of Hypothalamic–Pituitary–Adrenal (HPA) axis functioning. In addition, it has been suggested that women are more vulnerable to the negative effects of loneliness on health. Our aim was to analyze the effect of HPA-axis functioning as a mediator in the relationship between loneliness and cognitive function, and interactions depending on sex, in healthy older people. To do so, 86 healthy older people (52.3% female) from 60 to 80 years old (M = 67.44, SD = 4.37) completed the revised UCLA loneliness scale. A neuropsychological battery was administered to assess global cognition, processing speed, attention and executive function, working memory, and verbal memory immediate and delayed recall. Saliva samples were provided on two consecutive weekdays to obtain awakening and bedtime cortisol levels, the diurnal cortisol slope (DCS), and the area under the curve with respect to the ground (AUCg). Our results showed that loneliness was not directly associated with cognitive performance. Furthermore, loneliness was related to higher bedtime cortisol levels, but not to awakening cortisol, the DCS, or the AUCg. In addition, loneliness was associated with worse performance on attention and processing speed, executive function, and verbal memory immediate recall, via bedtime cortisol levels. Therefore, we suggest that HPA-axis functioning is one of the biological mechanisms that mediate the relationship between loneliness and poorer cognitive function. No sex differences were observed in these associations.

1. Introduction

The world population is aging, and projections indicate that the number of people over 60 years old will reach two billion in 2050 (UNFPA, 2012). Although dementia it is not a normal part of healthy ageing, it affects around 50 million people worldwide, and it has been recognized as a public health priority (WHO, 2019). Therefore, it is important to identify the factors that may contribute to these health problems in older people, and loneliness has been proposed as one of them (WHO, 2013).

Loneliness is defined as a subjective feeling of dissatisfaction with social relationships (Young, 1982). It is particularly important in older adults because one-third of them will experience it to some degree (Victor et al., 2005), especially women, who are at greater risk (see review: Pinquart and Sorensen, 2001). In fact, loneliness has been considered a major risk factor for physical and mental health problems in later life (see review: Ong et al., 2015), including reduced longevity (Holt-Lunstad et al., 2015).

1.1. Loneliness and cognitive function

Among the health problems associated with loneliness, an increased risk of cognitive decline and dementia can be highlighted (see reviews: Cacioppo and Hawkley, 2009; Cacioppo et al., 2014). In addition, in a review, Boss et al. (2015) concluded that in older people, greater loneliness was associated with lower cognitive functioning. However, studies included in this review reported mixed findings about the association between loneliness and global cognition (Gow et al., 2013; O'Luanaigh et al., 2012; Schnittger et al., 2012), processing speed (Gilmour, 2011; Gow et al., 2013; O'Luanaigh et al., 2012), executive function (Gilmour, 2011; Schnittger et al., 2012), and immediate and delayed memory (Gilmour, 2011; O'Luanaigh et al., 2012; Schnittger et al., 2012; Shankar et al., 2013; Wilson et al., 2007). Furthermore, these associations were weak, and some of them disappeared after controlling for psycho-sociodemographic variables (Boss et al., 2015).

These mixed findings may be due, at least in part, to the cognitive status of the participants. The absence of dementia was an inclusion

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criterion in some studies (Gilmour, 2011; Holwerda et al., 2012; O'Luanaigh et al., 2012; Schnittger et al., 2012; Wilson et al., 2007), but it was not specified in others (Donovan et al., 2016; Gow et al., 2007, 2013; Tilvis et al., 2004; Shankar et al., 2013). Additionally, most of the studies measured loneliness with one or two items asking participants directly if they felt lonely (Donovan et al., 2016; Gow et al., 2007, 2013; Holwerda et al., 2012; O'Luanaigh et al., 2012; Tilvis et al., 2004), which could lead to underreporting due to the social stigma associated with being identified as lonely (Pinquart and Sorensen, 2001). Gilmour (2011) measured loneliness with three items, whereas other authors used five (Wilson et al., 2007) or six items (Schnittger et al., 2012) from the de Jong-Gierveld Loneliness Scale. Shankar et al. (2013) used the three-item short form of the revised UCLA Loneliness Scale (R-UCLA), but none of the studies administered the 20-item R-UCLA scale. Moreover, most of the studies did not explore the role of sex in the association between loneliness and cognitive function, and therefore it is an unresolved issue that should be addressed.

1.2. Loneliness and hypothalamic–pituitary–adrenal axis

Some authors have suggested that loneliness is a psychological experience that contributes to biological stress (Steptoe et al., 2004), and several studies have explored its association with the Hypothalamic–Pituitary–Adrenal (HPA) axis. The HPA-axis is a neuroendocrine system that plays a key role in the stress response, and its end product is cortisol. In addition, cortisol follows a diurnal rhythm, reaching its highest levels early in the morning, with a decrease throughout the day, and the lowest levels in the evening. However, a dysregulation of the HPA-axis has been reported during chronic stress, showing a higher diurnal cortisol output and a flattened diurnal slope with lower morning and higher evening cortisol levels (Miller et al., 2007).

Several studies have explored the association between loneliness and both the diurnal cortisol output and the diurnal cortisol slope (DCS), with inconsistent findings. These relationships have been studied in young (Cacioppo et al., 2000; Doane and Adam, 2010; Drake et al., 2016; Lai et al., 2018; Pressman et al., 2005), middle-aged (Ebrecht et al., 2004; Grant et al., 2009; Steptoe et al., 2004), or older participants (Adam et al., 2006; Cole et al., 2007; Schutter et al., 2017). In this latter age group, two studies did not observe an association between loneliness and awakening cortisol levels or the DCS (Adam et al., 2006; Schutter et al., 2017), whereas another study found that lonelier individuals showed a blunted cortisol rhythm (Cole et al., 2007). None of these three studies analyzed the association between loneliness and the diurnal cortisol output or took sex differences into account. Therefore, more research is needed to clarify these issues.

1.3. Hypothalamic–pituitary–adrenal axis and cognitive function

In addition to stress and loneliness, a flatter DCS and higher diurnal cortisol levels, which reflect HPA-axis dysregulation, have been associated with physical and mental health problems, including poorer cognition (Adam et al., 2017; Lupien et al., 2005). The hippocampus and prefrontal cortex are brain areas with a high density of glucocorticoid receptors, and they play a role in memory and attention and executive function, respectively. Thus, HPA-axis dysregulation is one of the mediators proposed to explain impaired cognitive function in older people (see review: Lupien et al., 2007).

Flatter DCS has been associated with poorer cognition in older adults with memory deficits and depressive symptoms (Fiocco et al., 2006). Previous studies analyzing the association between the DCS and cognitive function in non-demented older people reported that worse cognitive performance or cognitive decline was related to both a steeper (O'Hara et al., 2007) and flatter DCS in cross-sectional (Stawski et al., 2011; Gerritsen et al., 2011) and follow-up (Beluche et al., 2010) studies. However, the absence of associations has also been reported (Ennis et al., 2016; Hidalgo et al., 2016; Singh-Manoux et al., 2014).

Analyzing the two components (i.e. awakening vs evening) of the DCS independently, mixed findings have also been found for the association between cortisol and cognition. Higher awakening cortisol levels have been associated with better (Ennis et al., 2016; Singh-Manoux et al., 2014) and worse cognitive performance in both cross-sectional (Beluche et al., 2010; O'Hara et al., 2007) and follow-up studies (Beluche et al., 2010). On the other hand, the relationship between higher evening cortisol levels and worse cognitive performance has been reported in cross-sectional studies (Gerritsen et al., 2011; Stawski et al., 2011), in follow-up studies (Li et al., 2006), and only in women (Singh-Manoux et al., 2014), with these results being more consistent.

Moreover, some studies in older people observed that higher diurnal cortisol levels were related to poorer cognitive performance, specifically on verbal memory and executive function (Li et al., 2006; Ouanes et al., 2017), but other studies in middle-aged and older people did not find these results (Ennis et al., 2016; Harris et al., 2017; Singh-Manoux et al., 2014). Therefore, the association between different cortisol indexes and cognitive performance during aging is complex and poorly understood.

1.4. Biological pathways mediating the association between loneliness and cognitive function

HPA-axis dysregulation is one of the mechanisms proposed as biological pathways underlying the association between loneliness and cognitive function (see reviews: Boss et al., 2015; Ong et al., 2015; Cacioppo and Hawkley, 2009; Cacioppo et al., 2014). However, to our knowledge, the mediating role of the HPA-axis in the relationship between loneliness and cognitive function has not been explored.

Our main goal was to analyze the role of the HPA-axis as a mediator in the relationship between loneliness and cognitive function in non-demented healthy older people. To do so, first, we explored the association between loneliness and both (i) HPA-axis functioning indexes and (ii) different cognitive domains, as well as (iii) the association between HPA-axis functioning and the different cognitive domains. Finally, we explored sex differences in these relationships, given that sex differences in loneliness are unclear, and that sex may play a role in both loneliness and health (see review: Brown et al., 2017).

Due to the inconsistent results from previous studies on the relationship between loneliness and the DCS (Adam et al., 2006; Cole et al., 2007; Schutter et al., 2017) and the lack of studies on the relationship between loneliness and the diurnal area under the curve with respect to the ground (AUCg) in older people, we were not able to define the direction of these relationships. We hypothesized a weak but significant negative association between loneliness and performance on different cognitive domains (see review: Boss et al., 2015). We also expected a negative association between cognitive function and awakening cortisol (Beluche et al., 2010; O'Hara et al., 2007), bedtime cortisol (Li et al., 2006; Stawski et al., 2011), the DCS (Beluche et al., 2010; Stawski et al., 2011), and the diurnal cortisol output (Li et al., 2006; Ouanes et al., 2017). In addition, we hypothesized that this dysregulated HPA-axis pattern would mediate the relationship between loneliness and poorer cognitive performance. Finally, we hypothesized that these associations would be more pronounced in women than in men because some authors have suggested that loneliness affects women's health more than men's (Christiansen et al., 2016).

2. Material and methods

2.1. Participants

The final sample was composed of 86 participants of both sexes (41 men and 45 women), ranging from 60 to 80 years old ($M = 67.44$, $SD = 4.37$). Participants' characteristics are presented in Table 1. There were no significant differences between men and women in age, loneliness, or depression (all $p \geq 0.184$), but there were differences in

Table 1
Characteristics of the study population for the total sample, and for men and women.

	Total (N = 86)	Men (N = 41)	Women (N = 45)	
Sex, (%)		47.7	52.3	
				p
Age, *M (SD)*	67.44 (4.37)	67.29 (3.97)	67.58 (4.74)	.764
Educational level, (%)				.001
Without studies	1.2	0	2.3	
Primary school	20.7	2.6	37.2	
Secondary school	18.3	15.4	20.9	
Graduate (3 years degree)	24.4	30.8	18.6	
Graduate (5 years degree)	32.9	46.2	20.9	
PhD	2.4	5.1	0	
Marital status N (%)				.025
Single	11.9	2.5	20.5	
Married	66.7	80.0	54.5	
Divorced	9.5	5.0	13.6	
Widower	11.9	12.5	11.4	
Depression, *M (SD)*	5.30 (4.22)	5.00 (3.58)	5.58 (4.75)	.529
Loneliness, *M (SD)*	34.05 (6.98)	35.10 (6.53)	33.09 (7.30)	.184

Note. *M* = mean; *SD* = standard deviation; % = percentages. Sex differences in age, depression, and loneliness were analyzed with Student-t tests, and in educational level and marital status with Chi-square tests.

educational level ($p = .001$) and marital status ($p = .025$). All the women were postmenopausal and had their last menstrual period more than 3 years before the testing time. None of the participants scored less than 27 on the Mini-Mental State Examination (MMSE), indicating the absence of cognitive impairment.

Participants were Caucasians, and they were recruited from classrooms in a study program at the University of Valencia (Spain) for people over 55 years of age. As compensation, they received a pen drive for participating in the study. Exclusion criteria were: age below 60 years old, smoking more than 10 cigarettes a day, alcohol or other drug abuse, non-corrected visual or hearing problems, diabetes, neurological or psychiatric disease, using any medication directly related to emotional or cognitive functioning or able to influence hormonal levels such as glucocorticoids, psychotropic substances, or sleep medications, having been under general anesthesia once or more than once in the past year, and the presence of a stressful life event during the past year, such as the death of a loved one, an accident, an important change in their habits, such as retirement, or any other event that they subjectively felt had affected them in a significant way. Of the 150 participants assessed, 42 were eliminated because they did not meet the inclusion criteria. Of the 108 participants who met the inclusion criteria, 22 participants were eliminated because they did not perform the neuropsychological evaluation (16 participants) and/or provide the saliva samples (7 participants). Therefore, the final sample was composed of 86 participants who met the inclusion criteria and completed the whole study.

2.2. Procedure

Participants who met the criteria were asked to attend one session that took place from 10:00 to 12:00 h in the Laboratory of Social Cognitive Neuroscience at the University of Valencia. Before the session, participants were asked to maintain their general habits, sleep as long as usual, refrain from heavy physical activity the day before the session, and not consume alcohol from the night before the first session. They were also instructed to drink only water, and not eat, smoke, take any stimulants (such as coffee, cola, caffeine, tea or chocolate), or brush their teeth at least 1 h prior to the session. All the participants provided written informed consent to participate in the study, which was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Research Ethics Committee of the University of Valencia. In this session, a neuropsychological battery was administered. Additionally, participants were asked to provide saliva samples at home on two consecutive weekdays in order to determine cortisol levels immediately after waking (awakening cortisol) and before going to sleep (bedtime cortisol). The participants were thoroughly instructed about how to provide the saliva samples, and they were given written instructions to drink only water and not eat or brush their teeth at least 1 h prior to each saliva sample. In addition, participants were asked to write down the time they provided the saliva samples at awakening and bedtime in a diary. A week later, participants returned to the laboratory to deliver the saliva samples and complete the questionnaires to obtain loneliness and depression scores.

2.3. Psychological tests

2.3.1. Loneliness

Loneliness was assessed with the Spanish adaptation (Vázquez and Jiménez, 1994) of the revised UCLA loneliness scale (R-UCLA) (Russell et al., 1980). This scale contains 20 items rated on a four-point Likert scale ranging from one (never) to four (often), producing a total score ranging from 20 (low) to 80 (high). The internal consistency (Cronbach's α) of the Spanish adaptation was .94, and in this sample, it was .82.

2.3.2. Depression

Depression was assessed with the Spanish version (Fernández-San Martín et al., 2002) of the Geriatric Depression Scale (GDS) (Yesavage et al., 1982) for detecting depression in older people. It consists of 30 items formulated as questions, with a dichotomous yes/no response. The lowest possible score is 0, and the highest is 30. The internal consistency (Cronbach's α) of the Spanish adaptation was .82, and in this sample, it was .81.

2.4. Neuropsychological tests

2.4.1. Global cognition

To measure global cognition, the Spanish version of the Mini-Mental State Examination (MMSE) (Lobo et al., 1999) was used. It includes eleven questions that measure cognitive functions, with higher values indicating better global cognitive function. The maximum score is 30, and a score of 23 or less is indicative of cognitive impairment.

2.4.2. Processing speed, attention, and executive function

These cognitive functions were measured with the Trail-Making Test (TMT). This test consists of two trials, TMT-A and TMT-B, each composed of 25 circles distributed on a white sheet of paper (Reitan, 1992). On TMT-A, the circles were numbered from 1 to 25, and the participant was asked to trace a line connecting the circles in numerical sequence as quickly as possible. The TMT-B included numbers from 1 to 13 and letters from A to L, and the participant was instructed to alternate between numbers and letters in ascending order. The score obtained was the number of seconds required to finish each trial. Errors were pointed out instantly by the examiner and contributed to the score due to the additional time needed for corrections. Two outcomes were obtained: (i) TMT-A: total number of seconds required to finish the TMT-A, which assesses attention and psychomotor processing speed, and (ii) TMT-B: total number of seconds required to finish the TMT-B, which evaluates attention-switching and executive function performance.

2.4.3. Working memory (WM)

To measure the participants' working memory performance, the Spanish version of the Letter-number sequencing (LNS) test from the Wechsler Memory Scale III was administrated (Wechsler, 1997). The experimenter read aloud series of mixed numbers (from 0 to 9) and letters (from A to Z) of increasing lengths (from 2 to 8 items). The

participant had to repeat the series, ordering the numbers in ascending order and the letters in alphabetical order. Each set length was tested three times. The test ended when the participant failed three consecutive trials of the same length. One point was given for each correctly recalled attempt. One outcome was obtained: LNS (total number of correctly recalled attempts).

2.4.4. Verbal memory

To measure verbal memory performance, the story recall subtest from the Spanish version of the Rivermead Behavioral Memory Test (Wilson et al., 1985) was used. The experimenter read two short stories aloud, and participants had to recall as many memory units or "ideas" as possible, immediately after their oral presentation and after a 20-min delay. Participants' answers were audio recorded and corrected by an expert, and the sum of the correctly recalled "ideas" from the two stories was calculated. From this test, two outcomes were used for subsequent analysis: (i) Rivermead Immediate recall: total "ideas" recalled from the two stories immediately after the oral presentation and (ii) Rivermead Delayed recall: total "ideas" recalled from the two stories after 20 min, compared to the number of "ideas" recalled from the two stories immediately after the oral presentation (Delayed recall/Immediate recall x100).

2.5. Salivary cortisol

Participants provided saliva samples by using salivettes (Sarstedt, Nümbrecht, Germany). They were instructed to keep the cotton swab in their mouths for exactly 2 min, not chew the cotton, move the swab around in a circular pattern to collect saliva from all the salivary glands, and then store the saliva samples in the refrigerator until they were delivered to the laboratory. Once in the laboratory, the samples were kept in the refrigerator until they were centrifuged at 3000 rpm for 5 min, resulting in a clear supernatant of low viscosity that was stored at −80 °C until the analyses of the salivary cortisol levels. HPA-axis activity was measured by analyzing the salivary cortisol levels. Salivary cortisol concentrations were determined in duplicate with the salivary cortisol ELISA kit from Salimetrics (Newmarket, UK). Assay sensitivity was < .007 ug/dL. For each subject, all the samples were analyzed in the same trial. The inter- and intra- assay variation coefficients of raw optical densities were 1.365% and 1.48%, respectively. Cortisol levels were expressed in nmol/L.

2.6. Statistical analysis

Participants' characteristics were described using percentages or means (standard deviation, *SD*), when appropriate, for the total sample and for men and women independently. To investigate sex differences in age, depression, and loneliness, independent sample Student-t tests were performed, whereas sex differences in educational level and marital status were analyzed with Chi-square tests.

Although the HPA- axis functioning is expected to be stable, in order to obtain better reliability, saliva was collected on two consecutive days to ensure that the cortisol data truly reflected the baseline functioning of the HPA-axis. This was verified with the correlation analyses, which allowed us to work with the average cortisol levels for both days (for awakening cortisol: $r = .517$, $p < .001$ and for bedtime cortisol: $r = .483$, $p < .001$). Thus, we obtained four indexes: (i) awakening cortisol: mean cortisol immediately after waking on the two days ($M = 6.576$, $SD = 3.158$), (ii) bedtime cortisol: mean cortisol before going to sleep on the two days ($M = 1.782$, $SD = 1.649$), (iii) the diurnal cortisol slope (DCS): bedtime cortisol minus awakening cortisol/time interval between awakening and bedtime, and (iv) the AUCg to measure the diurnal cortisol output (Pruessner et al., 2003). The mean awakening time was 7:15 am and the mean bedtime was 12:05 pm. If awakening or bedtime cortisol values were only obtained for one of the two days (n = 6 and n = 10, respectively), data from only one day were included in the analysis, rather than the average. Bedtime cortisol levels were not obtained from three participants on either of the two days. Thus, awakening and bedtime cortisol levels were obtained from 86 and 83 participants, respectively. Missing values were treated by ignoring these data when performing the statistical analyses.

Before performing the statistical analyses, participants who scored ± 3 *SD* from the mean were identified, and z scores were winsorized. Moreover, standardized residuals were used to detect multivariate outliers (± 3 *SD*). Specifically, we detected, and excluded from the respective analysis, one outlier for each of the following associations: (i) loneliness and bedtime cortisol, (ii) loneliness and AUCg, (iii) loneliness and TMT-A, (iv) awakening cortisol and TMT-A, (v) awakening cortisol and TMT-B, (vi) DCS and MMSE, (vii) DCS and TMT-A, (viii) DCS and TMT-B, (ix) AUCg and MMSE, and, finally, (x) AUCg and TMT-B.

Linear regression analyses were performed to study the association between (i) loneliness and cortisol indexes, (ii) loneliness and cognitive function outcomes, and (iii) cortisol indexes and cognitive function outcomes. All these analyses were performed unadjusted and adjusted for covariates. Adjusted analyses controlling for age, sex, marital status, educational level, and depression were performed because most of the studies on loneliness and cognitive function have included these covariates (see review: Boss et al., 2015). In addition, we tested whether sex moderated these relationships.

First, to investigate whether there was an association between loneliness and the cortisol indexes, separate analyses were performed for each cortisol index (awakening cortisol, bedtime cortisol, DCS, and AUCg) as dependent variable. For unadjusted analyses, we included loneliness in step one. For adjusted analyses, we conducted hierarchical analyses, including the covariates in step one and loneliness in step two. Then, in order to analyze whether there was a moderating effect of sex on the association between loneliness and cortisol indexes, we repeated these analyses, including the covariates, loneliness, and sex in step one, and the interaction between loneliness and sex (loneliness*sex) in step two.

Second, to investigate the associations between loneliness and the different cognitive outcomes, separate linear regression analyses were performed for each cognitive domain outcome (MMSE, TMT-A, TMT-B, LNS, Rivermead Immediate recall, and Rivermead Delayed recall) as dependent variable. For the unadjusted analyses, we included loneliness in step one. For adjusted analyses, we conducted hierarchical analyses including the covariates in step one, and loneliness in step two. Then, in order to analyze whether there was a moderating effect of sex on the association between loneliness and each cognitive domain, we repeated these analyses, including the covariates, loneliness, and sex in step one, and the interaction between loneliness and sex (loneliness*sex) in step two.

Third, to investigate the associations between cortisol indexes and the different cognitive domains, separate analyses were performed for each cognitive domain outcome as dependent variable. For unadjusted analyses, we included one cortisol index (awakening cortisol, bedtime cortisol, DCS and AUCg) in step one. For adjusted analyses, we conducted hierarchical analyses, including the covariates in step one, and one cortisol index in step 2. To analyze whether sex moderated the association between the cortisol indexes and each cognitive domain, we repeated these analyses, including the covariates, one cortisol index, and sex in step one, and in step 2, the interaction between one cortisol index and sex (i.e. awakening cortisol*sex, bedtime cortisol*sex, DCS*sex or AUCg *sex) in step two.

Finally, when we observed a significant association between loneliness and a particular cortisol index (awakening cortisol, bedtime cortisol, DCS or AUCg) in the adjusted analyses, along with a significant association between this same cortisol index and a cognitive domain (MMES, TMT-A, TMT-B, LNS, Rivermead Immediate recall, or Rivermead Delayed recall), we analyze whether this cortisol index mediated the relationship between loneliness and a specific cognitive

domain. For this purpose, we conducted regression models using PROCESS (v2.13.6), with the cognitive measure as the dependent variable, loneliness as the independent variable, and the cortisol index as the mediator variable, adjusted for covariates.

To perform these statistical analyses, version 25.0 of SPSS was used. All p values were two-tailed, and the level of significance was taken as $p < 0.05$.

3. Results

First, Pearson correlation analyses of the cortisol indexes were performed. Thus, the DSC was negatively related to awakening cortisol ($r = -.853$, $p \leq .001$) and positively related to bedtime cortisol ($r = .366$, $p = p \leq .001$). The AUCg was positively related to awakening ($r = .871$, $p \leq .001$) and bedtime cortisol ($r = .572$, $p \leq .001$), and negatively to the DCS ($r = -.496$, $p \leq .001$). No association was observed between awakening and bedtime cortisol ($r = .118$, $p = .287$).

3.1. Relationship between loneliness and cortisol indexes

When analyzing the relationship between loneliness and the cortisol indexes, results showed a significant positive association between loneliness and bedtime cortisol ($B = .365$, $p = .001$ and $B = .366$, $p = .001$), for unadjusted and adjusted analyses, respectively). No significant associations were observed between loneliness and awakening cortisol, DCS, or AUCg in unadjusted or adjusted analyses (all $p \geq .215$). In addition, there were no significant interactions between loneliness and sex for any of the cortisol indexes in either unadjusted or adjusted analyses (all $p \geq .172$) (Table 2).

3.2. Relationship between loneliness and cognitive function

Results showed that loneliness scores were significantly and positively associated with time performing the TMT-B and, therefore, with worse performance on executive function in the unadjusted analyses ($B = .223$, $p = .039$), but this association was marginal in the adjusted analyses ($B = .196$, $p = .064$). Likewise, loneliness scores were marginally and positively associated with time performing the TMT-A and, therefore, with worse performance on processing speed and attention in unadjusted ($B = .208$, $p = .056$) and adjusted analyses ($B = .179$, $p = .088$). None of the other associations between loneliness and cognitive outcomes were statistically significant (all $p \geq .191$). In addition, there were no significant interactions between loneliness and sex in any of the cognitive domains (all $p \geq .314$) (Table 3).

Table 2
Regression analyses with loneliness or loneliness*sex as predictors, and the cortisol indexes (awakening cortisol, bedtime cortisol, DCS or AUCg cortisol) as dependent variables, unadjusted and adjusted for covariates.

	Unadjusted analyses		Adjusted analyses	
	Loneliness			
	R^2 change	Beta	R^2 change	Beta
Awakening cortisol	.002	−.050	.001	−.034
Bedtime cortisol	.133	.365 **	.129	.366**
DCS	.010	.101	.009	.092
AUCg cortisol	.013	.114	.022	.149
	Loneliness*sex			
Awakening cortisol	.000	−.011	.000	.018
Bedtime cortisol	.016	−.169	.022	−.212
DCS	.002	.058	.001	.052
AUCg cortisol	.017	−.174	.014	−.177

Note. DCS: diurnal cortisol slope. AUCg: area under the curve with respect to the ground; *$p < .05$. **$p < .01$.

Table 3
Regression analyses with loneliness or loneliness*sex as predictors, and cognitive outcomes (MMSE, TMT-A, TMT-B, LNS, Rivermead immediate recall or Rivermead delayed recall) as dependent variables, unadjusted and adjusted for covariates.

	Unadjusted analyses		Adjusted analyses	
	Loneliness			
	R^2 change	Beta	R^2 change	Beta
MMSE	.015	.122	.022	.150
TMT-A	.043	.208#	.029	.179#
TMT-B	.050	.223*	.035	.196#
LNS	.002	−.048	.000	−.016
Rivermead Immediate Recall	.004	.065	.001	−.025
Rivermead Delayed Recall	.019	−.139	.007	−.083
	Loneliness*sex			
MMSE	.000	−.029	.001	−.031
TMT-A	.011	−.138	.010	−.139
TMT-B	.001	−.030	.001	−.040
LNS	.000	−.029	.000	.003
Rivermead Immediate Recall	.000	−.002	.001	.053
Rivermead Delayed Recall	.000	−.028	.006	−.106

Note. MMSE: Mini-Mental State Examination; TMT: Trail-Making Test; LNS: Letter-number sequencing. #$p < .09$. *$p < .05$. **$p < .01$.

3.3. Relationship between cortisol indexes and cognitive function

When investigating the association between the cortisol indexes and the different cognitive domain outcomes, results showed that bedtime cortisol levels were significantly and negatively related to performance on the MMSE in unadjusted analyses ($B = -.235$, $p = .035$) and marginally in adjusted analyses ($B = -.218$, $p = .056$). Furthermore, bedtime cortisol levels were significantly and negatively related to performance on the LNS ($B = -.230$, $p = .036$ and $B = -.209$, $p = .047$, for unadjusted and adjusted analyses, respectively) and on Rivermead immediate recall ($B = -.323$, $p = .003$ and $B = -.326$, $p = .002$, for unadjusted and adjusted analyses, respectively). In addition, bedtime cortisol levels were significantly and positively associated with time performing (i.e. worse performance) the TMT-A ($B = .403$, $p \leq .001$ and $B = .371$, $p \leq .001$, for unadjusted and adjusted analyses, respectively) and the TMT-B ($B = .352$, $p = .001$ and $B = .303$, $p = .003$, for unadjusted and adjusted analyses, respectively). Moreover, the results showed a significant, negative association between the DSC and the MMSE in unadjusted analyses ($B = -.262$, $p = .022$); that is, a smaller decrease in cortisol levels during the day was related to worse cognitive function performance, but the association was marginal in adjusted analyses ($B = -.218$, $p = .057$). In addition, although not reaching significance, in unadjusted analyses, the DCS was marginally and positively associated with time performing TMT-B ($B = .199$, $p = .082$) and negatively with Rivermead Immediate Recall performance ($B = -.215$, $p = .059$). Furthermore, the AUCg cortisol index was only significantly and positively associated with time performing the TMT-B (i.e. worse performance) ($B = .217$, $p = .048$) in adjusted analyses. The AUCg was also marginally and positively associated with time performing the TMT-A ($B = .204$, $p = .076$ and $B = .186$, $p = .082$, for unadjusted and adjusted analyses, respectively), and negatively with Rivermead immediate recall performance ($B = -.193$, $p = .091$ and $B = -.204$, $p = .071$, for unadjusted and adjusted analyses, respectively). Moreover, sex only significantly moderated the association between AUCg cortisol, and both TMT B ($B = -.351$, $p = .011$) and LNS ($B = .310$, $p = .032$) performance in unadjusted analyses. However, in adjusted analyses, the association between AUCg cortisol and TMT-B remained marginal ($B = -.244$, $p = .075$), and the association with LNS disappeared ($B = .142$, $p = .321$). Likewise, sex marginally moderated the association between DCS and TMT-A performance in adjusted analyses ($B = -.299$, $p = .079$), and with Rivermead Delayed Recall performance

Table 4
Regression analyses with cortisol indexes (awakening cortisol, bedtime cortisol, DCS or AUCg cortisol) or cortisol indexes*sex interaction terms, as predictors and cognitive outcomes (MMSE, TMT-A, TMT-B, LNS, Rivermead immediate recall and Rivermead delayed recall) as dependent variables, unadjusted and adjusted for covariates.

	Unadjusted analyses		Adjusted analyses	
	Awakening cortisol			
	R^2 change	Beta	R^2 change	Beta
MMSE	.028	.167	.029	.170
TMT-A	.000	.012	.000	.014
TMT-B	.001	−.106	.002	−.049
LNS	.010	.100	.003	.058
Rivermead Immediate Recall	.001	.032	.000	−.019
Rivermead Delayed Recall	.004	−.064	.004	−.062
	Bedtime cortisol			
	R^2 change	Beta	R^2 change	Beta
MMSE	.055	−.235*	.047	−.218#
TMT-A	.162	.403**	.134	.371**
TMT-B	.124	.352**	.087	.303**
LNS	.053	−.230*	.043	−.209*
Rivermead Immediate Recall	.104	−.323**	.106	−.326**
Rivermead Delayed Recall	.018	.133	.015	.121
	DCS			
	R^2 change	Beta	R^2 change	Beta
MMSE	.068	−.262*	.046	−.218#
TMT-A	.029	.171	.024	.157
TMT-B	.040	.199#	.022	.150
LNS	.034	−.186	.010	−.103
Rivermead Immediate Recall	.046	−.215#	.030	−.176
Rivermead Delayed Recall	.029	.172	.030	.173
	AUCg cortisol			
	R^2 change	Beta	R^2 change	Beta
MMSE	.014	−.118	.008	−.089
TMT-A	.041	.204#	.034	.186#
TMT-B	.030	.175	.046	.217*
LNS	.006	−.078	.015	−.125
Rivermead Immediate Recall	.037	−.193#	.042	−.204#
Rivermead Delayed Recall	.002	.046	.002	.047
	Awakening cortisol*sex			
	R^2 change	Beta	R^2 change	Beta
MMSE	.000	−.005	.001	−.036
TMT-A	.000	−.006	.004	.096
TMT-B	.015	−.185	.002	−.076
LNS	.006	.121	.002	−.067
Rivermead Immediate Recall	.003	.083	.000	.002
Rivermead Delayed Recall	.001	.056	.003	.086
	Bedtime cortisol*sex			
	R^2 change	Beta	R^2 change	Beta
MMSE	.000	−.007	.001	−.044
TMT-A	.000	.008	.000	−.005
TMT-B	.002	.049	.003	.060
LNS	.001	.052	.002	−.051
Rivermead Immediate Recall	.000	.024	.000	.004
Rivermead Delayed Recall	.005	−.086	.005	−.087
	DCS*sex			
	R^2 change	Beta	R^2 change	Beta
MMSE	.020	.219	.033	.287
TMT-A	.019	−.211	.036	−.299#
TMT-B	.020	.216	.005	.108
LNS	.010	−.152	.000	.008
Rivermead Immediate Recall	.002	.065	.009	.147
Rivermead Delayed Recall	.036	−.292#	.052	−.357#
	AUCg cortisol*sex			
	R^2 change	Beta	R^2 change	Beta
MMSE	.021	.188	.006	.103
TMT-A	.008	−.116	.002	−.051
TMT-B	.074	−.351*	.034	−.244#
LNS	.057	.310*	.012	.142
Rivermead Immediate Recall	.021	.187	.007	.110
Rivermead Delayed Recall	.000	.006	.001	.049

Note. DCS: diurnal cortisol slope; AUCg: area under the curve with respect to the ground; MMSE: Mini-Mental State Examination; TMT: Trail-Making Test; LNS: Letter-number sequencing. #$p < .09$. *$p < .05$. **$p < .01$.

($B = -.292$, $p = .095$ and $B = -.357$, $p = .058$, in unadjusted and adjusted analysis, respectively). None of the other associations were statistically significant or marginal (all $p \geq .104$) (Table 4).

3.4. Mediation models

Because we observed significant associations between loneliness and bedtime cortisol, and between bedtime cortisol and several cognitive domains (assessed by TMT-A, TMT-B, LNS, and Rivermead immediate recall), separate mediation analyses adjusted for covariates were performed to examine the indirect effect of loneliness on these cognitive domains via bedtime cortisol. First, the model assessing the mediation effect of bedtime cortisol in the association between loneliness and TMT-A performance revealed significant effects of loneliness on bedtime cortisol (path *a:* $B = .217$, $SE = .081$, $t = 2.654$, $p = .009$) and of bedtime cortisol on TMT-A (path *b*: $B = .458$, $SE = .160$, $t = 2.864$, $p = .005$), but not a significant total effect (path *c*: $B = .211$, $SE = .113$, $t = 1.860$, $p = .067$) or a direct effect of loneliness on TMT-A (path *c'*: $B = .111$, $SE = .113$, $t = .984$, $p = .328$). However, there was a significant indirect effect of loneliness on TMT-A via bedtime cortisol levels (path *ab*: $B = .099$, $SE = .055$, *95% CI:* .000, .219) (Fig. 1).

Likewise, the model assessing the mediation effect of bedtime cortisol in the association between loneliness and TMT-B performance revealed significant effects of loneliness on bedtime cortisol (path *a:* $B = .213$, $SE = .081$, $t = 2.611$, $p = .011$) and of bedtime cortisol on TMT-B (path *b*: $B = .384$, $SE = .161$, $t = 2.384$, $p = .019$), but neither the total effect (path *c*: $B = .114$, $SE = .112$, $t = 1.017$, $p = .312$) nor the direct effect of loneliness on TMT-B was significant (path *c'*: $B = .033$, $SE = .114$, $t = .288$, $p = .774$). Finally, a significant indirect effect of loneliness on TMT-B via bedtime cortisol levels was found (path *ab*: $B = .081$, $SE = .055$, *95% CI:* .000, .211) (Fig. 2).

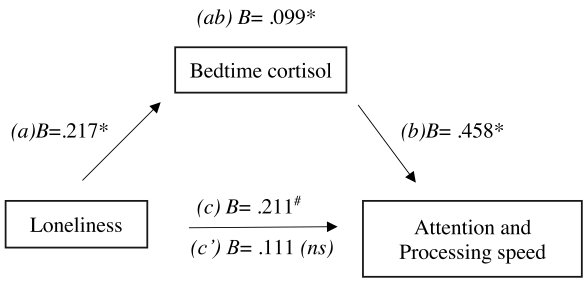

Fig. 1. Mediation model to test the indirect effect of loneliness on attention and processing speed (Trail-Making Test A), via bedtime cortisol.

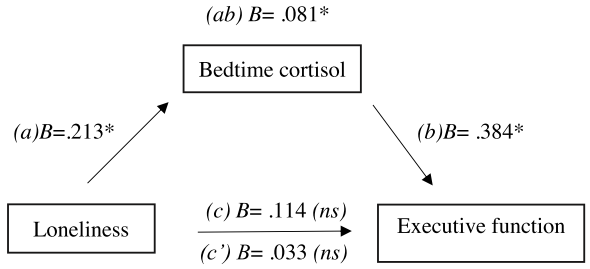

Fig. 2. Mediation model to test the indirect effect of loneliness on executive function (Trail-Making Test B), via bedtime cortisol.

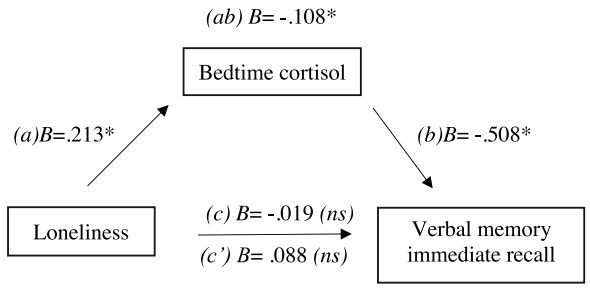

Fig. 3. Mediation model to test the indirect effect of loneliness on verbal memory immediate recall (Rivermead immediate recall), via bedtime cortisol.

Table 5
Mediation models to test the indirect effect of loneliness on cognitive performance (TMT-A, TMT-B, LNS and Rivermead immediate recall) via bedtime cortisol.

	B	*SE*	*t*	*p*
Effect of loneliness on bedtime cortisol (a)	**.217**	**.081**	**2.654**	**.009**
Effect of bedtime cortisol on TMT-A (b)	**.458**	**.160**	**2.864**	**.005**
Total effect of loneliness on TMT-A (c)	.211	.113	1.860	.067
Direct effect of loneliness on TMT-A (c')	.111	.113	.984	.328
	B	*SE*	*CI*	*95%*
Indirect effect of loneliness on TMT-A via bedtime cortisol *(ab)*	**.099**	**.055**	**.004**	**.219**
	B	*SE*	*t*	*p*
Effect of loneliness on bedtime cortisol *(a)*	**.213**	**.081**	**2.611**	**.011**
Effect of bedtime cortisol on TMT-B *(b)*	**.384**	**.161**	**2.384**	**.019**
Total effect of loneliness on TMT-B *(c)*	.114	.112	1.017	.312
Direct effect of loneliness on TMT-B *(c')*	.033	.114	.288	.774
	B	*SE*	*CI*	*95%*
Indirect effect of loneliness on TMT-B via bedtime cortisol *(ab)*	**.081**	**.055**	**.000**	**.211**
	B	*SE*	*t*	*p*
Effect of loneliness on bedtime cortisol *(a)*	**.213**	**.081**	**2.611**	**.011**
Effect of bedtime cortisol on LNS *(b)*	−.261	.159	−1.634	.106
Total effect of loneliness on LNS *(c)*	.122	.109	1.116	.268
Direct effect of loneliness on LNS *(c')*	.178	.113	1.567	.121
	B	*SE*	*CI*	*95%*
Indirect effect of loneliness on LNS via bedtime cortisol *(ab)*	−.055	.057	−.199	.021
	B	*SE*	*t*	*p*
Effect of loneliness on bedtime cortisol *(a)*	**.213**	**.081**	**2.611**	**.011**
Effect of bedtime cortisol on Rivermead immediate recall *(b)*	**−.508**	**.184**	**−2.747**	**.007**
Total effect of loneliness on Rivermead immediate recall *(c)*	−.019	.131	−.150	.880
Direct effect of loneliness on Rivermead immediate recall *(c')*	.088	.131	.673	.502
	B	*SE*	*CI*	*95%*
Indirect effect of loneliness on Rivermead immediate recall via bedtime cortisol *(ab)*	**−.108**	**.071**	**−.273**	**−.004**

Note. TMT: Trail-Making Test; LNS: Letter-number sequencing. Values in bold represent significant *p* values.

Similarly, the model assessing the mediation effect of bedtime cortisol in the association between loneliness and Rivermead immediate recall performance revealed significant direct effects of loneliness on bedtime cortisol (path *a:* $B = .213$, $SE = .081$, $t = 2.611$, $p = .011$) and of bedtime cortisol on Rivermead immediate recall (path *b*: $B = -.508$, $SE = .184$, $t = -2.747$, $p = .007$), but not a total effect (path *c*: $B = -.019$, $SE = .131$, $t = -.150$, $p = .880$) or a direct effect of loneliness on Rivermead immediate recall (path *c'*: $B = .088$, $SE = .131$, $t = .673$, $p = .502$). However, a significant indirect effect of loneliness on Rivermead immediate recall via bedtime cortisol levels (path *ab*: $B = -.108$, $SE = .071$, *95% CI:* −.273, −.004) was found (Fig. 3). By contrast, a significant indirect effect of loneliness on LNS via bedtime cortisol levels was not observed (path ab: $B = -.055$, $SE = .057$, *95% CI:* −.199, .021) (Table 5).

4. Discussion

Our results showed that loneliness was significantly associated with higher bedtime cortisol levels, but not with the other cortisol indexes analyzed. Moreover, higher bedtime cortisol levels were related to worse cognitive performance on processing speed and attention, executive function, working memory, and verbal memory immediate recall. Furthermore, although we did not find a direct association between loneliness and cognitive function, we observed that bedtime cortisol levels mediated the association between loneliness and worse performance on attention and processing speed, executive function, and verbal memory immediate recall. No sex differences were observed in these associations.

Our results showed that loneliness was related to higher bedtime cortisol levels, but not to awakening cortisol, the DCS or the AUCg. These results are consistent with previous studies in older people that did not find an association between loneliness and awakening cortisol levels (Schutter et al., 2017) or the DCS (Adam et al., 2006; Schutter et al., 2017). However, Cole et al. (2007), in a smaller and selected sample of individuals with extreme high and low loneliness scores that were stable over 3 years, observed that highly lonely individuals showed a blunted diurnal cortisol slope compared to less lonely participants. To our knowledge, this is the first study to analyze the relationships between loneliness and both bedtime cortisol and the AUCg in older people.

We did not observe significant associations between loneliness and cognitive function. We only found that higher loneliness was marginally associated with worse performance on processing speed and attention (TMT-A), and significantly with executive function (TMT-B), but after controlling for sociodemographic factors, these associations disappeared. Schnittger et al. (2012) observed that emotional loneliness was related to worse performance on TMT-A, but not on TMT-B and verbal fluency, whereas social loneliness was related to worse performance on verbal fluency, but not on TMT-A and B. Other studies also observed that loneliness was related to worse performance on processing speed or executive function in cross-sectional studies (Gow et al., 2013; Gilmour, 2011; O'Luanaigh et al., 2012; Shankar el al., 2013) and in a follow-up study (Wilson et al., 2007, except Shankar et al., 2013). However, as in our study, other studies found that the association between loneliness and processing speed or executive function did not persist after controlling for sociodemographic factors and depression (Gilmour, 2011; Gow et al., 2013).

In line with this study, Schnittger et al. (2012) failed to find an association between loneliness and global cognition. By contrast, other studies did find this association (Gow et al., 2013; O'Luanaigh et al., 2012), but it disappeared after controlling for depression (Gow et al., 2013). In addition, no association between loneliness and working memory has been reported (O'Luanaigh et al., 2012; Schnittger et al., 2012; Wilson et al., 2007), consistent with our results. We did not find an association between loneliness and immediate or delayed verbal memory recall. Previous studies reported an association between

loneliness and verbal memory at baseline (Gow et al., 2013; Shankar et al., 2013; Wilson et al., 2007) and in the decline over time (Shankar et al., 2013), but others did not (Gow et al., 2013; Wilson et al., 2007). In addition, an association between loneliness and verbal memory immediate recall, but not delayed recall, has been reported (Gilmour, 2011; O'Luanaigh et al., 2012). However, this association disappeared after controlling for psycho-sociodemographic variables (O'Luanaigh et al., 2012). Therefore, it is important to clarify which factors play a role in the relationship between loneliness and these cognitive domains.

Interestingly, we did not find significant associations between loneliness and any of the cognitive domains, but we observed an indirect effect of loneliness on attention and processing speed, executive function, and verbal memory immediate recall via bedtime cortisol levels. When analyzing mediation models, the indirect effect of loneliness on both TMT-B and Rivermead immediate recall was greater in magnitude than the direct effect. However, the indirect effect of loneliness on TMT-A was smaller than the direct effect. As previously noted, the power to detect an indirect effect may be higher than the power to detect a total and direct effect (e.g., Loeys et al., 2015). Therefore, the results for the total and direct effects should be interpreted with caution because we cannot rule out the possibility of a direct effect of loneliness on these cognitive domains that could be observed with greater statistical power. Several studies have proposed that HPA-axis functioning is one of the biological mechanisms that could mediate between loneliness and cognition (reviews: Boss et al., 2015; Cacioppo and Hawkley, 2009; Cacioppo et al., 2014; Ong et al., 2015). To our knowledge, this is the first study to explore this relationship, verifying a mediating effect of bedtime cortisol on the associations between loneliness and some cognitive functions. With all this in mind, the mediating effects may explain mixed findings regarding the relationship between loneliness and cognitive function.

Although it has been reported that healthier daily cortisol profiles, including a steeper DCS, higher morning cortisol levels, and lower afternoon and evening cortisol levels, are related to higher cognitive function (Stawski et al., 2011), this relationship has not always been observed. Some studies reported that a flatter DCS was related to poorer executive function (Stawski et al., 2011) and memory performance (Gerritsen et al., 2011), and a decline in visuospatial and visual memory performance in men and verbal fluency in women (Beluche et al., 2010). However, other studies reported no association between DCS and cognitive performance (Ennis et al., 2016; Hidalgo et al., 2016; Singh-Manoux et al., 2014), or even an association between a steeper DCS and worse performance on verbal memory delayed recall (O'Hara el al., 2007). In our study, we only observed that a higher DCS was marginally related to poorer performance on global cognition, but not on the rest of the cognitive domains measured.

No association between awakening cortisol levels and cognitive function was observed; however, higher bedtime cortisol levels were related to worse cognitive performance on processing speed and attention, executive functioning, working memory, and verbal memory immediate recall. Although previous literature on the relationship between awakening cortisol levels and cognition shows heterogeneous results, the relationship between evening cortisol levels and cognitive function seems more consistent. Stawski et al. (2011) reported that lower cognitive function (i.e. episodic memory and executive function) was associated with lower awakening and higher bedtime cortisol levels. However, after performing these analyses independently for these two components, worse executive function performance was only related to higher bedtime cortisol levels, but not to awakening cortisol levels. In addition, other studies reported that higher bedtime cortisol levels were associated with poorer performance on memory, processing speed, and executive functioning (Geerlings et al., 2015; Li et al., 2006; Tene et al., 2018), but awakening levels were not (Geerlings et al., 2015; Tene et al., 2018). Furthermore, Geerlings et al. (2015) also observed that higher bedtime cortisol levels were associated with smaller total brain volume, whereas higher morning cortisol levels were associated with slightly greater than normal white matter volume and better cognitive performance. Moreover, similarly to Li et al.'s study (2006), we observed that higher diurnal cortisol output (AUCg) was only related to worse performance on executive function measured with the TMT-B test, but not to verbal recall, working memory, or global cognition. However, a recent study (Ouanes et al., 2017) observed that higher diurnal cortisol levels were related to poorer global cognitive performance, specifically on episodic memory. Nevertheless, no association has been found between the diurnal cortisol output and cognitive performance in middle-aged and older people (Ennis et al., 2016; Harris et al., 2017; Singh-Manoux et al., 2014).

Finally, it is worth noting that there were no sex differences in the relationship between loneliness and HPA-axis functioning or cognitive function, or in the association between HPA-axis functioning and cognitive function. Our study is the first to explore sex differences in the association between loneliness and awakening cortisol, bedtime cortisol, and the diurnal cortisol slope in older adults, showing no significant differences. Steptoe et al. (2004) did not observe a sex interaction in the association between loneliness and HPA-axis function in middle-aged adults either. Sex differences in the loneliness-poorer cognitive function link have been explored very little. Although Gow et al. (2007) found this association only in women, but not in men, conclusions about sex differences in this relationship cannot be drawn because they did not perform interaction tests. As in Holwerda et al. (2012), we did not observe a moderating effect of sex in the relationship between loneliness and cognitive function, either directly or indirectly, via cortisol levels. We expected these associations to be more pronounced in women than in men because loneliness has been associated with greater health problems in women than in men (Christiansen et al., 2016). One possible explanation for this lack of sex differences in the association between loneliness and HPA-axis functioning and cognitive function is that we did not find differences in loneliness between men and women, even though being a woman has been associated with greater loneliness (see review: Pinquart and Sorensen, 2001).

One limitation of our study is that, due to the correlational nature of the results, we cannot claim causal relationships. In addition, it is possible that, given the sample size, there was not enough statistical power to detect sex differences in the associations between loneliness and cortisol levels and cognition. Thus, a larger sample size would be necessary to explore sex differences in these relationships. Moreover, the fact that we ran multiple regression analyses to assess the association between the cortisol indexes and the different cognitive domains could lead to an inflation of Type 1 error. Furthermore, we did not include some neuropsychological functions that have shown an association with loneliness in previous studies, such as verbal fluency (Schnittger et al., 2012; Shankar et al., 2013), visual memory (O'Luanaigh et al., 2012; Schnittger et al., 2012), and visuospatial ability (Wilson et al., 2007). Moreover, in our study, we only included two cortisol data points (awakening and bedtime cortisol); future studies should include more cortisol data points during the day to calculate the DCS and the cortisol awakening response (CAR), which have also shown significant associations with loneliness (Adam et al., 2006; Schutter et al., 2017) and cognitive function (Evans et al., 2012; Hidalgo et al., 2016) in older adults. Despite these limitations, this study is the first to examine the mediating effect of HPA-axis functioning in the relationship between loneliness and poorer cognitive function in older people, providing interesting results to continue advancing in this area.

Declarations of interest

None.

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