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RESEARCH ARTICLE

Mediation of perceived stress and cortisol in the association between neuroticism and global cognition in older adults: A longitudinal study

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Abstract

Neuroticism has been associated with a greater dementia risk, but its association with cognitive decline in healthy older adults remains unclear. Stress has been proposed as one of the mechanisms that could explain this relationship. Our aim was to analyse, in healthy older people, the mediating role of perceived stress and the Hypothalamic–Pituitary–Adrenal (HPA) axis in the association between neuroticism and global cognition. At Waves 1 and 2 (4-year follow-up), 87 older people (49.4% women; M age = 65.08, SD = 4.54 at Wave 1) completed a neuropsychological battery and the Perceived Stress Scale (PSS), and provided saliva samples on two (Wave 1) and three (Wave 2) consecutive days to measure the wake-to-bed slope. In Wave 2, neuroticism was assessed with the NEO-Five-Factor Inventory. PSS, but not the wake-to-bed slope, mediated the negative associations between neuroticism and global cognition (Waves 1, 2 and change). Regarding gender differences, PSS (Waves 1, 2 and change) and the wake-to-bed slope (Wave 2 and change) mediated these associations in men. Our results suggest that perceived stress and HPA-axis dysregulation could act as mechanisms underlying the association between neuroticism and cognitive functioning and decline, at least in older men.

KEYWORDS
cognition, cortisol, neuroticism, older people, perceived stress

1 | INTRODUCTION

The increase in life expectancy has led to the dramatic ageing of the world's population, and projections indicate that between 2015 and 2050, the proportion of the world's population over 60 years old will nearly double, going from 12% to 22% (World Health Organization [WHO], 2018). This age group is more likely to experience several adverse health conditions, including cognitive decline and dementia, which are public health priorities (WHO, 2019). However, there is great heterogeneity in the way people age. Whereas most older adults show slow cognitive decline, others experience moderate or rapid decline (Hayden et al., 2011). Therefore, it is important to understand which factors could account for these individual differences in cognitive change, and the personality trait of neuroticism has been

proposed as one of these factors (Curtis et al., 2015; Luchetti et al., 2016). Neuroticism has been related to an increased risk of dementia (see reviews and meta-analysis: Low et al., 2013; Terracciano et al., 2014). However, the association between neuroticism and cognitive decline in healthy older adults remains unclear, and a better understanding of the mechanisms underlying this association could help to shed light on this question (see review: Curtis et al., 2015).

Stress has been proposed as one of these underlying mechanisms (Caselli et al., 2016; Chapman et al., 2012; Curtis et al., 2015), and there is evidence that individuals higher in neuroticism are more likely to experience stressful events and show more pronounced and less well-regulated emotional responses to these events (Lahey, 2009). Neuroticism is defined as a tendency to experience negative emotions, such as anger, anxiety, and depressed mood (Costa & McCrae, 1992; McCrae & John, 1992), and, therefore, psychological distress (Lahey, 2009). Moreover, neuroticism has been suggested as the main driver of perceived stress (Conard & Matthews, 2008). Perceived stress is defined as the degree to which situations in a person's life are viewed as stressful, and it has been widely measured by the Perceived Stress Scale (PSS) (Cohen et al., 1983). However, although neuroticism has been positively associated with perceived stress (Ebstrup et al., 2011), these two measures are independent constructs (Rietschel et al., 2014).

In addition to perceived stress, neuroticism has been associated with Hypothalamic–Pituitary–Adrenal (HPA) axis functioning. The HPA axis is one of the biological systems that is activated in response to stress conditions, and its end product is cortisol (Soliemanifar et al., 2018). In basal situations, cortisol follows a diurnal rhythm, peaking early in the morning and steadily decreasing throughout the day, reaching the lowest levels in the evening (Adam & Kumari, 2009). The degree of change in cortisol from morning to evening is conceptualized as the diurnal cortisol slope (DCS), one of the key components of the diurnal cortisol rhythm (Adam et al., 2017). A flattened DCS, indicating HPA-axis dysregulation, has been associated with exposure to chronic stress (see meta-analysis: Miller et al., 2007) and mental and physical health outcomes (Adam et al., 2017).

Although the stress response is a necessary and adaptive response, the allostatic load model proposes that the cumulative impact of stress can predispose individuals to disease. Allostasis refers to the body's adaptive responses that maintain homoeostasis in the presence of stressors, which involves HPA-axis functioning. However, when an individual is repeatedly exposed to stress, the chronic activation of the HPA-axis can produce wear and tear on the body and brain, referred to as the allostatic load, leading to cognitive problems (McEwen, 2002; McEwen & Stellar, 1993). Previous literature highlighted the importance of adequate HPA-axis regulation in cognitive preservation. In fact, the association between HPA-axis dysregulation and impaired cognitive functioning is explained by the fact that 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 (see review: Lupien et al., 2007). In healthy older adults, a flattened DCS has been associated with poorer cognition in some cross-sectional studies (Gardner et al., 2019; Stawski et al., 2011), but not in others (Ennis et al., 2016; Hidalgo et al., 2016). Similarly, the association between a flatter DCS and cognitive impairment has been observed in some longitudinal studies (Beluche et al., 2010; Tsui et al., 2020), but two other studies failed to observe this association (Gerritsen et al., 2011; Singh-Manoux et al., 2014). Similarly, greater perceived stress at baseline predicted accelerated cognitive decline in some follow-up studies (Aggarwal et al., 2014; Munoz et al., 2015; Turner et al., 2017), but not in all of them (Chen et al., 2019). However, the question of whether change in perceived stress predicts change in cognitive functioning has been studied less. In a 2-year follow-up study, Munoz et al. (2015) did not observe that change in perceived stress predicted cognitive decline. However, in another 2-year follow-up study, Feeney et al. (2018) observed that an increase in perceived stress predicted cognitive decline in immediate word recall, but not in other cognitive domains. Thus, examining the association between change in perceived stress and change in global cognitive decline in longer follow-up studies is a pending question.

Finally, in a review, Gaffey et al. (2016) highlight the importance of considering age and gender to obtain a better understanding of the association between stress, the HPA-axis and health in the ageing population. Specifically, at older ages, men seem to be more vulnerable to HPA-axis dysregulation, with its implications for health and longevity (Gaffey et al., 2016). However, only a few studies have explored whether there are differences between men and women in the association between perceived stress (Aggarwal et al., 2014; Munoz et al., 2015) or the DCS (Hidalgo et al., 2016; Singh-Manoux et al., 2014) and cognitive function/decline, and they failed to observe a gender moderation effect.

On the whole, there is evidence that neuroticism has been associated with both perceived stress and HPA-axis functioning, and, in turn, these two stress components have been related to cognitive function and decline. Therefore, although this topic has not been studied, perceived stress and HPA-axis functioning could be two of the mechanisms underlying the association between neuroticism and cognitive decline. Thus, the aim of this study was to analyse the mediating role of both psychological (perceived stress) and physiological (HPA-axis) stress components in the relationship between neuroticism and global cognition in healthy older people, using both cross-sectional and longitudinal approaches. We hypothesized that higher perceived stress and a flattened DCS (showing HPA-axis dysregulation) would mediate the association between higher neuroticism and poorer global cognition. We also hypothesized that an increase in perceived stress and a flattening of the DCS would mediate the association between higher neuroticism and greater cognitive decline. Finally, we aimed to explore the moderating role of gender in the associations between the two stress components and global cognition.

2 | METHODS

2.1 | Participants

The sample consisted of Spanish older individuals who were recruited at the University of Valencia for people over 55 years of age. At baseline (Wave 1, 2011–2012), 128 participants participated in the study. Exclusion criteria at baseline were smoking more than 10 cigarettes a day, alcohol or other drug abuse, 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, or having been under general anaesthesia once or more than once in the past year. We also excluded participants who reported the presence of an important 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, because these types of events can influence HPA axis functioning. However, we did not exclude participants who reported everyday stress. Four years later (Wave 2, 2015–2016), participants were contacted by telephone and invited to take part in a follow-up study, and 87 individuals agreed to participate (44 men and 43 women). Participants' ages ranged from 55 to 77 years old in Wave 1 (M = 65.08, SD = 4.54). None of the participants scored less than 27 on the Spanish version of the Mini-Mental State Examination (Lobo et al., 1999), indicating the absence of cognitive impairment.

2.2 | Procedure

At baseline (Wave 1) and the 4-year follow-up (Wave 2), participants were asked to attend a neuropsychological session that took place at 10:00 or at 12:00 h in our laboratory. 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 session. They were also instructed to drink only water, and not eat, smoke or take any stimulants (such as coffee, cola, caffeine, tea or chocolate) at least 1 h prior to the session. In addition, in Waves 1 and 2, participants were asked to fill out the PSS (Cohen et al., 1983) and provide saliva samples at home, immediately after awakening and immediately before bedtime, on two consecutive days (four saliva samples) in Wave 1, and on three consecutive days (six saliva samples) in Wave 2. We obtained the wake-to-bed slope which is one of the common types of slopes described to measure the DCS (Adam et al., 2017). The participants received thorough instructions about how to provide the saliva samples, and they were given written instructions to drink only water and not eat, brush their teeth or exercise at least 1 h prior to each saliva sample. In addition, to objectively verify participant adherence to the saliva sampling time at home, salivettes were stored in MEMS TrackCap containers (MEMS 6 TrackCap Monitor, Aardex Ltd.), and participants were asked to write down the time they provided the saliva samples at awakening and bedtime in a diary. Finally, in Wave 2, participants were also asked to fill out the NEO-Five Factor Inventory (NEO-FFI) to assess the neuroticism trait (Costa & McCrae, 1992). They were asked if they had diabetes or a neurological or psychiatric disease, or if they were taking any medication directly related to emotional or cognitive functioning or able to influence hormonal levels, such as glucocorticoids, psychotropic substances or sleep medications.

All the participants provided their 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.

2.3 | Neuroticism

The Spanish version (Costa & McCrae, 1999) of the NEO-FFI (Costa & McCrae, 1992) was administered to measure neuroticism. The NEO-FFI consists of 60 items that measure the Big Five personality traits (neuroticism, conscientiousness, extraversion, openness and agreeableness), with 12 items for each trait. The items are answered on 5-point scales, and higher scores indicate a higher degree of the trait. The internal reliability for the neuroticism subscale in the present study was good (Cronbach's alpha: 0.84).

2.4 | Global cognition

A global composite cognitive score was derived from a battery of six standard neuropsychological tests. Each participant completed the neuropsychological battery in Waves 1 and 2, and several cognitive domains were evaluated. Declarative memory was assessed with the Spanish version of the Rey Auditory Verbal Learning Test (RAVLT) (Miranda & Valencia, 1997), and three indexes were obtained: (i) total learning: total number of words recalled on the first five trials (trial I to V), (ii) immediate recall: percentage of total number of words recalled after the interference trial compared to the number of words recalled on trial V (trial VI/trial V × 100); and (iii) delayed recall: percentage of total number of words recalled after the 20-min delay compared to the number of words recalled on the immediate recall trial (trial VII/trial VI × 100). Working memory was assessed with the Digit Span (DS) (iv) forward and (v) backward and the (vi) Letter-number sequencing (LNS) tests from the Spanish version of the Wechsler Memory Scale III (Wechsler, 1997). Finally, executive functioning was assessed with the Trail-Making Test (TMT) (Reitan, 1992) (vii) A, and (viii) B and the (ix) Stroop Colour-Word Interference Test (Golden, 1978). Raw scores on the nine cognitive indexes were converted to z-scores and averaged to create a composite global cognitive domain, as in similar studies (Aggarwal et al., 2014; Lee et al., 2008; Turner et al., 2017). TMT-A and -B scores were reversed, such that higher scores indicated worse performance (longer times performing the test).

2.5 | Salivary cortisol sampling

Participants provided saliva samples by using salivettes (Sarstedt). 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 analysing the salivary cortisol levels. Salivary cortisol concentrations were determined in duplicate with the salivary cortisol enzymeimmunoassay kit from Salimetrics (Newmarket). Assay sensitivity was 0.007 μg/dL. For each subject, all the samples were analysed in the same trial. The inter- and intra-assay variation coefficients were all below 10%. Cortisol levels are expressed in nmol/L.

2.6 | Perceived stress

The Spanish version (Remor, 2006) of the PSS (Cohen et al., 1983) was used as a measure of perceived stress during the past month. This scale consists of 14 items rated on a 5-point Likert scale, with higher scores indicating higher perceived stress. The internal reliability for the PSS in the present study was good (Cronbach's alpha: 0.81 in Wave 1 and 0.80 in Wave 2).

2.7 | Statistical analysis

Participants' characteristics are described using percentages or means (standard deviation, SD) for the total sample and for men and women independently. To investigate gender differences in age, neuroticism, the PSS, wake-to-bed slope and the nine cognitive indexes in Waves 1 and 2, independent sample Student-*t* tests were performed, whereas differences in educational level were analysed with Chi-square tests.

Before performing the statistical analyses, participants who scored ±3 SD from the mean were identified, and z scores were winsorized. All participants completed the neuropsychological assessment and the PSS in Waves 1 and 2, but there was one missing value for the NEO-FFI ($N = 86$). Moreover, the wake-to-bed slope in Wave 1 was obtained for 84 participants (for 2 days in 82 participants, and for 1 day in two participants), and in Wave 2 for 79 participants (for 3 days in 76 participants, for 2 days in two participants, and for 1 day in one participant). Cortisol data were log-transformed (Log10). For each of the 2 days in Wave 1 and the 3 days in Wave 2, we calculated the wake-to-bed slope (bedtime minus awakening cortisol levels), which measures the absolute change in cortisol from awakening to bedtime (Adam et al., 2017). Thus, more negative values reflect a steeper decline from awakening to bedtime, whereas more positive scores reflect flatter cortisol slopes. We averaged the wake-to-bed slopes of the 2 days in Wave 1 and of the 3 days in Wave 2 to obtain reliable indicators, checking that they significantly correlated (Wave 1 Day 1–2 $r = 0.371$, $p = 0.001$ and Wave 2 Day 1–2: $r = 0.344$, $p = 0.002$; Day 2–3: $r = 0.358$, $p = 0.001$; Day 1–3: $r = 0.479$, $p \leq 0.001$).

Pearson's correlation analyses were performed to analyse the associations between all the variables (age, gender, educational level, medication/disease, neuroticism, the PSS, wake-to-bed slope and global cognition indexes [Waves 1 and 2]) (supplementary material: Table S1). In addition, repeated-measures ANOVAs were performed to assess change in the PSS and wake-to-bed slope (supplementary material: Table S2), and multiple repeated-measures ANOVAs to assess change in global cognition (supplementary material: Table S3) between Waves 1 and 2. Then, these analyses were repeated, including gender as a between-subject factor (supplementary material: Tables S4 and S5).

In the mediation models, we investigated whether the PSS or wake-to-bed slope mediated the relationship between neuroticism and global cognition in the cross-sectional (Waves 1 and 2) and longitudinal (change) studies, using the PROCESS macro in SPSS (v3.4) (Model 4) with 5000 bootstrapped samples. For the cross-sectional analysis, we conducted separate mediation models, including global cognition (Waves 1 or 2) as the dependent variable, neuroticism as the independent variable, and the PSS or wake-to-bed slope (Waves 1 or 2) as the mediator variable, controlling for the covariates (age, gender, educational level, medication/disease). Then, for the longitudinal model, we included global cognition in Wave 2 as the dependent variable, neuroticism as the independent variable, and the PSS or wake-to-bed slope in Wave 2 as the mediator variable, controlling for the covariates, global cognition in Wave 1, and the PSS or wake-to-bed slope in Wave 1. Finally, we repeated these analyses including the moderating effect of gender on these associations (Model 14).

To perform these statistical analyses, version 26.0 of SPSS was used. All *p* values were two-tailed, and the level of significance was taken as $p = 0.05$.

3 | RESULTS

3.1 | Participants' characteristics

There were no significant differences between men and women in age and educational level (all $p \leq 0.082$). However, women showed significantly higher scores than men on neuroticism and PSS in Wave 1, but no significant gender differences were observed in the wake-to-bed slope and PSS in Wave 2 or in the wake-to-bed slope (Waves 1 and 2). In addition, women performed better than men on RAVLT immediate recall in Wave 1 ($t(85) = 2.33$, $p = 0.022$). However, men performed better than women on DS-forward, DS-backward, LNS and TMT-B in Waves 1 and 2 (all $p \leq 0.039$) (see Table 1). Moreover, ANOVAs and

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

	Total ($N = 87$)	Men ($N = 44$)	Women ($N = 43$)	t/X^2	*gl*	*p*
Age (Wave 1)	65.08 (4.54)	65.50 (4.74)	64.65 (4.33)	−0.87	85	0.387
Educational level (%)				8.28	4	0.082
Primary school	17 (19.5)	4 (9.1)	13 (30.2)			
Secondary school	17 (19.5)	9 (20.5)	8 (18.6)			
Graduate (3-year degree)	26 (29.9)	13 (29.5)	13 (30.2)			
Graduate (5-year degree)	26 (29.9)	17 (38.6)	9 (20.9)			
PhD	1 (1.1)	1 (2.3)	0			
Neuroticism	28.27 (6.88)	14.33 (6.49)	18.30 (6.72)	2.79	84	0.007
Wake-to-bed slope Wave 1	−0.67 (0.27)	−0.71 (0.29)	−0.63 (0.26)	1.32	82	0.190
Wake-to-bed slope Wave 2	−0.67 (0.28)	−0.70 (0.29)	−0.64 (0.28)	0.87	77	0.388
PSS Wave 1	16.20 (6.15)	14.36 (5.13)	18.09 (6.58)	2.95	85	0.004
PSS Wave 2	16.76 (6.47)	15.84 (6.14)	17.70 (6.73)	1.34	85	0.182
RAVLT total learning Wave 1	51.15 (8.04)	50.29 (8.32)	52.02 (7.75)	1.00	85	0.319
RAVLT immediate recall Wave 1	87.95 (16.26)	84.04 (15.16)	91.96 (16.55)	2.33	85	0.022
RAVLT delayed recall Wave 1	98.67 (10.80)	98.22 (11.04)	99.14 (10.65)	0.40	85	0.691
Digit span forward Wave 1	8.90 (2.27)	9.82 (2.26)	7.98 (1.90)	−4.11	85	≤0.001
Digit span backward Wave 1	6.02 (1.98)	6.52 (1.85)	5.50 (2.00)	−2.47	84	0.016
Letter-number sequencing Wave 1	9.97 (2.27)	10.79 (2.24)	9.14 (1.99)	−3.62	85	≤0.001
Trail-making Test A Wave 1	39.23 (12.46)	37.49 (13.60)	40.98 (11.09)	1.30	84	0.196
Trail-making Test B Wave 1	98.78 (43.33)	87.18 (38.78)	110.39 (44.95)	2.56	84	0.012
Stroop Test Wave 1	−2.13 (7.40)	−1.35 (8.28)	−2.89 (6.44)	−0.94	79	0.351
RAVLT total learning Wave 2	50.05 (9.10)	48.57 (9.15)	51.56 (8.89)	1.54	85	0.126
RAVLT immediate recall Wave 2	81.85 (18.58)	82.44 (17.51)	81.23 (19.83)	−0.30	84	0.765
RAVLT delayed recall Wave 2	103.50 (18.68)	100.64 (17.55)	106.49 (19.56)	1.46	84	0.147
Digit span forward Wave 2	8.62 (1.98)	9.54 (1.96)	7.67 (1.51)	−4.99	85	≤0.001
Digit span backward Wave 2	6.16 (2.00)	6.61 (2.16)	5.70 (1.74)	−2.18	85	0.032
Letter-number sequencing Wave 2	10.15 (2.34)	10.66 (2.16)	9.62 (2.44)	−2.10	85	0.039
Trail-making Test A Wave 2	40.11 (15.12)	37.01 (15.32)	43.28 (14.41)	1,96	85	0.053
Trail-making Test B Wave 2	91.32 (37.59)	80.86 (33.34)	102.02 (39.02)	2.72	85	0.008
Stroop Test Wave 2	−2.21 (7.67)	−2.09 (8.00)	−2.33 (7.41)	−0.14	80	0.890

Abbreviations: M, mean; SD, standard deviation; PSS, Perceived Stress Scale; RAVLT, Rey Auditory Verbal Learning Test.

MANOVAs showed no significant changes between Waves 1 and 2 on the PSS, the wake-to-bed slope, or global cognition, or a significant gender interaction (see supplementary material: Tables S2–S5).

3.2 | Mediating effect of the PSS on the association between neuroticism and global cognition

Results showed that neuroticism was positively associated with PSS in Wave 1 (*path a*: $B = 0.417$, SE = 0.101, $t = 4.119$, $p \leq 0.001$, 95% CI: 0.215, 0.618) and Wave 2 (*path a:* $B = 0.564$, SE = 0.099, $t = 5.609$, $p \leq 0.001$, 95% CI: 0.367, 0.761). Moreover, higher neuroticism was significantly related to an increase in PSS (*path a:* $B = 0.365$, SE = 0.095, $t = 3.848$, $p \leq 0.001$, 95% CI: 0.176, 0.554). In addition, higher PSS was related to lower global cognition, only marginally in Wave 1 (*path b:* $B = -0.209$, SE = 0.115, $t = -1.815$, $p = 0.073$, 95% CI: −0.438, 0.020), but significantly in Wave 2 (*path b:* $B = -0.317$, SE = 0.111, $t = -2.863$, $p = 0.005$, 95% CI: −0.538, −0.097). Moreover, an increase in PSS was significantly related to global cognitive decline (*path b:* $B = -0.240$, SE = 0.080, $t = -3.008$, $p = 0.004$, 95% CI: −0.339, −0.081). Furthermore, results showed a

negative indirect effect of neuroticism on global cognition via PSS in Wave 1 (*path ab:* $B = -0.087$, SE = 0.049, 95% CI: −0.204, −0.012), Wave 2 ($B = -0.179$, SE = 0.082, 95% CI: −0.363, −0.036), and the longitudinal model (change) (*path ab:* $B = -0.088$, SE = 0.042, 95% CI: −0.181, −0.015) (Figure 1) (Table 2). There was no direct effect of neuroticism on global cognition in Waves 1, 2 or change (*path c*: all 95% CI included zero).

When analysing gender differences, gender only significantly moderated the association between the PSS and global cognition in Wave 2 ($B = -0.473$, SE = 0.184, $t = -2.564$, $p = 0.012$, 95% CI: −0.840, −0.106). Specifically, a negative association was observed between the PSS and global cognition only in men ($B = -0.559$, SE = 0.143, $t = -3.918$, $p \leq 0.001$, 95% CI: −0.843, −0.275). Moreover, a significant negative indirect effect of neuroticism on global cognition via the PSS was observed in both the cross-sectional (Waves 1 and 2) and longitudinal models only in men (all CI 95% did not include zero). However, gender only significantly moderated these mediation models in Wave 2 ($B = -0.264$, SE = 0.144, 95% CI: −0.555, −0.001) (Figure 2) (Table 3).

3.3 | Mediating effect of the wake-to-bed slope on the association between neuroticism and global cognition

Neuroticism was not significantly related to the wake-to-bed slope in Wave 1 (*path a:* $B = 0.132$, SE = 0.111, $t = 1.195$, $p = 0.236$, 95% CI: −0.188, 0.353). However, higher neuroticism was related to a greater (flattened) wake-to-bed slope in Wave 2 (*path a:* $B = 0.362$, SE = 0.116, $t = 3.115$, $p = 0.003$, 95% CI: 0.130, 0.594) and change (path a: $B = 0.341$, SE = 0.120, $t = 2.852$, $p = 0.006$, 95% CI: 0.102, 0.580). Moreover, in the cross-sectional models, the wake-to-bed slope was not significantly related to global cognition in Waves 1, 2 or in the longitudinal model (change). Nevertheless, an increase in the wake-to-bed slope, indicating a flattened slope, was marginally related to global cognitive decline (*path b*: $B = -0.110$, SE = 0.063, $t = -1.730$, $p = 0.088$). Results did not show a significant indirect effect of neuroticism on global cognition via the wake-to-bed slope in Waves 1, 2 or change (*path ab*: all 95% CI included zero) (Figure 3) (Table 2). Results did not show a direct effect of neuroticism on global cognition in Waves 1, 2 or change (*path c*: all 95% CI included zero).

Moreover, gender significantly moderated the association between the wake-to-bed slope and global cognition in Wave 2 ($B = -0.455$, SE = 0.196, $t = -2.318$, $p = 0.023$, 95% CI: −0.847, −0.064), and between wake-to-bed slope change and global cognition change ($B = -0.227$, SE = 0.115, $t = -2.414$, $p = 0.019$, 95% CI: −0.506, −0.048). Specifically, only in men, a negative association was observed between the wake-to-bed slope and global cognition in both the Wave 2 ($B = -0.318$, SE = 0.138, $t = -2.309$, $p = 0.024$, 95% CI: −0.593, −0.043) and change ($B = -0.237$, SE = 0.081, $t = -2.931$, $p = 0.005$, 95% CI: −0.399, −0.076) models. Furthermore, only in men, a negative indirect effect of neuroticism on global cognition via the wake-to-bed slope was observed in the Wave 2 (*path ab:* $B = -0.111$, SE = 0.062, 95% CI: −0.252, −0.016) and change (*path ab*: $B = -0.076$, SE = 0.047, 95% CI: −0.187, −0.009) models. Finally, gender significantly moderated the mediation models in Wave 2 ($B = -0.159$, SE = 0.093, 95% CI: −0.359, −0.006) and change ($B = -0.089$, SE = 0.056, 95% CI: −0.216, −0.004) (Figure 4) (Table 3).

4 | DISCUSSION

Our main goal was to analyse, in older people, the mediating role of perceived stress and HPA-axis functioning in the association between neuroticism and global cognition in both cross-sectional (Waves 1 and 2) and longitudinal (change) models. Our results showed that higher neuroticism was indirectly related to poorer global cognition via higher perceived stress in Waves 1 and 2. In turn, higher neuroticism was indirectly related to greater baseline (Wave 1) corrected cognitive performance in Wave 2 via increased perceived stress over 4 years. However, the wake-to-bed slope did not mediate the association between neuroticism and global cognition in the cross-sectional or longitudinal models. Moreover, when analysing gender differences, it was observed that perceived stress and the wake-to-bed slope mediated the association between neuroticism and global cognition and decline only in men.

4.1 | Neuroticism, perceived stress and HPA-axis

Neuroticism predicts the tendency to appraise events as highly threatening and coping resources as low (Carver & Connor-

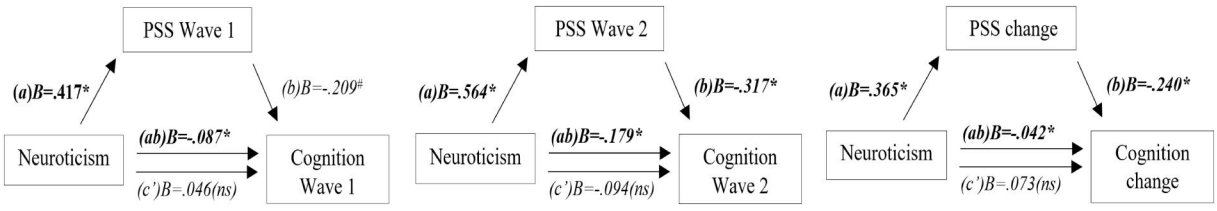

FIGURE 1 Mediation model to test the indirect effect of neuroticism on global cognition via PSS in cross-sectional (Waves 1 and 2) and longitudinal (change) models. *Note.* PSS, Perceived Stress Scale. Values in bold represent significant (CI 95% did not include zero*) or marginal (CI 90% did not include zero#) values

TABLE 2 Mediation analyses to test the indirect effect of neuroticism and cognitive function via the PSS or the wake-to-bed slope, both in cross-sectional (Waves 1 and 2), and longitudinal (change) models

	PSS in Wave 1					PSS in Wave 2					PSS Change				
	B	**SE**	***t***	***p***	**CI 95%**	**B**	**SE**	***t***	***p***	**CI 95%**	**B**	**SE**	***t***	***p***	**CI 95%**
Effect of neuroticism on PSS (a)	**0.417***	**0.101**	**4.119**	**≤0.001**	**0.215, 0.618**	**0.564***	**0.099**	**5.609**	**≤0.001**	**0.367, 0.761**	**0.365***	**0.095**	**3.848**	**≤0.001**	**0.176, 0.554**
Effect of the PSS on cognition (b)	−0.209	0.115	−1.815	0.073	−0.438, 0.020	**−0.317***	**0.111**	**−2.863**	**0.005**	**−0.538, −0.097**	**−0.240***	**0.080**	**−3.008**	**0.004**	**−0.399, −0.081**
Total effect of neuroticism on cognition (c)	−0.041	0.106	−0.392	0.696	−0.252, 0.169	−0.084	0.102	−0.824	0.412	−0.288, 0.120	0.014	0.070	−0.205	0.838	−0.154, 0.125
Direct effect of neuroticism on cognition (c')	0.046	0.115	0.398	0.691	−0.183, 0.274	0.094	0.116	0.811	0.420	−0.137, 0.326	0.073	0.073	1.004	0.319	−0.072, 0.218
Indirect effect: Neuroticism → PSS → cognition (ab)	**−0.087***	**0.049**			**−0.204, −0.012**	**−0.179***	**0.082**			**−0.363, −0.036**	**−0.088***	**0.042**			**−0.181, −0.015**
	Wake-to-bed slope in Wave 1					**Wake-to-bed slope in Wave 2**					**Wake-to-bed slope change**				
	B	**SE**	***t***	***p***	**CI 95%**	**B**	**SE**	***t***	***p***	**CI 95%**	**B**	**SE**	***t***	***p***	**CI 95%**
Effect of neuroticism on wake-to-bed slope (a)	0.132	0.111	1.195	0.236	−0.188, 0.353	**0.362***	**0.116**	**3.115**	**0.003**	**0.130, 0.594**	**0.341***	**0.120**	**2.852**	**0.006**	**0.102, 0.580**
Effect of the wake-to-bed slope on cognition (b)	−0.126	0.110	−1.148	0.254	−0.344, 0.092	−0.112	0.108	−1.032	0.305	−0.328, 0.104	−0.110	0.063	−1.730	0.088	−0.237, 0.017
Total effect of neuroticism on cognition (c)	−0.042	0.107	−0.387	0.700	−0.255, 0.172	−0.090	0.108	−0.840	0.404	−0.305, 0.124	−0.039	0.064	−0.613	0.542	−0.167, 0.088
Direct effect of neuroticism on cognition (c')	−0.025	0.108	−0.230	0.819	−0.240, 0.190	−0.050	0.115	−0.436	0.664	−0.278, 0.178	−0.002	0.067	−0.027	0.979	−0.135, 0.131
Indirect effect: Neuroticism → wake-to-bed slope → cognition (ab)	−0.017	0.022			−0.068, 0.021	−0.041	0.046			−0.143, 0.041	−0.037	0.031			−0.113, 0.007

Note: *Values in bold represent significant values (CI 95% not including zero).

Abbreviation: PSS, Perceived Stress Scale.

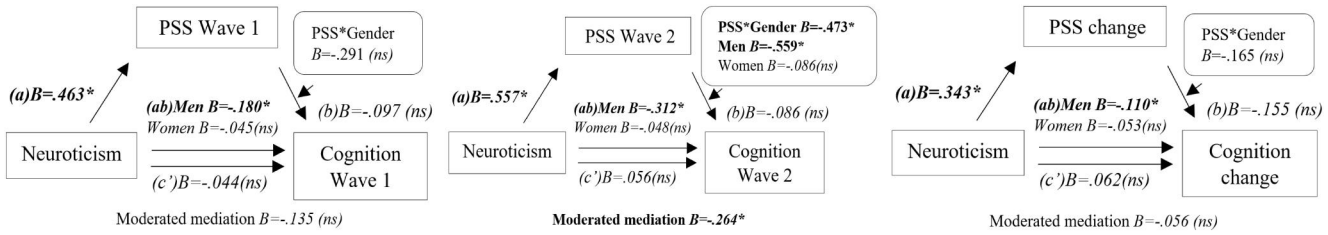

FIGURE 2 Mediation model to test the indirect effect of neuroticism on global cognition via PSS in cross-sectional (Waves 1 and 2) and longitudinal (change) models, including PSS*gender moderations. *Note.* PSS, Perceived Stress Scale. Values in bold represent significant values (CI 95% did not include zero*)

Smith, 2010), leading to higher psychological distress (Lahey, 2009). Thus, as we hypothesized, our results showed that higher neuroticism was related to greater perceived stress (Waves 1 and 2), as previously reported (Ebstrup et al., 2011), and to increased perceived stress over 4 years (change).

Similarly, we also observed that neuroticism was related to a flattened wake-to-bed slope in Wave 2 and to a flattening of the wake-to-bed slope over 4 years (change). We expected to observe these findings because individuals higher in neuroticism are more likely to experience stressful events (Lahey, 2009), and, in turn, chronic stress has been related to a flattened DCS (Miller et al., 2007). Moreover, supporting our findings, a recent study with participants with high neuroticism reported increasing stress experienced over 12 years and increasingly flatter cortisol slopes over time (Herriot et al., 2020). However, we failed to find a significant association between neuroticism and the wake-to-bed slope in Wave 1, possibly because individuals higher in neuroticism tend to experience greater distress (Lahey, 2009), and the cumulative impact of stress over time would lead to HPA-axis dysregulation and predispose these individuals to disease, as proposed by the allostatic load model (McEwen, 2002; McEwen & Stellar, 1993). Thus, Weston et al. (2015) suggested that the link between neuroticism and health may be cumulative over time, and this personality trait could have a greater influence on disease in older ages.

4.2 | Perceived stress, HPA-axis and cognitive functioning

As we expected, higher perceived stress was associated with poorer global cognition (only marginally in Wave 1 and significantly in Wave 2), as in other studies (Aggarwal et al., 2014; Chen et al., 2019). Moreover, an increase in perceived stress was related to a decline in global cognition. Several longitudinal studies in older adults observed that perceived stress at baseline was related to cognitive decline (Aggarwal et al., 2014; Munoz et al. 2015; Turner et al., 2017). However, contrary to our results, other 2-year follow-up studies failed to observe an association between change in perceived stress and change in processing speed, attention, working memory (Munoz et al., 2015), delayed recall and verbal fluency (Feeney et al., 2018). Nevertheless, Feeney et al. (2018) observed that an increase in perceived stress was related to a decline in immediate recall, which is similar to our findings. Thus, our results show that, at least in a 4-year follow-up study, an increase in perceived stress would predict a decline in global cognition.

Moreover, contrary to what we expected, we failed to find an association between the wake-to-bed slope and global cognition in the two cross-sectional studies (Waves 1 and 2). Supporting our findings, a review and meta-analysis concluded that there was weak evidence that greater diurnal decline was related to improvements found at older ages in cross-sectional studies (Gardner et al., 2019). However, a more recent study carried out with two large longitudinal datasets concluded that loss of diurnal variation in the HPA-axis (a flattened DCS) preceded and contributed to cognitive decline later in life (Tsui et al., 2020). Furthermore, in a long follow-up study, Ennis et al. (2017) suggested that cortisol dysregulations may be a preclinical marker of Alzheimer's disease. Although only marginally, our results showed that a flattening wake-to-bed slope was related to a decline in global cognition over 4 years. Singh-Manoux et al. (2014) suggested that the relationship between HPA-axis dysregulation and cognition only became evident at older ages, which is a sensitive period for cognitive decline, but not at younger ones. Moreover, as the allostatic load model indicates, the influence of stress on HPA-axis dysregulation and, in turn, on cognitive outcomes seems to increase over time (McEwen, 2002; McEwen & Stellar, 1993). Thus, it is possible that, given that our study was carried out with a healthy older sample, a longer follow-up (leading to an older sample) would be needed to observe an association between HPA-axis dysregulation and cognitive decline.

However, although for the total sample we failed to observe an association between HPA-axis dysfunction and global cognition in the cross-sectional or longitudinal models, we observed that gender moderated these associations in Wave 2, as well as change in cognition and the HPA-axis. Similarly, gender also moderated the association between perceived stress and global cognition only in Wave 2. In their review, Gaffey et al. (2016) highlighted the importance of considering age and gender when analysing stress and the HPA-axis in ageing because these two sociodemographic characteristics could explain discrepancies in the research. Two previous studies failed to observe gender moderation in the association between perceived stress and cognitive functioning (Aggarwal et al., 2014; Munoz et al., 2015). Similarly, we did not find that gender

TABLE 3 Mediation analyses to test the indirect effect of neuroticism and cognitive function via the PSS or the wake-to-bed slope, both in cross-sectional (Waves 1 and 2), and longitudinal (change) models, including wake-to-bed slope*gender or PSS*gender moderations

	PSS in Wave 1					PSS in Wave 2					PSS Change				
	B	**SE**	***t***	***p***	**CI 95%**	**B**	**SE**	***t***	***p***	**CI 95%**	**B**	**SE**	***t***	***p***	**CI 95%**
Effect of neuroticism on PSS (a)	**0.463***	**0.099**	**4.696**	**≤0.001**	**0.267, 0.659**	**0.557***	**0.094**	**5.809**	**≤0.001**	**0.370, 0.745**	**0.343***	**0.094**	**3.667**	**≤0.001**	**0.157, 0.530**
Effect of the PSS on cognition (b)	−0.097	0.142	−0.683	0.497	−0.379, 0.185	−0.086	0.140	−0.618	0.538	−0.365, 0.192	−0.155	0.101	−1.531	0.130	−0.357, 0.047
Gender*PSS	−0.291	0.216	−1.346	0.182	−0.722, 0.140	**−0.473***	**0.184**	**−2.564**	**0.012**	**−0.840, −0.106**	−0.165	0.122	−1.344	0.183	−0.408, 0.079
Women						−0.086	0.140	−0.618	0.538	−0.365, 0.192					
Men						**−0.559***	**0.143**	**−3.918**	**≤0.001**	**−0.843, −0.275**					
Direct effect of neuroticism on cognition (c')	0.044	0.114	0.389	0.699	−0.183, 0.272	0.056	0.113	0.495	0.622	−0.170, 0.282	0.062	0.073	0.850	0.398	−0.083, 0.207
Women indirect effect: Neuroticism → PSS → cognition (ab)	−0.045	0.053			−0.167, 0.045	−0.048	0.069			−0.197, 0.076	−0.053	0.039			−0.136, 0.013
Men indirect effect: Neuroticism → PSS → cognition (ab)	**−0.180***	**0.095**			**−0.384, −0.015**	**−0.312***	**0.132**			**−0.594, −0.072**	**−0.110**	**0.063**			**−0.259, −0.013**
Moderated mediation	−0.135	0.105			−0.350, 0.061	**−0.264***	**0.144**			**−0.555, −0.001**	−0.056	0.062			−0.193, 0.055

	Wake-to-bed slope in Wave 1					Wake-to-bed slope in Wave 2					Wake-to-bed slope change				
	B	**SE**	***t***	***P***	**CI 95%**	**B**	**SE**	***t***	***p***	**CI 95%**	**B**	**SE**	***t***	***p***	**CI 95%**
Effect of neuroticism on wake-to-bed slope (a)	0.161	0.106	1.514	0.134	−0.051, 0.373	**0.348***	**0.109**	**3.186**	**0.002**	**0.130, 0.566**	**0.321***	**0.114**	**2.808**	**0.006**	**0.093, 0.550**
Effect of the wake-to-bed slope on cognition (b)	−0.326	0.166	−1.966	0.053	−0.656, 0.004	0.137	0.150	0.913	0.364	−0.163, 0.437	0.040	0.087	0.457	0.649	−0.134, 0.214
Gender* wake-to-bed slope	0.355	0.223	1.597	0.114	−0.088, 0.799	**−0.455***	**0.196**	**−2.318**	**0.023**	**−0.847, −0.064**	**−0.227***	**0.115**	**−2.414**	**0.019**	**−0.506, −0.048**
Women						0.137	0.150	0.913	0.364	−0.163, 0.437	0.040	0.087	0.457	0.649	−0.134, 0.214
Men						**−0.318***	**0.138**	**−2.309**	**0.024**	**−0.593, −0.043**	**−0.237***	**0.081**	**−2.931**	**0.005**	**−0.399, −0.076**
Direct effect of neuroticism on cognition (c')	−0.019	0.107	−0.177	0.860	−0.232, 0.194	−0.059	0.111	−0.528	0.599	−0.281, 0.163	−0.009	0.065	−0.145	0.885	−0.138, 0.119

TABLE 3 (Continued)

	Wake-to-bed slope in Wave 1					Wake-to-bed slope in Wave 2					Wake-to-bed slope change				
	B	SE	t	P	CI 95%	B	SE	t	p	CI 95%	B	SE	t	p	CI 95%
Women indirect effect: Neuroticism → wake-to-bed slope → cognition (ab)	−0.053	0.039			−0.140, 0.011	0.048	0.059			−0.068, 0.162	0.013	0.028			−0.049, 0.067
Men indirect effect: Neuroticism → wake-to-bed slope → cognition (ab)	0.005	0.026			−0.046, 0.064	**−0.111***	**0.062**			**−0.252, −0.016**	**−0.076***	**0.047**			**−0.187, −0.009**
Moderated mediation	0.057	0.049			−0.015, 0.171	**−0.159***	**0.093**			**−0.359, −0.006**	**−0.089***	**0.056**			**−0.216, −0.004**

Note: Values in bold represent significant values (CI 95% did not include zero*).
Abbreviation: PSS, Perceived Stress Scale.

moderated these associations in Wave 1 or in the longitudinal model. However, in Wave 2, an association between higher perceived stress and lower cognitive functioning was observed only in men. Similarly, results showed that, in Wave 2, a flattened wake-to-bed slope was associated with poorer global cognition also only in men. Moreover, only in men, a flattening of the wake-to-bed slope was related to greater cognitive decline over 4 years (change). However, we did not observe an association between the wake-to-bed slope and cognitive functioning or gender differences in Wave 1 (mean age = 65 years), as in other studies with samples with similar (mean age = 64.47 years) (Hidalgo et al., 2016) or younger (mean age = 61 years) (Singh-Manoux et al., 2014) ages. Thus, our results suggest that the association between HPA-axis and cognitive functioning may only be detected in men, and at older ages. Supporting these findings, it has been suggested that although an allostatic mediator (HPA-axis) would produce wear and tear on the body and brain, where the ageing brain seems more vulnerable, oestrogens appear to provide resilience against stress (McEwen, 2002). Moreover, some studies reported that older age and the male gender were associated with flattened DCSs (Adam et al., 2006; Dmitrieva et al., 2013), as well as with a greater cortisol peak, nadir and overall output (AUC) (Karlamangla et al., 2013), indicating HPA-axis dysregulation. In addition, Gaffey et al. (2016) argued that this age-related HPA-axis dysregulation in men could reflect greater cumulative stress because men generally show a greater cortisol acute stress response (Kudielka & Kirschbaum, 2005).

4.3 | Mediation of perceived stress and the HPA-axis in the association between neuroticism and global cognition

As we hypothesized, perceived stress mediated the association between neuroticism and global cognition in the cross-sectional models (Waves 1 and 2). Moreover, increased perceived stress also mediated the association between neuroticism and cognitive decline over 4 years (change). However, contrary to our expectations, the wake-to-bed slope did not mediate the neuroticism and cognitive functioning (Waves 1 and 2) or decline (change) relationship when considering the total sample. Interestingly, our results showed that, only in men, a flatter wake-to-bed slope mediated the association between neuroticism and global cognition, but only in Wave 2. Similarly, a flattening of the wake-to-bed slope was related to greater cognitive decline over 4 years only in men. Moreover, perceived stress mediated the negative association between neuroticism and global cognition in both the cross-sectional and longitudinal models in men, but not in women (although the moderated mediation was only significant in Wave 2). Therefore, our results show that both psychological and physiological stress could be mechanisms underlying the relationship between neuroticism and cognitive function and decline, mainly in men. Supporting our findings, Wilson et al. (2007) found that the association between neuroticism and risk of Mild Cognitive Impairment was stronger in

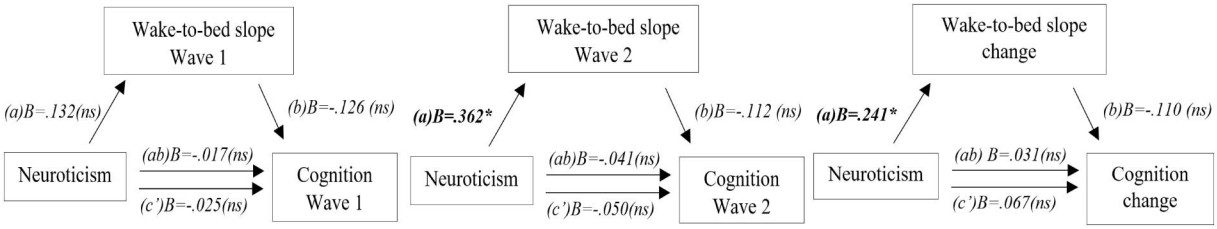

FIGURE 3 Mediation models to test the indirect effect of neuroticism on global cognition via wake-to-bed slope in cross-sectional (Waves 1 and 2) and longitudinal (change) models. *Note*. Values in bold represent significant values (CI 95% did not include zero*)

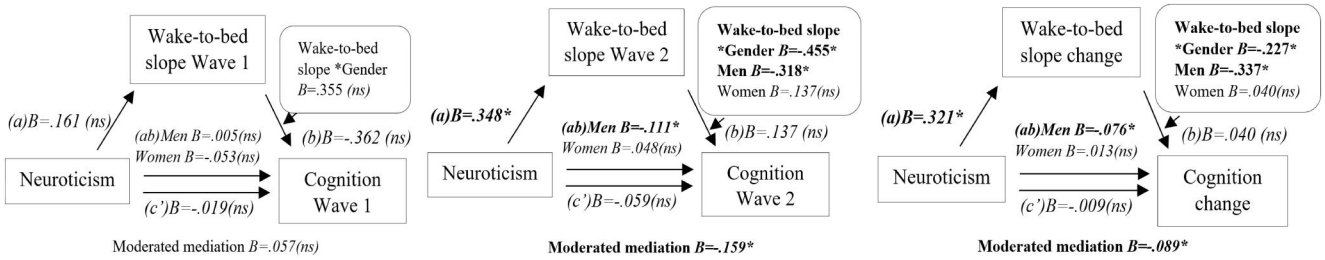

FIGURE 4 Mediation model to test the indirect effect of neuroticism on global cognition via wake-to-bed slope in cross-sectional (Waves 1 and 2) and longitudinal (change) models, including wake-to-bed slope*gender moderations. *Note*. Values in bold represent significant values (CI 95% did not include zero*)

men than in women. It is important to note that, although our results showed that higher neuroticism was indirectly related to poorer global cognition via higher perceived stress and HPA-axis dysregulation (in men), we did not observe that higher neuroticism was directly related to poorer global cognition or greater cognitive decline, as found in other studies (Jelicic et al., 2003; Williams et al., 2013). Thus, this result highlights the complex dynamics underlying the association between neuroticism and cognitive functioning and the importance of exploring the mechanisms involved in this relationship in order to shed light on this question. Moreover, although neuroticism was related to both the psychological (perceived stress) and physiological (HPA-axis) stress components, which were in turn related to global cognition, these components were not related to each other (see supplementary material: Table S1), as in other studies (Geng et al., 2016; Strait et al., 2018), confirming the different nature of these mechanisms, rather than a mere overlap.

Some limitations should be considered. First, neuroticism was only assessed at follow-up. Although there is a large body of longitudinal research on mean-level changes that show that neuroticism remains stable later in life (Costa & McCrae, 1980, 1990, 1994; Martin et al., 2002; Steunenberg et al., 2005), more recent studies reported lower personality stability in the oldest ages (Lucas & Donnellan, 2011; Specht et al., 2011; Terracciano et al., 2018; Wortman et al., 2012). Moreover, the optimal number to assess the DCS is 3–6 samples per day (Adam et al., 2017), whereas we included only two samples. In addition, the wake-to-bed slope was assessed on three consecutive days in Wave 2, but only on two days in Wave 1. However, the number of days does not appear to increase the size of the association between the DCS and health outcomes (Adam et al., 2017). In addition, the strict exclusion criteria make it possible to obtain a healthy older sample and control the effect of confounding variables, but the results cannot be generalized to all older people. Moreover, the small sample size provided limited statistical power, especially for the analysis assessing gender differences. Thus, future studies should include a larger sample size to obtain greater statistical power when investigating the association between neuroticism and change in the DCS. However, our study also has important methodological strengths. The PSS, wake-to-bed slope and global cognition were assessed in Waves 1 and 2. Moreover, global cognition was assessed with a large neuropsychological battery that included different cognitive domains, and the wake-to-bed slopes were measured on 2–3 consecutive days. Furthermore, this is the first study to explore the mediating role of both psychological and physiological stress components simultaneously in the association between neuroticism and global cognition/change in older men and women.

In conclusion, our results suggest that both higher levels of perceived stress and HPA-axis dysregulation could be mediating mechanisms underlying the association between neuroticism and poorer cognitive functioning and greater cognitive decline, at least in older men. This result would be due to the fact that men seem to be more vulnerable to the adverse effects of both psychological and physiological stress on global cognition. Therefore, early detection of individuals with high neuroticism and interventions to modify stress and anxiety management could be especially useful to prevent cognitive decline in older men.

Finally, our results may have important practical implications, given that the ultimate goal of research on personality and health is to create effective interventions to promote health. Although

neuroticism is a relatively stable trait, some related cognitive-behavioural patterns can be modified, such as stress and anxiety management (Lahey, 2009). Therefore, early detection of individuals with higher risk (high neuroticism) and the implementation of preventive interventions to modify stress and anxiety management may help to prevent cognitive decline, especially in older men.

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CONFLICT OF INTEREST

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions. Teresa Montoliu: conception and design, acquisition of data, analysis and interpretation of data, and drafting the manuscript. Matías M. Pulopulos: conception and design, acquisition of data, and revising the manuscript. Sara Puig-Pérez: conception and design, acquisition of data, and revising the manuscript. Vanesa Hidalgo: conception and design, and revising the manuscript. Alicia Salvador: conception and design, and revising the manuscript. All authors given the final approval of the manuscript, and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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