Sex differences in cortisol and memory following acute social stress in amnestic mild cognitive impairment

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Highlights:

- Amnestic MCI (aMCI) is associated with higher morning cortisol
- Stress negatively influences memory in aMCI individuals
- Sex may moderate the effects of aMCI on cortisol and memory following stress
- The relationship between cortisol and memory may depend on brain health

Abstract

Older adults with amnesic mild cognitive impairment (aMCI) develop Alzheimer's-type Dementia approximately ten times faster annually than the normal population. Higher levels of adrenal hormones are associated with both aging and cognitive decline. In this study, salivary cortisol was sampled diurnally and during memory testing to explore differences in the relationship between cortisol and memory function in males and females with normal cognition and those with aMCI. Participants with aMCI (n=14, mean age=75) were compared to age-matched controls (n=14, mean age=75) on tests of episodic, associative, and working memory across two sessions with a psychosocial stressor in the second session. The aMCI group performed worse on the memory tests than controls and males with aMCI had consistently elevated cortisol levels on both test days. Immediate episodic memory performance was enhanced by stress in controls but not in the aMCI group, indicating that aMCI is associated with increased vulnerability to stress-induced alterations in cortisol that can negatively impact memory function.

KEYWORDS: cortisol, mild cognitive impairment, normal aging, memory, stress, psychosocial stressor, sex differences, men, women, aMCI

1. Introduction

Normal aging results in declines in some cognitive domains, such as episodic memory, but not others, such as fund of knowledge (Cullum et al., 2000; Hedden & Gabrieli, 2004). Cognitive decline with aging is correlated with region specific changes in prefrontal cortex and medial temporal lobe (MTL), a key change being hippocampal volume loss (Raz, 2000; Raz & Rodrigue, 2006). These declines are accelerated in Alzheimer's Disease (AD)(Mungas et al., 2002; Shi, Liu, Zhou, Yu, & Jiang, 2009). Older adults with mild cognitive impairment (MCI) develop AD at a rate of 10-30% annually, depending on MCI subtype, whereas those without MCI develop dementia at a rate of only 1% to 2% annually (Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003; Dawe, Procter, & Philpot, 1992; Lupien et al., 1998; Petersen et al., 1999). Thus, it is critical to identify neurobiological factors that may distinguish MCI from normal aging, such as differences in cortisol levels and their response to stress.

The stress hormone cortisol has been linked to memory performance, AD, and hippocampal volume (Lupien et al., 1998; Newcomer et al., 1999; Pruessner, Pruessner, Hellhammer, Bruce Pike, & Lupien, 2007). Indeed, AD participants have higher levels of plasma cortisol than controls (Hartmann, Veldhuis, Deuschle, Standhardt, & Heuser, 1997) and cerebrospinal fluid cortisol levels are higher in AD or MCI of AD type (aMCI) participants, as compared to controls or MCI of other types. Moreover, aMCI individuals with higher baseline cerebrospinal fluid cortisol levels experienced accelerated clinical worsening and cognitive decline (Popp et al., 2015). That study, however, did not measure diurnal cortisol or biological sex, both factors which may contribute to the findings. Although previous studies have identified sex differences in cortisol levels in response to stress (Kirschbaum, Wüst, & Hellhammer, 1992; Kudielka & Kirschbaum, 2005), few studies to date have examined the relationships between cortisol, stress, and memory and potential differences between males and females, particularly with regards to MCI or AD.

Sex differences are seen in incidence of MCI (Au, Dale-McGrath, & Tierney, 2017; Burke et al., 2019; Gale, Baxter, & Thompson, 2016; Koran, Wagener, Hohman, & Alzheimer's Neuroimaging Initiative, 2017; Mielke, Vemuri, & Rocca, 2014), with males more likely to develop MCI (both amnestic [aMCI] and non-amnestic subtypes) than females (Caracciolo et al., 2008; Jack et al., 2019; Roberts et al., 2012), although there are conflicting reports that are likely due to methodological differences (e.g. (Au et al., 2017; Mielke et al.,

2014)). However, AD disproportionately affects females, with significant sex differences observed with regards to severity, neuropathological markers, and rates of cognitive decline (Duarte-Guterman et al., 2019; Hebert, Weuve, Scherr, & Evans, 2013; Irvine, Laws, Gale, & Kondel, 2012; Sohn et al., 2018). Sex differences in incidence of AD is not uniformly seen (Jack et al., 2019) and may depend on geographic location (reviewed by Nebel et al 2018) or to men dying at younger ages (prior to development of or progression to AD) from other causes (Mielke et al., 2014). However, there are other sex differences in MCI to AD progression and symptom severity in AD. For example, women tend to develop MCI at a later age, perhaps benefitting from their established superior verbal memory (Sundermann et al., 2017), but progress to AD more rapidly than men when adjusted for age (Andersen et al., 1999; Fratiglioni et al., 1997; Letenneur et al., 1999; Liu et al., 1998; Ott et al., 1999; Roberts et al., 2014; Ruitenberg, Ott, van Swieten, Hofman, & Breteler, 2001; Yoshitake et al., 1995). In a recent meta-analysis, sex differences in AD diagnosis and pathology were most pronounced in participants with MCI (Koran et al., 2017). Of MCI individuals who had increased AD biomarkers (i.e. total-tau and amyloid-beta [Aβ42] ratio in cerebrospinal fluid), declines in cognitive ability were significantly worse in women compared to men (Sohn et al., 2018). The differences in verbal learning and delayed recall, as well as visual learning and memory, between healthy and MCI women were significantly greater than between healthy and MCI men (Gale et al., 2016). These differences persisted in those with AD (Gale et al., 2016). Thus, sex differences in severity and progression to AD are seen in individuals with MCI and identifying the biological causes of this phenomenon is critical to treatment and prevention.

Gonadal production of sex steroids is reduced, but not entirely eliminated, with age in women and, to a lesser extent, men; however, adrenal cortisol production increases with age (Laughlin & Barrett-Connor, 2000; Yen & Laughlin, 1998). Intriguingly, in addition to producing the stress hormone cortisol, the adrenal glands are also capable of producing androgens, which can be converted to estrogens in many tissues, including in the brain. While both sexes show increased cortisol levels with increased age, this effect is 3 times more pronounced in women (Otte et al., 2005) and increased cortisol levels are linked to poorer cognition and smaller hippocampal volume in older age (Lupien et al., 1998). Furthermore, women with AD present with more affective symptoms, increased hippocampal atrophy, and faster cognitive decline than men (Holland, Desikan, Dale, McEvoy, & Alzheimer's Disease Neuroimaging Initiative, 2013; Hua et al., 2010; Sinforiani et al., 2010), highlighting that

the underlying pathophysiology of AD may be different in men and women and should be further explored. Although sex differences in AD have been identified, studies are scarce and even more so in MCI groups.

In this study we explored the relationship between diurnal fluctuations in cortisol, stress-induced cortisol, and memory performance in aMCI and control participants. A spatial working memory task known to be reliant on the integrity of the prefrontal cortex (Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998) and an episodic and associative memory task known to be reliant on hippocampal integrity (Eichenbaum, 2017) were selected based on the known affinity of cortisol for these brain regions (Dedovic, Duchesne, Andrews, Engert, & Pruessner, 2009) and the potential of fluctuations in cortisol to influence cognitive efficiencies (Lupien, McEwen, Gunnar, & Heim, 2009). Because little is known as to whether there are sex differences in the relationship between aMCI and cortisol, we also used exploratory analyses of sex effects in the present study. We hypothesized that diurnal increases in cortisol release and increased release under stress, *via* the application of a psychosocial stressor (Trier Social Stress Test)(Kirschbaum, Pirke, & Hellhammer, 1993), would worsen memory scores in individuals with aMCI compared to controls and that there would be sex differences in these effects.

2. Methods

2.1 Participants

Older adults with age-normal memory (controls) and with mild memory decline (aMCI) suggestive of neurodegenerative disease of the Alzheimer type (Albert et al., 2011) were recruited for this study and provided informed voluntary consent to participate. As Table 1 shows, there was no significant difference in the ratio of females to males between the two participant groups (χ=0.72; p<0.39) nor were there group differences on demographic variables relating to age, education, estimated verbal intellectual ability, or mood status (all ps>0.43). Although participants in the aMCI group performed within the normal range on a general index of cognitive status (Mini Mental Status Examination [MMSE])(Folstein, Folstein, & McHugh, 1975), their overall performance was significantly lower than the controls ($t_{(1,26)}$=2.36 p<0.05, d=0.89). A detailed description of the participant groups follows.

Table 1: *Demographic and Descriptive Data for the Participant Groups*

	Control (n = 14)	aMCI (n = 14)	Cohen's d
Age (years)	75.3 (8.7)	74.6 (8.0)	0.08
Female:Male ratio	7:7	5:9	
Education (years)	14.4 (3.5)	14.9 (3.0)	0.15
MMSE	29.0 (1.0)	27.7 (1.9)	0.89
Vocabulary SS	13.6 (2.9)	13.8 (2.7)	0.07
HADS Depression Scale	2.6 (2.3)	2.6 (2.3)	0
HADS Anxiety Scale	5.1 (3.8)	5.6 (2.5)	0.16

Note. Mean scores with standard deviations in parentheses. aMCI = amnestic mild cognitive impairment; MMSE = Mini-Mental Status Exam; SS = age-corrected scaled score. HADS = Hospital Anxiety Depression Scale with scores < 7 considered within normal limits.

2.1.1. Control group. Fourteen healthy older adults (age 61-86 years) were recruited *via* community talks, newspaper advertisements, and databases of research volunteers. Prior to invitation to participate, normal general cognitive status, using the Telephone Interview for Cognitive Status (Brandt, Spencer, & Folstein, 1988), and health status were confirmed in a telephone screening interview. At the first of two sessions, health history was further queried to verify that there was no history of a neurological, medical, or psychiatric disorder, substance abuse, or medications affecting cognition. Performance was within normal limits for age and education on measures of: a) general cognitive status (MMSE)(Folstein et al., 1975); b) memory (Rey-Osterrieth Figure Recall)(Spreen & Strauss, 1998); and c) self-reported mood (Hospital Anxiety and Depression Scale, HADS)(Zigmond & Snaith, 1983).

2.1.2. aMCI group. Fourteen individuals (age 59-85 years), recruited from physician referrals, from databases of research volunteers, and from newspaper advertisement, were classified as meeting the National Institute on Aging-Alzheimer's Association classification criteria for aMCI (Albert et al., 2011). The aMCI

status of 11 participants had been previously established and the stability of this classification was confirmed by the interview and neuropsychological testing administered during session 1. Three additional aMCI participants were identified based on the session 1 testing.

2.2. Procedure

Participants completed alternate versions of episodic, associative, and spatial memory tasks across two test sessions (Figure 1) conducted 7-14 days apart. Multiple salivary cortisol samples were taken using the Salivette™ method (Sarstedt Inc, Sarstedtstraße, Numbrecht, Germany). All memory tests were completed in the morning between 10:00h and 12:00h. Saliva was collected at 10:10h and 12:00h at the first test session. Basal salivary cortisol samples were taken from participants across three agreed upon days intervening between the test sessions. Participants were instructed not to eat, drink, or smoke for at least 30 minutes prior to saliva collection and to rinse their mouths with water 5 minutes before collecting the saliva. Five samples were collected per day on the following schedule: 30-minutes after awakening (ranged from 5:30 am to 8:30h), 09:00, 16:00, 19:00, and 21:00h. Phone call reminders and verifications were provided by the examiner for each of the 4 specified clock times on all three collection days. Participants were given pre-labeled saliva collection tubes and instructed to store their collected samples in the home refrigerator. Collection time of day was further verified by requiring participants to record the collection time on a label provided on the collection tube. The basal samples were gathered from participants when they returned for the second test session. Additional saliva samples were collected during the second session on the following schedule: 10:10h; immediately following the anticipation period to the application of a psychosocial stressor (~10:30h); 30 minutes following the application of the psychosocial stressor (~11:00h); and at about 12:00h, at the conclusion of the second test session. At the end of the study all saliva samples were packed in dry ice and shipped for analysis to the University of Western Ontario (EH, London, Ontario).

In addition to the memory tests of interest administered during both test sessions (see sections 2.2.1.-2.2.3.), the following neuropsychological measures were administered during session 1: cognitive screening (MMSE; (Folstein et al., 1975)), self-reported mood (HADS; (Zigmond & Snaith, 1983)), auditory attention span (Digit Span; (Wechsler, 1997)), confrontation naming (Boston Naming Test; (Kaplan, Goodglass, &

Weintraub, 1983)), visuospatial construction and immediate recall (Rey-Osterrieth Complex Figure-copy; (Spreen & Strauss, 1998)), and the Trail Making Test (Delis, Kaplan, & Kramer, 2001; Spreen & Strauss, 1998). Variations of certain neuropsychological measures were also administered during session 2, including self-reported mood status (Beck Depression Inventory, (Beck, Steer, & Carbin, 1988) and Coping Strategies Scale, (Robinson et al., 1997)) and Trail Making Test (Delis et al., 2001; Spreen & Strauss, 1998). Participant groups performed similarly on these neuropsychological measures, except in the measures of immediate memory for a complex figure ($F_{(1,24)}$=11.11, p=0.003, η^2=0.316) and Trail Making Test B ($F_{(1,26)}$=7.852, p=0.009, η^2=0.232). Although aMCI participants were significantly poorer than matched controls on these latter two measures, only performance on the immediate recall of the complex figure was below expectations based on normative data for age and education. The psychosocial stressor was applied during the second test session and is described subsequent to the memory tasks of interest.

2.2.1. Episodic memory. Two highly correlated versions (forms 5 and 6) of the HVLT-R (Brandt & Benedict, 2001) were used (Session 1: form 6; Session 2: form 5; with the exception of one aMCI participant to whom they were presented in the opposite order). This task involves an oral presentation of a 12-item word list over three learning trials, followed by a 20-minute delayed recall trial and a forced choice yes/no recognition trial. The recognition trial consists of 24 items comprised of the 12 target words, six semantically related foils, and six un-related foils. Measures of interest included total recall across three learning trials, total delayed recall, retention, and recognition discrimination accuracy measured as hits minus false alarms (H-FA).

2.2.2. Associative recognition. A face-name associative recognition test, created by Troyer and colleagues ((Troyer, D'Souza, Vandermorris, & Murphy, 2011; Troyer et al., 2012); modeled after (Mayes et al., 2004)), was used. Stimuli consisted of visually presented black-and-white images of faces (half male and half female) paired with aurally presented first names. Two versions of the task were used, each with 28 gender-appropriate face-name pairs. During the task, 20 faces were individually presented on the computer screen for 6 seconds each with an inter-stimulus interval of 0.5 seconds; the examiner read the name associated with each face at the onset of each new face stimulus. Two study phases, differing only in stimulus presentation order, were administered in succession because our previous research (Troyer et al., 2008) indicated that item memory and association memory differences increase after repeated learning trials. Only 16 of the 20 face-name pairs

were considered test items as the first and last pairs in each study phase presentation were excluded to reduce primacy and recency effects on recognition accuracy. Following a 30 second delay, yes/no recognition testing was conducted with 24 face-name pairs presented, including eight intact pairs, eight recombined pairs, and eight new pairs presented in random order. During testing the examiner orally presented the name in the form of a question "Did I tell you this was [NAME]?" when the face appeared on the screen. Participants were instructed to say "yes" only to faces they had seen before that were paired with the correct name and "no" to faces they had not seen before, faces that were paired with the wrong name, or names they had not heard before. Immediately following testing, procedure verification was undertaken (i.e. participants retold the yes/no rules to the examiner). Participants were presented with unique, but equivalent (Troyer et al., 2011), sets of face-name pairs during sessions 1 and 2. Because we were specifically interested in memory for accurate associations, we manipulated the computation formula A' = ½ [(H-FA)(1+H-FA)] / 4H(1-FA)] developed by (Grier, 1971) and reviewed by (Donaldson, 1992)) where H = the proportion of correctly identified intact pairs and FA = the proportion of false alarms to recombined pairs.

2.2.3 Spatial working memory. This task was modeled after the stimuli and procedures of Duff and Hampson (Duff & Hampson, 2000, 2001). A 4x5 rectangular array, measuring approximately 27cm in length and 34cm in width, consisting of coloured squares (10 colours, each represented twice) that were hidden under removable covers, was presented on a tabletop at which participants were seated. The coloured squares were randomly arranged on a uniform white backing and completely concealed beneath uniform white covers that could be temporarily lifted by participants to reveal the coloured square beneath. Participants were instructed to find all 10 pairs of matching coloured squares in as few choices as possible by lifting the covers two at a time. Prior to beginning the task, participants were familiarized with the colours of the test stimuli by having them view and name a set of 10 individual coloured squares. Each time a matching pair was located on the stimulus array, the examiner placed an individual coloured square representing the colour of the pair discovered at the top of the rectangular array, so participants did not need to remember which colour pairs had been found. Measures of interest included: the number of choices (squares uncovered) made in discovering all 10 matching pairs (criterion) and the time taken to reach criterion. Participants were told they would be timed and that they should attempt to locate all 10 pairs in as few choices as possible. Once they reached criterion, a second trial was

immediately administered, with a third trial administered following a 30-minute delay. The second trial permitted examination of immediate memory for the discovered locations and the third trial, after a delay, permitted examination of maintenance or continued savings on participants' efficiencies in reaching criterion. Locations of the coloured squares was constant within session but changed between sessions 1 and 2.

2.2.4. Psychosocial stressor. The psychosocial stressor used in this study was modeled after the TSST (Kirschbaum et al., 1993). The stressor was introduced immediately following the first saliva collection at 10:10h. Participants were instructed to prepare a five-minute speech on the topic of '*The effect of tuna fishing on the dolphins and other ocean animals*' to be presented to a panel of three evaluators, including the examiner. They were given a pencil and paper and told to write down the points they would like to make in their speech for which they would have 10-minutes to prepare. The examiner then left the room and returned 10 minutes later, collected a saliva sample from the participant (anticipation period), and then led the participant to a conference room to give their speech. Participants were instructed to leave their written notes behind, to give their speech from memory, and to try and speak for five minutes, which was timed by the examiner. Immediately following the public speech, participants engaged in a five-minute serial subtraction task in which they were asked to count backwards aloud by 13 from the number 1022 as quickly and accurately as possible in front of the panel of evaluators. When an error was committed the participant was instructed to begin again from the number 1022. Following the subtraction task, participants were led back to the test room to undertake further memory testing and to provide additional saliva samples.

Session 1

10:00	Consent, interview, and instructions
10:10	Saliva Sample #1
10:15	Face / Name Associative Memory Version A – Immediate
10:30	Hopkins Verbal Learning Test-Revised: Form 6 – Immediate
10:35	Spatial Working Memory Version A – Immediate
10:45	Trail Making Test – A & B
10:50	Face / Name Associative Memory Version A - Delay
10:58	Hopkins Verbal Learning Test-Revised: Form 6 - Delay
11:00	Mini-Mental Status Exam
11:05	Spatial Working Memory Version A – Delay (20-25 minutes)
11:10	WAIS-III Digit Span
11:20	Boston Naming Test (split half - odds)
11:30	Rey-Osterreith Figure Copy and Immediate Recall
11:40	WAIS-III Vocabulary (split half - odds)
11:50	Hospital Anxiety and Depression Scale
11:55	Saliva Sample #2, schedule at-home saliva collection, book session 2
12:05	Session ends

Session 2

10:00	Beck's Anxiety and Depression Inventories
10:10	Saliva sample #1 (~20 minutes before TSST)
10:13	Instructions and consent for Trier Social Stress Test
10:18	Trier Social Stress Test – preparation of speech
10:28	Saliva sample #2 (immediately before TSST Speech)
10:31	Trier Social Stress Test
10:43	Hopkins Verbal Learning Test-Revised: Form 5 – Immediate
10:48	Face / Name Associative Memory Version B – Immediate
11:03	Saliva Sample #3 (~30 minutes after beginning of TSST)
11:06	Spatial Working Memory Version B – Immediate
11:16	Hopkins Verbal Learning Test-Revised: Form 5 – Delay
11:18	Face / Name Associative Memory Version B – Delay
11:23	Spatial Working Memory Version B – Delay
11:28	Trail Making Test – A
11:33	Coping Strategies Scale, SF-36 Health Survey
11:43	Saliva Sample #4 (~60 minutes after beginning of TSST)
11:44	Session ends

Figure 1. Timeline of Sessions and Testing within Sessions. Exact times varied based on individual variability.

2.3. Saliva Collection and Analysis

Saliva was collected using the Salivette™ method, centrifuged at 1500g, and kept frozen at -20°C prior to analysis. Cotton-based collection is suitable for cortisol determinations but not for sex steroids, whose concentrations can be inflated as much as 200% by the use of cotton devices (Büttler et al., 2018). Salivary cortisol was analyzed in duplicate by the Neuroendocrinology Assay Laboratory at the University of Western Ontario. An established ^{125}I solid-phase radioimmunoassay was used (Norman et al., 2010), based on antibody and tracer obtained from Siemans Healthcare Diagnostics (Deerfield, IL). The Laboratory specializes in saliva determinations. Briefly, saliva was analyzed directly, without extraction, using a 200µL aliquot and an extended 3hr incubation at room temperature. The calibration curve was diluted 1:10 and ranged from 0-138 nmol/L. The intra-assay coefficient of variation calculated across low, medium, and high pools averaged 4.2% and the sensitivity of the assay was < 0.25 nmol across 3 assay runs. All samples from a given participant were analyzed in the same assay run and the average salivary cortisol concentration across the two duplicates (in nmol/L) was the value used for all statistical analyses.

2.4. Data Analyses

Statistical analyses were performed using Statistica TIBCO Software (Palo Alto, CA, USA). Analyses of Variance (ANOVAs) were conducted on dependent variables of interest using group (control, MCI) and sex (male, female) as the between-subject factors. On cortisol measures and certain cognitive tests, time and/or session (1, 2) were also used as a within-subjects factor. Age was used as a covariate in all analyses. *Post hoc* analyses used Newman-Keul's comparisons. Due to the small sample size, exploratory analyses on possible sex effects were run using a Bonferroni correction on *a priori* analyses. A two-tailed significance criterion of p=0.05 was used for all statistical tests conducted.

3. Results

3.1. Male aMCI participants have prolonged higher levels of cortisol in the morning compared to sex-matched controls, a pattern that is not observed in women.

Only 21 of 28 participants completed all five time points for cortisol collection across three consecutive days. Analysis of these 21 participants revealed a main effect of time ($F_{(4,68)}$=34.39, p<0.001, η_p=0.669; Figure 2). *Post hoc* analyses revealed that awakening cortisol was higher than 09:00h cortisol among controls, both of which were higher than all other time points; there were no differences between the evening samples. Among male aMCI participants, the diurnal pattern of salivary cortisol was different with no significant difference between awakening and 09:00h (p=0.82), and significant differences between control and aMCI participants at the 09:00h timepoint only. Furthermore, at the 09:00h time point, male aMCI participants had higher cortisol than controls (p=0.007; Cohen's d=0.428) but no other differences between controls and aMCI participants were evident at any other timepoint (all p's >0.4 for males; p>0.6 for females). These findings indicate that aMCI is associated with higher morning cortisol levels than in controls in males. Unfortunately, very few women in the aMCI group completed all of the samples for saliva collection (n=2). However, it is clear that these effects are driven by the aMCI men, as observed in Figure 2 and in a subsequent analysis with sex as a factor. In that analysis, men with aMCI had significantly higher levels of cortisol at 09:00h compared to controls (p=0.007) with no significant differences observed between women with or without aMCI across any time point: ps>0.69. There were no significant differences between groups in time of awakening.

We also calculated average cortisol area under the curve (AUC)(Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003) across all three days. With estimates for missing values, there was a trend for a main effect of sex with males showing higher cortisol than females ($F_{(1,24)}$=3.848, η^2=0.138, p=0.062), but no other significant effects (ps >0.9).

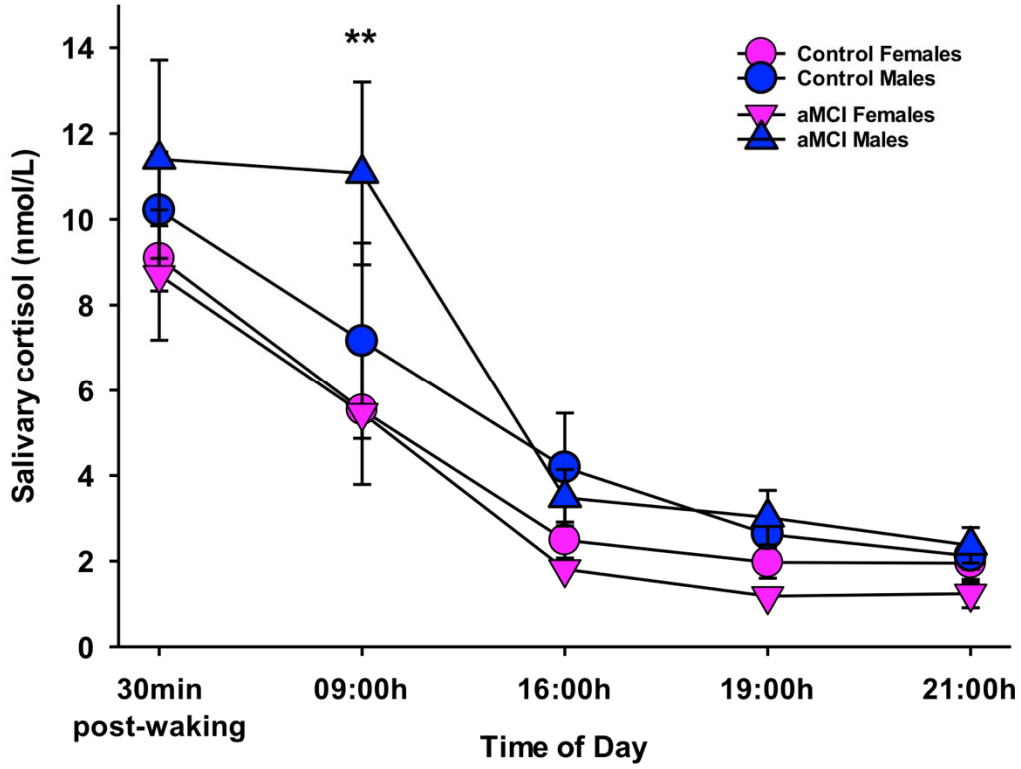

Figure 2. Mean salivary cortisol across five time points averaged across three days. The time points included 30 minutes after awakening, 09:00, 16:00, 19:00, 21:00h on three consecutive days. Samples were collected in the home setting. Participants with aMCI, particularly males, showed a different pattern of diurnal cortisol release with levels of cortisol higher and prolonged during the morning compared to the evening and compared to matched controls. Males with aMCI had higher levels of cortisol at 09:00h compared to all other groups. Due to a number of people submitting incomplete saliva collection packages the sample size is (Control=13: females=7, males=6; MCI=8: females=2, males=6). **p=0.007 aMCI males vs control males. Error bars represent standard error of the mean.

3.2. Males with aMCI had higher levels of cortisol than controls in session 1 and during the first two time points in session 2. aMCI status and sex influence cortisol levels during TSST.

Cortisol levels during the two test sessions were analyzed separately as the psychosocial stressor (TSST) was conducted during session 2. For cortisol on session 1, two outliers were removed from time point 1 (both men: 1 control, 1 aMCI). Men with aMCI had significantly higher levels of cortisol than any other group at the first time point (10:10) (all ps<0.0006; time by group by sex interaction: $F_{(1, 25)}$=5.096, p=0.032, η_p=0.17; Figure

3). There were also main effects of sex and time (main effect of sex: $F_{(1,27)}$=9.05, p=0.0056, η_p=0.25; main effect of time: $F_{(1,27)}$=13.05, p=0.00012, η_p=0.33).

During session 2, in which the TSST was performed, females had lower cortisol than males (main effect of sex: $F_{(1, 27)}$=11.13, p=0.0025, η_p=0.29). Furthermore, cortisol levels were highest 30min after the TSST was initiated compared to all other time points as expected (all ps<0.013; main effect of time: $F_{(3,81)}$=4.90, p=0.0035, η_p=0.15). However, aMCI participants had marginally higher cortisol levels than controls (main effect of group: $F_{(1,27)}$=3.95, p=0.057, η_p=0.13). *A priori* analyses indicated that males with aMCI had significantly higher levels of cortisol during the first two time points in the second session prior to the TSST (both ps<0.001) whereas females with aMCI had significantly higher levels of cortisol 30min post-TSST than control females (p=0.007) but not at any other time point (all ps>0.23; Figure 3).

We also examined the TSST cortisol levels as AUC and found that females had lower levels of cortisol than males (main effect of sex: $F_{(1,27)}$=8.99, p<0.006, η_p=0.25) and aMCI had higher levels than controls (main effect of group: $F_{(1, 27)}$=4.167, p=0.051, η_p=0.134).

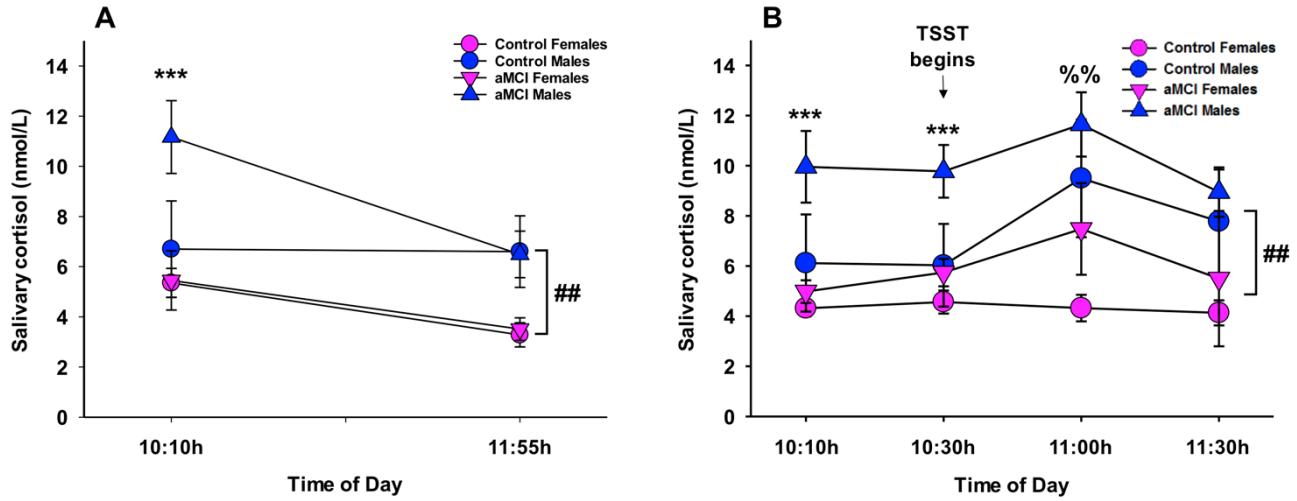

Figure 3. Salivary cortisol measures across two test sessions. A) Session 1 saliva samples were taken at 10:10h and after cognitive testing at 11:55h. Overall males had higher levels of cortisol than females, with males with aMCI having the highest levels at the beginning of the test period. *** ps<0.0006 aMCI males vs all other groups, ## p=0.0056 main effect of sex. B) Session 2 saliva samples were collected *via* salivettes at 10:10h (10 min after arrival and 20 minutes prior to the Trier Social Stress Test (TSST)), 10:30, 11:00, 11:30h. The TSST was initiated at 10:30h, so that the last sample was taken 60 min after the beginning of the TSST. Males had higher cortisol overall than females, with males with aMCI exhibiting the highest levels during the first two time points, prior to the stress testing. Thirty minutes after the TSST, all groups exhibited the highest levels of cortisol release (except control females). *** ps<0.001 aMCI males vs all other groups, %% p=0.007 aMCI females vs control females, ## p=0.0025 main effect of sex. Error bars represent standard error of the mean.

3.3. TSST was endorsed as anxiety provoking by females more than males with aMCI

Both sexes in the control group endorsed the TSST as anxiety provoking, with 57% of participants indicating that the TSST was anxiety provoking. However, among aMCI participants 80% of females but only 11% of males indicated the TSST was anxiety provoking (χ^2=6.169, p=0.013). Of those participants who rated the TSST as anxiety provoking there was no significant difference in the rating of the anxiety level (ps>0.29).

3.4. Stress enhanced immediate recall and word learning in the controls but not in participants with aMCI

Immediate recall of HVLT-R was enhanced after the TSST in session 2 compared to session 1 in the controls (p=0.004), but no such enhancement was seen in participants with aMCI (p=0.245; interaction: group by session: $F_{(1,27)}$=7.6, p=0.010, η_p=0.22). Breaking this down by sex, aMCI males had impaired immediate recall (p=0.04, d_4=0.55) on session 2 following the stressor, but there was no significant difference in aMCI females (p=0.47; Figure 4).

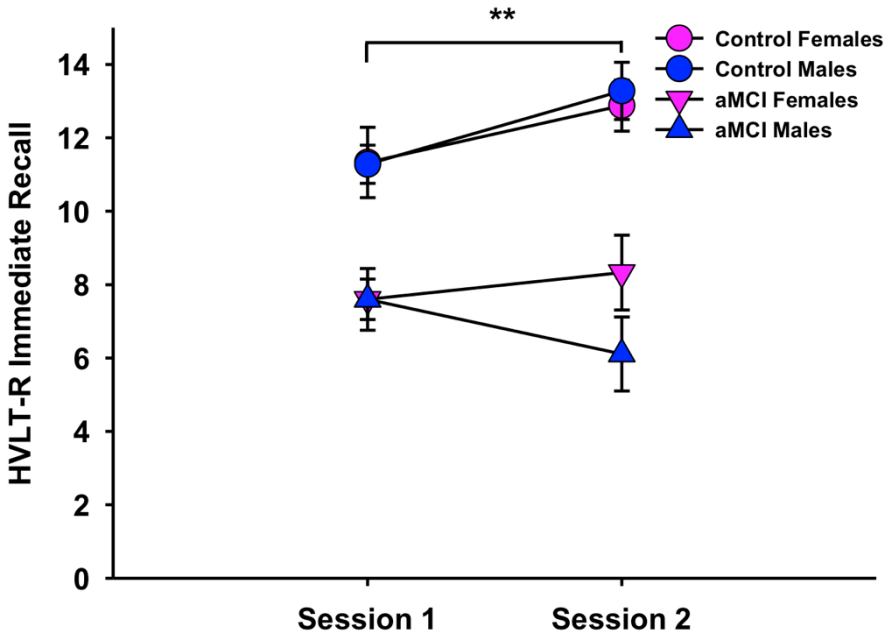

Figure 4. Stress enhanced immediate recall in the control participants but not in the aMCI participants. There was a Group by Session interaction (p=0.01) with control participants showing greater recall after the Trier Social Stress Test (TSST) delivered in session 2 compared to session 1 (p=0.004) but no such significant improvement in participants with aMCI (p=0.25), an effect driven by males with aMCI. ** p=0.004 session 1 vs session 2 control participants. Error bars represent standard error of the mean.

3.5. aMCI participants required more choices to complete the spatial working memory task than controls.

During sessions 1 and 2, aMCI participants made more choices than controls across all trials (main effect of group: Session 1: $F_{(1, 27)}$=7.66, p=0.01, η_p=0.22; Session 2: $F_{(1, 27)}$= 15.38, p=0.0006, η_p=0.37). Furthermore, all participants required fewer choices by the delay trial (all ps<0.035; main effect of trial (Session 1: $F_{(2,54)}$=3.15, p=0.0508, η_p=0.10; Session 2: $F_{(2,52)}$=4.23, p=0.02, η_p=0.14). There were no other significant main effects or interactions (all ps>0.41; Figure 5A).

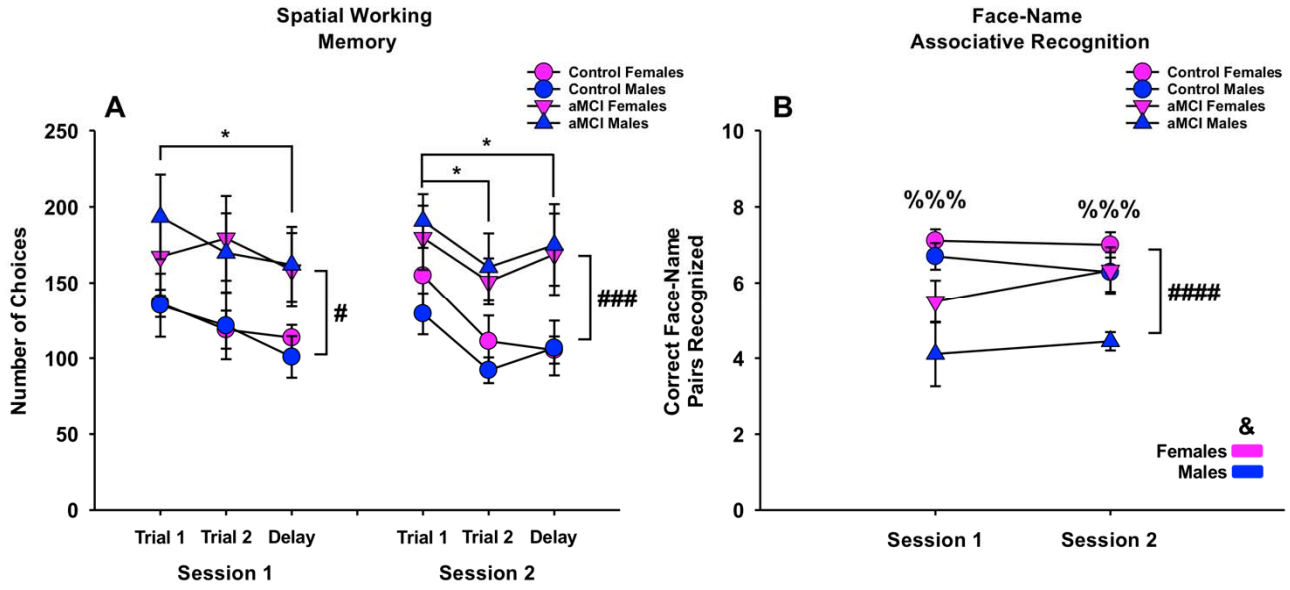

Figure 5. Spatial working memory and face-name associative recognition performance. A) aMCI participants performed worse than controls in both session 1 (p=0.01) and session 2 (p=0.0006). Overall, participants made fewer choices on the third trial (delayed testing) during both sessions and immediate recall in session 2 only. B) aMCI participants correctly recognized fewer face-name pairs than controls (p<0.00001). This was driven by the aMCI males who performed worse than male controls in both sessions (ps<0.001). Additionally, despite aMCI females performing similarly to female controls in session 2, there was a significant main effect of sex (p=0.01). Error bars represent standard error of the mean. # p=0.01 aMCI vs controls session 1 spatial working memory, ### p=0.0006 aMCI vs controls session 2 spatial working memory, #### p<0.00001 aMCI vs controls face-name associative recognition, * p<0.05 intertrial differences for all participants in spatial working memory, %%% p<0.001 aMCI males vs control males within session, & p=0.01 main effect of sex.

3.6. aMCI participants performed worse on HVLT-R retention, delayed recall, and face-name pairs.

As expected, aMCI participants performed worse on the retention of the HVLT-R (main effect of group: $F_{(1,27)}$=29.00, p<0.00001, η_p=0.52) and face-name pairs (main effect of group: $F_{(1,27)}$=17.65, p<0.00001, η_p=0.40), regardless of session. There were no other significant main or interaction effects for HVLT-R retention (all ps>0.20). For face-name pairs, females remembered more pairs than males (main effect of sex: $F_{(1,27)}$=7.53, p=0.01, η_p=0.22). Intriguingly, aMCI participants performed worse than controls except for females with aMCI during session 2 after the TSST (p=0.334), whereas males with aMCI recalled fewer face-name pairs across both

sessions (p=0.0004 and 0.0009, respectively; Figure 5B). Finally, aMCI participants performed worse on HVLT-R delayed recall (main effect of group: $F_{(1,27)}$=63.22, p<0.00001, η_p=0.70) and all participants performed better on session 2 than session 1 (main effect of session: $F_{(1,27)}$=7.15, p<0.013, η_p=0.21). There were no other significant effects on delayed recall.

There were no differences among groups or sex on Trial Making (all ps>0.12), but there was a main effect of session ($F_{(1, 27)}$=5.017, p=0.033, η_p=0.16). All participants performed better in session 2 than session 1. For MMSE there were no significant main or interaction effects, but the main effect of group approached significance ($F_{(1,27)}$=3.434, p<0.075, η_p=0.11).

3.7 aMCI participants rated their general health as better than controls

Controls (X=2.467±0.17) rated their general health as worse than aMCI (X=1.786±0.21) participants ($F_{(1,25)}$=5.99, p=0.028, η_p=0.18). However, given that the group means only differed by 0.681, it is doubtful that this is clinically relevant.

3.8 Females endorsed more depressive symptoms on Beck Depression Inventory than males.

Females, on average, scored higher than males on the Beck Depression Inventory ($F_{(1,27)}$=5.75, p=0.023, η_p=0.18). However, no participants reached criterion for suspicion of clinical depression. There were no other significant effects in the depression scores (p>0.1). Moreover, there were no significant group or sex differences in Beck's Anxiety Scale (all ps>0.54).

3.9 Correlations between salivary cortisol and memory

There was a positive correlation between retention on the HVLT-R and cortisol levels in session 1 in the controls (r=0.59, p=0.025) but not in participants with aMCI (r=-0.18, p=0.53; see Figure 6). These correlations were significantly different (Fisher's z=2.04, p=0.041). When broken down by sex, there was a negative correlation between immediate recall on the HVLT-R and salivary cortisol during session 1 for females with aMCI (r=-0.85 p=0.03, n=6) and positive correlations with stress-induced cortisol in females with aMCI and learning (r=0.83, p=0.041) and learning slope on HVLT-R (r=0.91, p=0.012) but no significant correlations in

males with aMCI (*p*s>0.4, n=9) or control males or females (*p*s >0.09). The correlations of immediate recall with session 1 salivary cortisol (Fisher's z=-2.31, *p*=0.021) and TSST-induced cortisol with learning slope (Fisher's z=1.99, *p*=0.047) were significant between the sexes, whereas TSST-induced cortisol and learning were not (*p*=0.11).

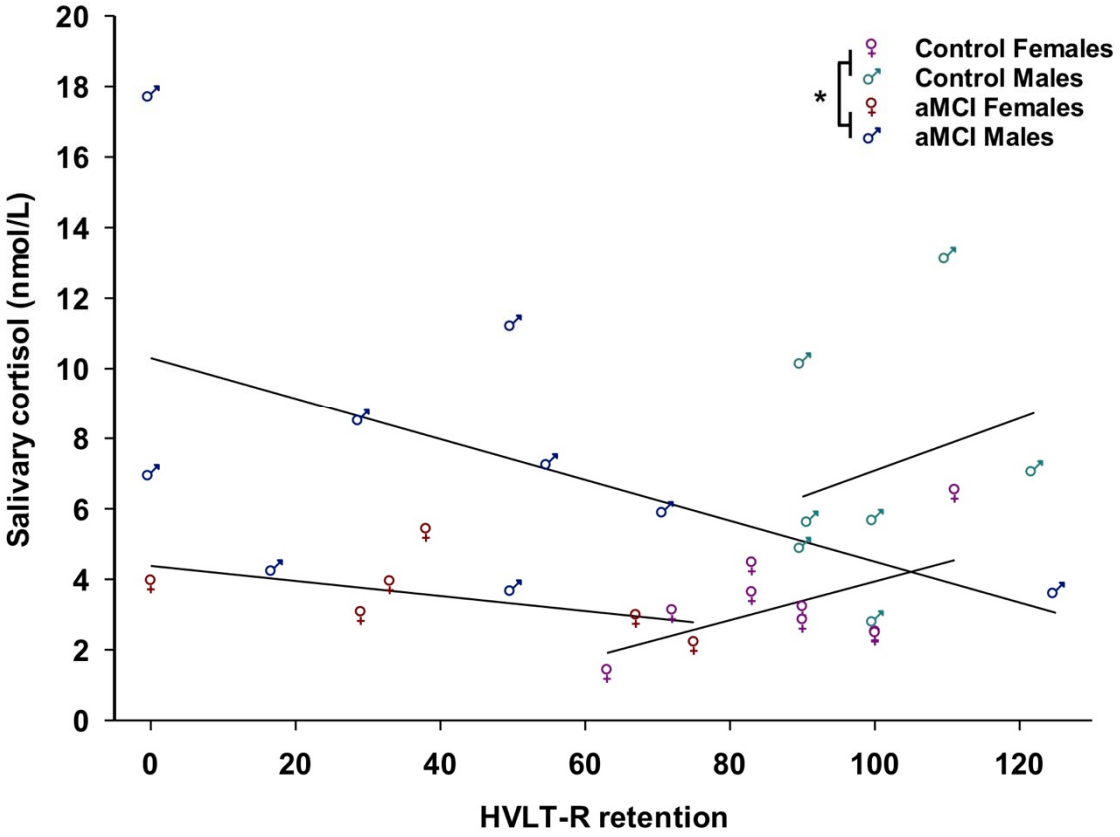

Figure 6. Scatterplot of session 1 salivary cortisol levels plotted against HVLT-R retention by group (control, aMCI) and sex (male, female). Overall, there was a positive correlation between retention scores and cortisol levels in controls (r=0.59, *p*=0.025) but no significant relationship in MCI (r=-0.18, *p*=0.53), with these correlations being significantly different (Fisher's z=2.04, *p*=0.041). * *p*<0.05.

4. Discussion

Cortisol levels were significantly higher in individuals with aMCI, an effect that was seen predominately in males and in morning samples. aMCI participants showed a different pattern of morning cortisol release than controls, with a higher and prolonged elevation at 9AM, an effect that was driven primarily by the males. Indeed, controls showed a significant decrease in cortisol from thirty minutes after awakening to 09:00h, while the only group to not show this decrease in cortisol were aMCI males. These results are partially consistent with previous findings (Beluche, Carrière, Ritchie, & Ancelin, 2010; Dijckmans et al., 2017; Evans et al., 2011; Tortosa-

Martínez, Manchado, Cortell-Tormo, & Chulvi-Medrano, 2018; Wang et al., 2018). Stress, as applied by the TSST, improved immediate verbal recall in controls, but not in participants with aMCI. Furthermore, our data revealed positive correlations between morning cortisol levels and verbal memory in controls, but there was no evidence for a positive relationship in participants with aMCI. These results highlight that morning cortisol is elevated in participants with aMCI, which may be related to negative performance on measures of immediate recall and retention of verbal memory. Furthermore, the opposite relationship was seen in controls with positive associations between salivary cortisol and verbal memory performance. While our sample size was small, our results are suggestive of sex differences in the relationship between cortisol (diurnal and stress-induced) and memory among control and aMCI participants, with males showing the most pronounced effects.

4.1. Morning cortisol levels are higher in males with aMCI.

Amnestic MCI males had higher salivary cortisol levels as shown in diurnal home measurements, as well as at 10:00h in both of the sessions conducted in the laboratory. This finding is in partial contrast to a study investigating morning salivary cortisol levels in MCI participants of amnestic, non-amnestic, and multidomain type (Venero et al., 2013). That study found that salivary cortisol levels upon awakening were significantly higher in the non-amnestic and multidomain type but not in the amnestic type; however, in that study, partially consistent with our own, the mean awakening cortisol level was higher in amnestic participants than in controls. Although our study only included MCI of the amnestic type, we did find a significant increase in salivary cortisol at multiple time points and over several days: 30 minutes after awakening, at 09:00h in samples collected at home across three days, and at 10:00h in the two samples taken in the laboratory. In our study, these increases were mainly found in male participants. However, given that the Venero study (in which 69% of participants in the amnestic category were female) did not find any associations with diurnal cortisol and aMCI compared to our study where the findings were stronger in males, the lack of consideration of sex by those authors may have contributed to the inconsistences between the two studies (Venero et al., 2013). Nevertheless, it is compelling that, in both their study and our own, increased morning levels of salivary cortisol are associated with MCI in general. While our sample size is much smaller than in the Venero study, we consistently observed high morning cortisol levels across 5 different days and under different conditions (i.e. home and laboratory),

suggesting a strong multiday effect. Our results suggest that further investigation into sex differences in diurnal cortisol levels is necessary in individuals with aMCI.

4.2. Stress-induced increases in cortisol were associated with enhanced recall in controls but not in aMCI

As expected, the TSST induced an increase in cortisol levels, which was associated with enhanced verbal recall in the HVLT-R in controls but not in aMCI participants. These findings are consistent with a study by Wolf et al. (Wolf, Convit, Thorn, & de Leon, 2002), which found that there were negative correlations between average cortisol and immediate recall of paragraphs in MCI participants but not in controls. Similarly, healthy elderly have been found to exhibit a positive correlation between high cortisol and memory performance, whereas aMCI subjects exhibit a negative correlation (Souza-Talarico, Chaves, Lupien, Nitrini, & Caramelli, 2010). Collectively, the present data and previous findings suggest that cortisol has opposing relationships with memory and recall in MCI vs normal aging.

4.3. Sex may influence the effects of diurnal and stress-induced cortisol on memory in aMCI

In a number of our major findings, males with aMCI showed a stronger relationship with cortisol level than did females with aMCI. This is intriguing and suggests that sex should be considered in future studies and research on age-related cognitive impairment. This is of particular relevance considering that a number of studies investigating memory and cortisol have had an imbalance of males or females in their test groups (e.g. (Souza-Talarico et al., 2010; Wolf et al., 2002)). However, due to a limited sample size in the current work, our sex-based analyses are exploratory and due caution should be paid when generalizing the results.

Our findings of marked sex differences are congruent with previous studies demonstrating epidemiological, symptomatic, and physiological differences between males and females with MCI. The prevalence of MCI has been found to be greater in males than females, with aMCI as the most common type (Petersen et al., 2010). Furthermore, the incidence of MCI is greater in males than in females (Roberts et al., 2012) and recent studies have uncovered sex-specific risk factors for MCI to AD progression (Kim et al., 2015). Although MCI is more prevalent in males, females exhibit faster deterioration in cognitive and functional measures over time (Lin et al., 2015). Sex differences are also evident in neurophysiological changes with

cognitive impairment, as females experience accelerated brain atrophic rates (Hua et al., 2010), as well as faster hippocampal atrophy (Ardekani, Convit, & Bachman, 2016). These findings, in accord with our data, emphasize the need to account for sex differences in future research in memory and cognition. Intriguingly, decreases in hippocampal volume predict progression to probable AD (and MCI) in women, whereas increases in white matter hyperintensities in men predict progression to MCI (Burke et al., 2019). Optimistically, there is preliminary evidence that cognitive training in those with aMCI is more effective in women than men (Rahe, Liesk, et al., 2015) but remains effective in both sexes (Kalbe et al., 2018; Rahe, Becker, et al., 2015; Rahe, Liesk, et al., 2015; Rahe, Petrelli, et al., 2015).

4.4. The relationship between cortisol and memory may depend on brain health

Higher cortisol levels should not always be thought of as detrimental to brain function. Indeed, in the present study we found a positive correlation between delayed word-list recall on the HVLT-R and cortisol levels in session 1 in the control participants. No significant relationship was found in aMCI participants (and the direction of the effect was negative). These findings are consistent with at least two other studies (Souza-Talarico et al., 2010; Wolf et al., 2002). Souza-Talarico et al. (2010) showed a positive relationship between cortisol and delayed recall in controls but a negative relationship in people with MCI. Furthermore, Wolf et al. (2002) showed a negative correlation between average cortisol and immediate story recall in MCI participants but no relationship to average cortisol in controls. While the correlations had opposing findings being significant in either controls or MCI, the relationships between cortisol and memory are consistently opposing whether considering normal aging or MCI. This is provocative in that these findings collectively span multiple cortisol measures (average, awakening, test session) and memory components (immediate or delayed recall, retention).

In our study, we found that aMCI females exhibited a negative correlation between immediate recall on the HVLT-R and salivary cortisol during session 1. Furthermore, a positive correlation between stress-induced cortisol and learning and learning slope on HVLT-R was observed in the females with aMCI. Neither males with aMCI nor controls (either sex) displayed any significant correlations.

Finally, it is important to be aware that increased cortisol is not always associated with poorer memory performance. A clear example of this is observed in our study: stress-induced increases in cortisol by the TSST

were followed by an improved immediate recall in the HVLT-R in controls but not in aMCI participants. This again suggests that cortisol may play an adverse role in memory in aMCI but a positive role in healthy participants, particularly in males. One can speculate that an exaggerated stress response in aMCI participants increases cortisol to a detrimental level, whereas in controls the moderate increase in cortisol is enough to enhance performance. Indeed, other research has found a positive association between cortisol and memory (Vogel & Schwabe, 2016). For example, physical exercise can be linked to improved cognition (Barha, Davis, Falck, Nagamatsu, & Liu-Ambrose, 2017) and increased cortisol (Hötting, Schickert, Kaiser, Röder, & Schmidt-Kassow, 2016), even in participants with MCI (Barha, Hsiung, et al., 2017; Liu-Ambrose, Barha, & Best, 2018; Tortosa-Martínez et al., 2018), albeit it is not clear the nature or direction of this relationship. Furthermore, there are well known sex differences in the effects of corticosterone in animal models, thus it is probable that males and females will show opposing or different effects (Gobinath, Workman, Chow, Lieblich, & Galea, 2016). For example, acute stress can facilitate learning in male rats but impair conditioning in female rats (Wood & Shors, 1998). However, the effects of age and stress on learning are not as well studied (S. J. Lupien, Maheu, Tu, Fiocco, & Schramek, 2007). In light of these findings, we encourage the research community to make it a priority to examine sex as a factor in analyses of aging and cognition.

5. Conclusions

The present study shows clear effects of aMCI on diurnal and stress-effected cortisol levels, as well as stress-induced impairments in spatial memory; however, these effects are driven primarily by males in our sample, as they showed greater increases in cortisol and greater impairments when compared to same-sex controls than females did. While our sex-based analyses are exploratory as a result of low sample size, sex differences were observed in both cortisol levels and memory performance, with aMCI as a moderating factor. It is critical that future studies explore sex as a biological variable in this area as we have presented evidence herein that suggests that effects at the confluence of aMCI and stress can be obfuscated or otherwise eliminated when males and females are grouped. For real understanding and advancement to take place in this field, biological sex must be considered and statistically analyzed.

Estimates of the prevalence of MCI in the elderly show high variability, ranging from ~3-42% (Ward, Arrighi, Michels, & Cedarbaum, 2012), due to differences in study methodology (Sachdev et al., 2015), especially with regards to the sample population (age, ethnicity, education-level, etc.). Regardless, there is a clear health care burden associated with MCI (Lin & Neumann, 2013; Ton et al., 2017). As those with MCI are more likely to develop AD (Busse et al., 2003; Dawe et al., 1992; Lupien et al., 1998; Petersen et al., 1999) and the health care burdens of AD are more severe than those of MCI (Lin & Neumann, 2013; Ton et al., 2017), understanding this prevalent condition is important to those with the condition and their caregivers, as well as to policymakers. Future studies should make examining sex differences (their nature, underlying mechanisms, outcomes, etc.) in aMCI a priority, as well as expand upon the influence of cortisol in aMCI and the interactions between these factors.

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Disclosure statement

The authors have nothing to disclose.

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