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Neuropsychiatric symptoms influence differently cognitive decline in older women and men

Ronat Lucas [a,b], Monchi Oury [a,c,d], Hanganu Alexandru [a,e,*], for the Alzheimer's Disease Neuroimaging Initiative[1], National Alzheimer's Coordinating Center

[a] Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Montréal, Québec, Canada
[b] Département de Médecine, Faculté de Médecine, Université de Montréal, Québec, Canada
[c] Département de Radiologie, Radio-Oncologie et Médecine Nucléaire, Faculté de Médecine, Université de Montréal, Québec, Canada
[d] Hotchkiss Brain Institute, Cumming School of Medicine, Calgary, AB, Canada
[e] Département de Psychologie, Faculté des Arts et des Sciences, Université de Montréal, Québec, Canada

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ABSTRACT

Objective: The potential impact of sex on cognitive performance in normal aging and participants with Alzheimer's disease (AD) has been outlined previously. Nevertheless, differences in neuropsychiatric symptoms (NPS) have been also outlined. We aimed to study a potential association between NPS and cognitive performances according to sex, in older individuals with and without cognitive impairment.

Methods: Demographic, neuropsychiatric and neuropsychological data from the ADNI and NACC databases were merged into a dataset of 506 participants with healthy cognitive performance, 467 patients with mild cognitive impairment, and 238 patients with AD. Cognitive performance in each group was evaluated according to sex and the presence of NPS.

Results: Based on sex, cognitive performance differed according to clinical stage: in the healthy controls and AD groups, women had better fluency performance, while in the mild cognitive impairment group, women had better working memory and men better oral naming. Regardless of sex, depression showed a negative effect on processing speed in AD. Finally, there was an interaction between sex and NPS in mild cognitive impairment, where women with apathy had better working memory performance, and in AD, women with depression had better fluency performance. The opposite pattern being was observed in men, where men with depression have worse focused attention.

Conclusion: Cognitive performance is influenced by sex, yet this influence has different manifestations at normal cognition, MCI or AD. Furthermore, apathy and depression seem to influence differently women and men at different types of cognitive decline.

1. Introduction

It has been reported that during the lifespan, sex differences in cognitive functions are stable with women performing better than men for episodic memory, semantic fluency and visual recognition and men performing better for visuospatial functions (de Frias et al., 2006). There are also sex differences with respect to risks of developing Alzheimer's Disease (AD): women account for nearly two-thirds of AD patients (Hebert et al., 2013) however, the age-specific prevalence estimates did not include stratification by sex. Prevalence and incidence are higher in women than men and these data increase with age (Gao et al., 1998; Niu et al., 2017). Also, with same high Aβ-42 and total tau levels, Women showed more rapid hippocampal atrophy and cognitive decline than Men, particularly in Mild Cognitive Impairment (MCI) (Koran et al., 2017). Neuropsychiatric Symptoms (NPS) are commonly defined as behavioral and psychological disturbances and they were shown to occur during pre-dementia syndromes such as MCI (Mortby et al., 2018). Some studies reported that NPS can precede the occurrence of MCI, may

* Corresponding author. M6828, 4545 ch. Queen Mary, H3W 1W6, Montréal, QC, Canada.
E-mail address: alexandru.hanganu@umontreal.ca (H. Alexandru).

[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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accelerate cognitive decline and could increase the risk of dementia (Rosenberg et al., 2013; Teng et al., 2007). In addition, Rosenberg et al. (2013) observed that progression to dementia occurs relatively rapidly in participants with NPS, which is consistent with the hypothesis that NPS in MCI may be an early symptom of dementia and AD. Though NPS in the elderly has been previously investigated (Fernández et al., 2010; Fernandez-Martinez et al., 2010; Van der Mussele et al., 2013), the influence of NPS on the cognitive performance with respect to sex, has received much less attention. Specifically, most NPS such as depression or apathy appeared to be associated with poorer memory and executive performance, while visuospatial and language reductions appeared to be more specific to psychotic symptoms (David et al., 2016; Gulpers et al., 2016; Quaranta et al., 2015; Ready et al., 2003; Robert et al., 2006; Wilson et al., 2000).

Previous prevalence-based studies have shown that NPS in women are more varied and more severe (Fernández et al., 2010). Their types are also different, Women with MCI have higher prevalence of delusions, while Women with AD exhibit predominantly anxiety, irritability, delusion, depression and disinhibition (Inamura et al., 2020; Spalletta et al., 2010; Tao et al., 2018; Xing et al., 2015). In men, on the other hand, MCI was associated with more irritability, while AD was linked to irritability, agitation and apathy. From a cognitive perspective, longitudinal studies showed that women with mild anxiety and healthy cognitive performance (HC) had a higher likelihood of developing dementia compared to women without anxiety and with HC (Kassem et al., 2017). Furthermore, anxiety led to a greater reduction in mental flexibility but not a higher risk of dementia after a follow-up of 5 and 3.4 years in men (Kassem et al., 2018). Other trends were reported regarding depression. Men with HC and with depression had a higher incidence of cognitive impairment after 2 years of follow-up than those without depression (Ng et al., 2009). In patients with mild amnestic MCI or mild AD, duration of cognitive decline was positively correlated with delusions severity in women, whereas the severity of irritability was negatively correlated with global cognition in men (assessed with the MMSE) (Inamura et al., 2020). To our knowledge, no other study than those mentioned above has investigated the impact of NPS on cognitive performance according to sex. Moreover, these studies did not consider both the full range of neuropsychiatric differences between the sexes and the effects on a broader neuropsychological assessment.

1.1. Objective and hypothesis

Several significant limitations impede the proper interpretation of previous results, specifically the (1) small sample size; (2) single-site protocols (3) inclusion of a single ethnic group (4) brief assessments of cognitive performance (5) usage of clinical scales that are not adapted to the elderly population. Today, NPS are quantified using subjectively answered questionnaires, in which questions are answered either by the participant or by a caregiver. The realization of a multi-site study, using different databases, makes it possible to remedy the limitations previously mentioned (large sample size, more comprehensive neuropsychological assessment, assessment of numerous NPS). In the present study, we aimed to verify three hypotheses: 1) NPS have a different prevalence in women and men at different types of cognitive performance (HC, MCI or AD); 2) NPS influence differently cognitive performance when quantified per specific cognitive functions; and 3) sex and NPS have a different impact on cognitive performance in HC, MCI and AD.

2. Methods

2.1. Participants

Participants were selected from the ADNI (Alzheimer's Disease Neuroimaging Initiative) and NACC (National Alzheimer's Coordinating Center) databases. The ADNI database is a large compilation of longitudinal data, that was started in 2003 and is led by the principal investigator Michael W. Weiner, MD (Mueller et al., 2005; Shaw et al., 2007) (http://www.adni-info.org/). The NACC database was established in 1999 and is a large compilation of longitudinal data (https://naccdata.org). Participants that were included in our study from this database originated from the NACC UDSv1-2 dataset.

Three distinct groups were selected from each of the databases. Participants with HC included only those with cognitive performance within the expected range for their age, sex, and level of education. The Mild Cognitive Impairment group (MCI) from the ADNI database consisted of individuals whose cognitive characteristics meet the criteria for MCI. Entry criteria for patients with amnestic MCI included a Mini-Mental State Examination score of >24 and a Memory Box score of at least 0.5. The MCI participants from the NACC database had to have cognitive changes from the person's previous assessment (complaint) and a disorder in at least one cognitive domain (Albert et al., 2013).

Patients with Alzheimer's disease (AD) from the ADNI database were composed of individuals meeting the National Institute of Neurological and Communication Disorders/Alzheimer's Disease and Related Disorders Association criteria for probable AD (McKhann et al., 1984). They were only mildly impaired (mild-AD), had a Mini-Mental State Examination score between 20 and 26 and a global Clinical Dementia Rating between 0.5 and 1. Similarly, the patients with AD from the NACC database have met the NINCDS/ADRDA criteria for probable or possible AD (McKhann et al., 1984).

Exclusion criteria used for this study were: (i) incomplete assessments, (ii) incomplete neuropsychiatric and neuropsychological assessments, (iii) presence of psychiatric history (major depression, schizophrenia, bipolar disorder, substance abuse, post-traumatic stress, obsessive-compulsive disorder), (iv) presence of neurological history (stroke, head injury, brain tumor, anoxia, epilepsy, alcohol dependence and Korsakoff, neurodevelopmental disorder), (v) prematurity, (vi) diagnostic criteria in favor of other neurodegenerative or neurological etiology (Parkinson's disease, frontotemporal degeneration, progressive supranuclear paralysis, corticobasal degeneration, Lewy body dementia, amyotrophic lateral sclerosis, multiple sclerosis, multi-system atrophy, vascular dementia). After the exclusion, the final sample for analyses consisted of 505 HC, 467 MCI, 239 AD (HC/MCI/AD: ADNI = 223/367/175; NACC = 282/100/64) (Table 1).

Ethics committee approval and individual patient consents were received by the ADNI and NACC databases (http://adni.loni.usc.edu/methods/documents/& https://naccdata.org/data-collection/forms-documentation/uds-3) for each participant. This study was approved by the Comité d'éthique de la recherche vieillissement-neuroimagerie CER VN 19-20-06.

Table 1
Demographic characteristics and comparison in each group and subgroup depending on sex.

Group	HC (N = 506)		MCI (N = 467)		AD (N = 238)	
Age, m (sd)	74,38 (7,56)		75,10 (7,62)		75,73 (7,49)	
Age, range	42–93		54–96		55–92	
Women (%)	55.5		37.7***		49.2	
Sex	W (N = 281)	M (N = 225)	W (N = 176)	M (N = 291)	W (N = 117)	M (N = 121)
Age, m (sd)	74.13 (7.93)	74.7 (7.09)	74.01 (7.65)	75.76 (7.55)*	75.38 (7.93)	76.06 (7.05)
Education, m (sd)	15.56 (2.68)	16.86 (6.13) ***	14.95 (3.01)	16.06 (2.91) ***	14.07 (3.06)	15.64 (3.16) ***
MMSE, m (sd)	29.17 (1.07)	28.94 (1.12)*	27.01 (1.89)	27.14 (1.82)	23.09 (2.53)	23.55 (2.68)

Legend: W = Women; M = Men; HC = Healthy Controls; MCI = Mild Cognitive Impairment; AD = Alzheimer's disease; N = sample size per group and sex; m = mean; sd = standard deviation; *p < .05; ***p < .001.

2.2. Neuropsychiatric and neuropsychological assessments

All participants underwent a comprehensive neuropsychological examination and a neuropsychiatric assessment via the Neuropsychiatric Inventory, that was completed by participants' relatives/caregiver in both datasets. The Neuropsychiatric Inventory assessed the presence vs. absence of 12 neuropsychiatric symptoms: delusions, hallucinations, agitation/aggressiveness, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviors, nighttime behaviors and appetite/eating changes. The behaviors assessed are for the previous month and focus on behavioral changes, compared to the assessed individual's previous functioning (Cummings, 2020; Lai, 2014). The potential bias from relatives' answers was accounted for by ADNI using an interrater reliability assessment in different domains, which achieved and was reconfirmed to be excellent (Cummings, 1997; Cummings and McPherson, 2001).

The neuropsychological assessment evaluated eight cognitive functions, as per available tests in both datasets: (1) global cognitive efficiency (assessed with the total score of Mini-Mental State Examination), (2) focused attention (completion time of Trail Making Test A), (3) processing speed (Total items correct of Wechsler Adult Intelligence Scale, Coding), (4) mental flexibility (completion time of Trail Making Test B), (5) visuoconstructive planning (copy score of the Clock test), (6) working memory (raw scores of the Digit Span forward and backward Tests), (7) semantic fluency (assessed based on the total correct words of the Semantic Lexical Evocation animal and vegetable) and (8) oral naming (total correct responses of the Boston Naming Test). Only assessments common for both databases were included. Thus, episodic memory evaluation was not included because different tests were used (Rey auditory verbal learning test in ADNI and Logical Memory in NACC).

2.3. Statistical analysis

Independent variables were the (1) sex (woman or man), (2) clinical group (HC, MCI, or AD) and (3) NPS. Dependent variables were the raw cognitive performance. Data was analyzed using IBM SPSS Statistics version 26. First, the prevalence of NPS were compared between women and men in each clinical group using chi-square tests. Secondly, we determined the model for analyzing the effects of sex and NPS on cognitive performance (ANOVA vs. ANCOVA) accounting for age, years of education, and the MMSE score based on Student's t tests. Since the groups were not completely equal on these parameters, we used an ANCOVA model. Finally, the NPS that showed a significantly different prevalence between women and men were included in our ANCOVA model, specifically: agitation, depression, apathy, irritability. The model included the confounding variables: age, years of education, and MMSE score. This allowed us to test the interaction effects of sex and NPS on cognitive performance. Three ANCOVAs were performed, comparing in each clinical group the differences in cognitive performance according to sex, NPS and the interaction of the two. The significance level was .05 for all tests. A Bonferroni correction was applied to comparisons of the estimated marginal means of the model.

3. Results

3.1. Demographic comparisons

Demographic data and comparisons between and within each group by sex are summarized in Table 1 ***[Table 1 here]***. Student's t tests reported a significant but low difference between women and men regarding age in the MCI group (W/M: 74.01/75.76, t = 2.409), MMSE score in the HC group (W/M: 29.17/28.94, t = −2.206) as well as number of years of education in all clinical groups (W/M: HC, 15.56/16.86, t = 3.213; MCI, 14.95/16.06, t = 3.938; AD, 14.07/15.64, t = 3.888).

3.2. Prevalence of NPS

For each clinical group, the sample sizes as well as the prevalence of NPS by sex are presented in Table 2 and Figs. 1–3 ***[Table 2 and Figs. 1–3 here]***. Women with HC presented less agitation than men with HC (0.7% vs. 3.6, Chi-square = 5.216, p = .022). Women with MCI, when compared to Men with MCI, showed less apathy (8.5% vs. 15.1, Chi-square = 4.325, p = .038) and less irritability (16.5% vs. 32.0, Chi-square = 13.620, p < .001). Finally, in AD patients, women had less irritability than men (23.1% vs. 41.3, Chi-square = 9.048, p = .003), but a greater tendency to depression (32.5 vs 21.5%, Chi-square = 3.655, p = .056).

3.3. Impacts of sex and NPS on cognitive performance

From the 12 neuropsychiatric symptoms only depression, agitation, apathy and irritability showed a significantly different prevalence between women and men and were included in further analysis. The prevalence of NPS did not necessarily imply a significant impact on cognitive performance. Specifically, irritability showed a high prevalence both in MCI and in AD, nevertheless, it did not show a significant impact on any of the cognitive evaluations. On the other hand, apathy had a lower prevalence but a significant impact on working memory ***[Table 3 here]***.

In the HC group, the ANCOVA model showed a simple effect of sex on the semantic fluency domain (specifically vegetable fluency), with women performing better than men (F = 4.423, ddl = 1, p = .036). This simple effect was confirmed by comparison of the estimated marginal means (p = .004).

In the MCI group, women showed better performance compared to men in the working memory domain (F = 7.558, ddl = 1, p = .006) and worse performance in the oral naming domain (F = 12.850, ddl = 1, p <

Table 2
Neuropsychiatric prevalence per group and sex.

Group	HC (N = 506)		MCI (N = 467)		AD (N = 238)	
Sex	**W** (N = 281)	**M** (N = 225)	**W** (N = 176)	**M** (N = 291)	**W** (N = 117)	**M** (N = 121)
NPS, n (%)						
Agitation	2 (0.7)	8 (3.6) *	24 (13.6)	54 (18.6)	26 (22.2)	32 (26.4)
Depression	11 (3.9)	9 (4.0)	32 (18.2)	49 (16.8)	38 (32.5)	26 (21.5)†
Apathy	1 (0.4)	2 (0.9)	15 (8.5)	44 (15.1)*	33 (28.2)	42 (34.7)
Irritability	13 (4.6)	15 (6.7)	29 (16.5)	93 (32.0) ***	27 (23.1)	50 (41.3) **
Not included in the ANCOVA model:						
Delusion	0 (0)	0 (0)	2 (1.1)	3 (1.0)	13 (11.1)	8 (6.6)
Hallucination	0 (0)	1 (0.4)	0 (0)	1 (0.3)	4 (3.4)	3 (2.5)
Anxiety	11 (3.9)	6 (2.7)	34 (19.3)	49 (16.8)	32 (27.4)	37 (30.6)
Euphoria	0 (0)	0 (0)	2 (1.1)	10 (3.4)	3 (2.6)	6 (5.0)
Disinhibition	0 (0)	1 (0.4)	9 (5.1)	23 (7.9)	17 (14.5)	20 (16.5)
Aberrrant motor behavior	0 (0)	2 (0.9)	6 (3.4)	13 (4.5)	19 (16.2)	16 (13.2)
Nightime Behaviors	13 (4.6)	12 (5.3)	20 (11.4)	36 (12.4)	20 (17.1)	29 (24.0)
Appetite changes	3 (1.1)	1 (0.4)	15 (8.5)	30 (10.3)	13 (11.1)	21 (17.4)

Legend: W = Women; M = Men; HC = Healthy Controls; MCI = Mild Cognitive Impairment; AD = Alzheimer's disease; NPS = Neuropsychiatric Symptoms; n = sample size per NPS; N = sample size per group and sex; †.05<p < .10; *p < .05; **p < .01; ***p < .001.

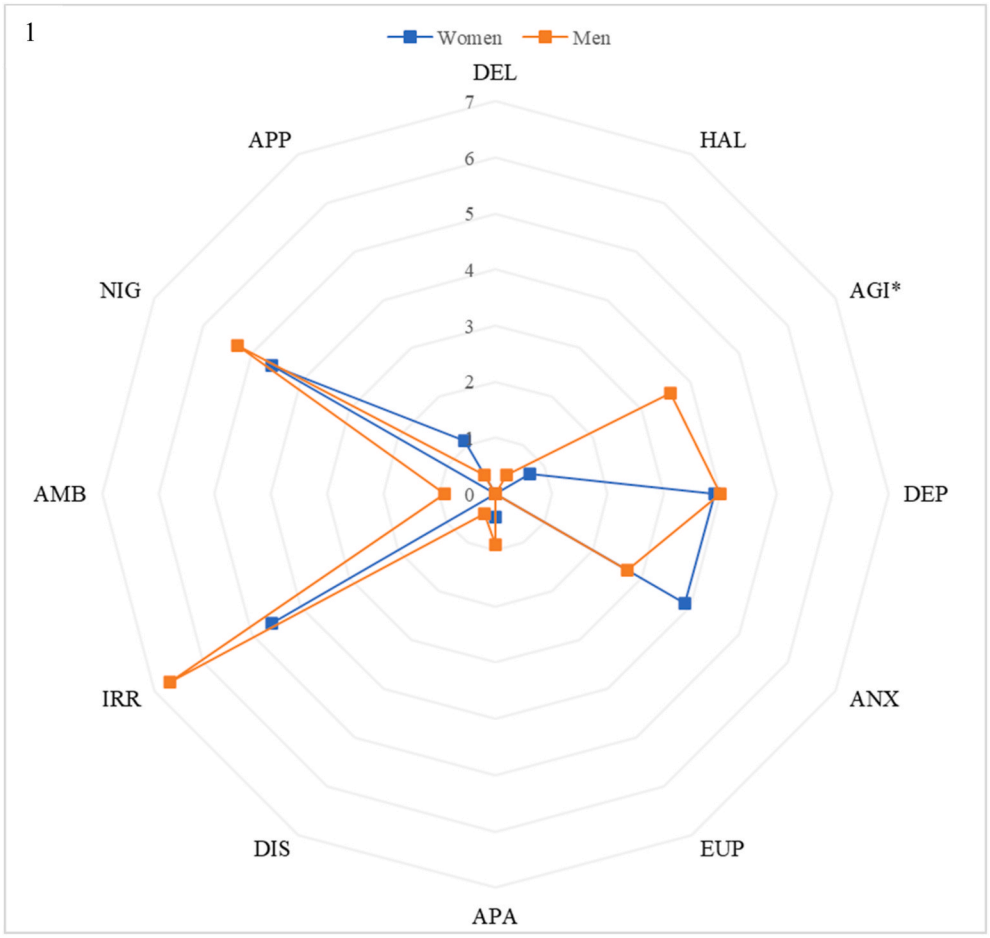

Fig. 1. Radar of neuropsychiatric symptoms prevalence in HC group (in %).
Legend: DEL = Delusion; HAL = Hallucination; AGI = Agitation; DEP Depression; ANX = Anxiety; EUP = Euphoria; APA = Apathy; DIS = Disinhibition; IRR = Irritability; AMB = Aberrant Motor Behaviors; NIG = Nighttime Behaviors; APP = Appetite Changes; *Chi^2 p-value for comparison of NPS prevalence between women and men <.05. **NOTE: all 3 radar figures have different scales.**

.001). This performance was further shown to be influenced by apathy, since the single interaction analysis showed that women with apathy performed better in working memory compared to both women and men without apathy as well as men with apathy (F = 5.321, ddl = 1, p = .022).

In the AD group, women performed better than men on semantic fluency (vegetable fluency) (F = 4.274, ddl = 1, p = .040), confirmed with the estimated marginal means (p = .011). This effect was also influenced by the presence of depression, as women with depression showed better semantic fluency (animal fluency) performance than women without depression, while in men, those with depression had worse performance than those without (F = 5.373, ddl = 1, p = .021). On the other hand, depression was shown to influence focused attention in men, but not in women. Specifically, men without depression showed better performance on focused attention compared to depressed men (F = 6.011, ddl = 1, p = .015), while no effect was observed in women. These results should also be regarded in light of a potential impact of a simple effect of depression on processing speed (F = 4.350, ddl = 1, p = .038), since the presence of depression reduced the performance in all participants.

4. Discussion

Our results indicate that: 1) NPS have a different prevalence in women and men at different stages of cognitive performance; specifically, agitation is more specific for men with HC, apathy – for Men with MCI, irritability is more prevalent in Men with MCI and Men with AD, depression is more prevalent in Women with AD; (2) sex and NPS have a different impact on cognitive performance at different cognitive clinical stages; specifically, regarding semantic fluency (HC Women perform better than HC Men, Women with AD > than Men with AD, Women with AD and with depression > Women with AD without depression, while Men with AD without depression > Men with AD with depression), working memory (Women with MCI > Men with MCI, Women with MCI with apathy > Women with MCI without apathy), oral naming (Men with MCI > Women with MCI), focused attention (Men with AD with depression > Men with AD without depression); (3) high prevalence of NPS does not necessarily indicate a significant impact on cognitive performance.

Our results are in line with some of the previously published reports that observed that some certain NPS are more prevalent in men than in women, specifically agitation, apathy, and irritability in MCI and AD (Inamura et al., 2020; Tao et al., 2018; Zuidema et al., 2009). In addition, we show that NPS are also present in HC participants, and our results of prevalence in this group are in line with previously published data from Mortby et al. (2018). On the other hand, our results contradict the study of Xing et al. who found that NPS prevalence was similar in both women and men and the study of Inamura et al. that women had more delusions than men (Inamura et al., 2020; Xing et al., 2015). Concerning apathy, Zuidema et al. (2009) suggested that apathy is more prevalent in men because of the higher prevalence of vascular disease in these patients. Thus, apathy in women could be caused by other factor than vascular etiology. Nevertheless, previous findings used smaller sample sizes and the MCI group had different quantification criteria, significantly diminishing the potential comparisons to them.

To explain these neuropsychiatric differences, some studies point to genetic predispositions as well as hormonal fluctuations in men and women including the menopausal process (Kyomen et al., 1999; Mielke, 2018; Sukonick et al., 2001; Xing et al., 2012). As examples of the contribution of menopause to cognitive decline, it can be stated that

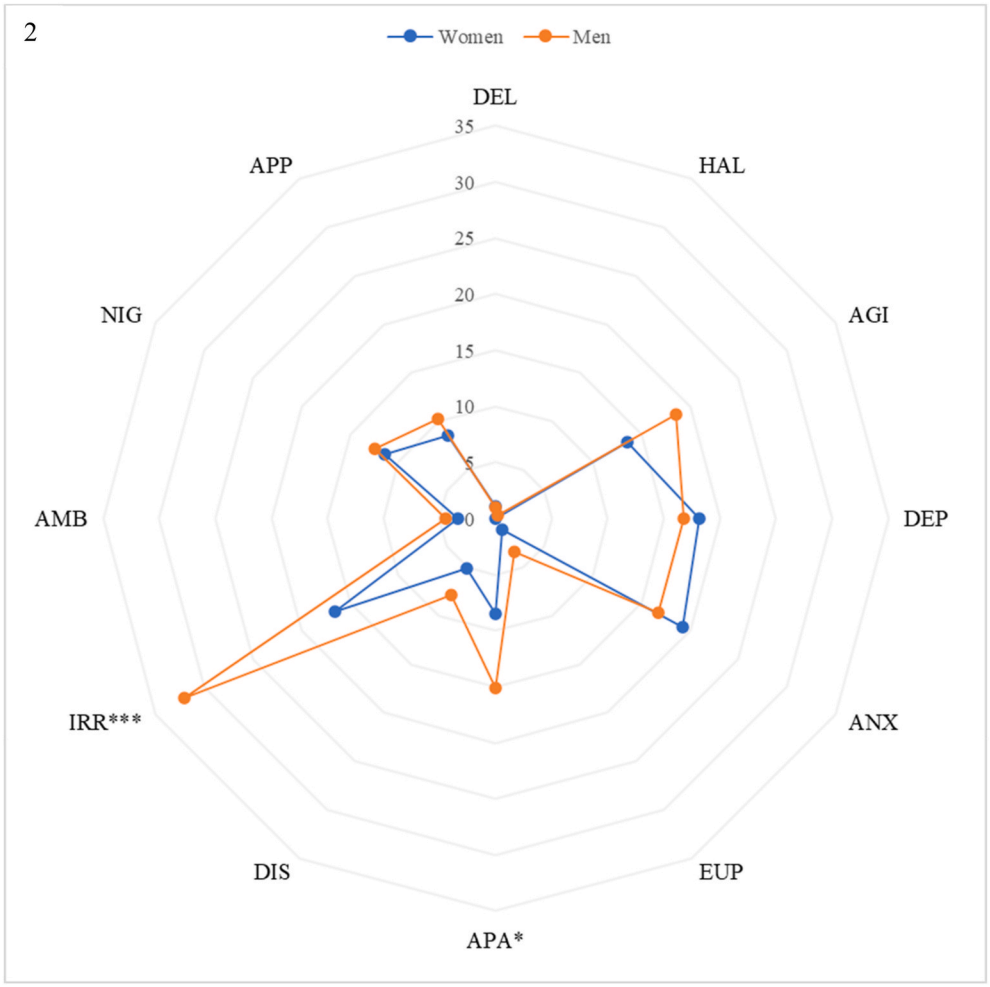

Fig. 2. Radar of neuropsychiatric symptoms prevalence in MCI group (in %).
Legend: DEL = Delusion; HAL = Hallucination; AGI = Agitation; DEP Depression; ANX = Anxiety; EUP = Euphoria; APA = Apathy; DIS = Disinhibition; IRR = Irritability; AMB = Aberrant Motor Behaviors; NIG = Nighttime Behaviors; APP = Appetite Changes; *Chi^2 p-value for comparison of NPS prevalence between women and men <.05; ***p < .001. **NOTE: all 3 radar figures have different scales.**

although menopause is a common process in women who live to midlife, this transition can be associated with decreased verbal memory (Epperson et al., 2013) and early menopause has been associated with an increased risk of cognitive decline or dementia (Rocca et al., 2011). Differences in NPS also appear to be due to the amyloid status of individuals or to hormone/amyloid status interactions, particularly in women (Xing et al., 2012, 2015). Finally, these prevalence may vary depending on the presence of other NPS. For example, Tao et al. (2018) focused on patients with agitation/aggression. Among them, with equal levels of agitation, women appeared to have more anxiety and irritability than men (Tao et al., 2018).

Based on our sex related prevalence differences, associations between NPS and cognitive performance were tested according to agitation, irritability, apathy and depression. Our results showed that women performed better overall in semantic fluency (HC and AD groups), and oral naming (MCI group), as well as in verbal working memory (MCI group) than men. In this sense, these data are consistent with previous literature regarding better verbal performance in women. However, men were not found to have better visuospatial performance than women. This is quite distinct from other studies reporting that older women show better cognitive preservations than men in most cognitive domains, except for visuospatial and perceptual-motor domains (de Frias et al., 2006; McCarrey et al., 2016). Furthermore, cognitive aging, depending on sex, appears to be mediated by different brain changes (Reas et al., 2021).

Concerning sex and NPS interactions on cognitive performance, in the HC group, agitation did not show a different effect on cognitive performance by sex. This is not surprising given the lack of studies showing relationships between NPS and cognition in HC participants. Indeed, while the presence of NPS is frequently demonstrated in HC participants (at least one NPS in 42% from Fernandez-Martinez et al., 2010), their relationships with cognition are poorly studied, and do not show significant results (Brodaty et al., 2012; Fernandez-Martinez et al., 2010). Indeed, in MCI patients, Brodaty et al. (2012) reported associations between depression and dysexecutive disorders, anxiety and processing speed/selective attention, agitation and memory disorders as well as visuospatial disorders in relation to agitation, anxiety and apathy; but no associations in HC. Moreover, in controls and patients with MCI neither the neuropsychological test nor daily living scales were related to the presence of any NPS in the study of Fernandez-Martinez et al. (2010). In contrast, it appears that the presence of NPS shows long-term negative effects on future cognitive decline (Brodaty et al., 2012; Burhanullah et al., 2020; Ng et al., 2009). For example, more rapid decline in executive function was predicted by the presence of anxiety at baseline, whereas decline in language was predicted by agitation, whereas NPI total score at baseline was associated with accelerated memory and language decline and anxiety was related to accelerated decline of processing speed (Brodaty et al., 2012). These data suggest that NPS would be better predictors of future cognitive decline than current cognitive performance.

In the MCI group, the interaction effect between apathy and sex on working memory showed a benefit in women. Indeed, those with apathy showed better performance than those without. This effect was not present in men. This could be due to the different apathy profiles between women and men. Indeed, apathy may involve different brain networks (cognitive, affective, motivational, goal-directed e.g.) and thus

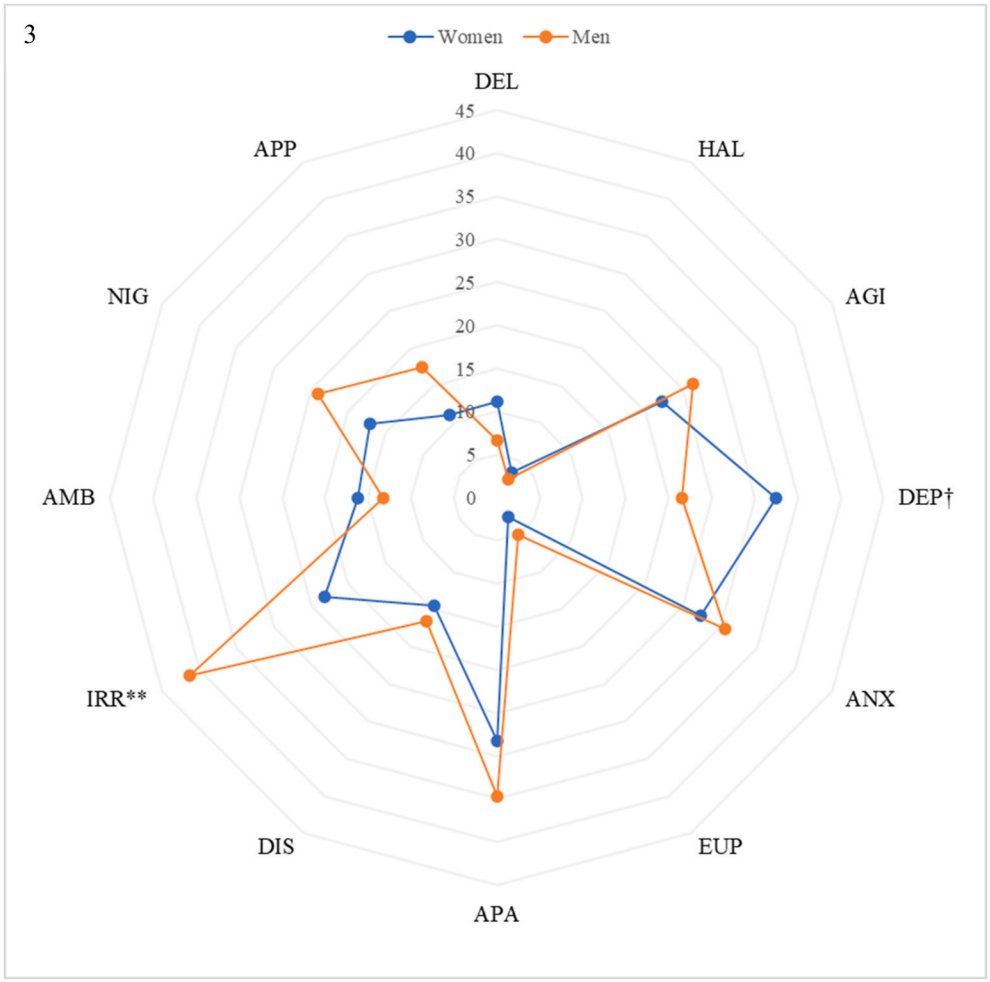

Fig. 3. Radar of neuropsychiatric symptoms prevalence in AD group (in %).
Legend: DEL = Delusion; HAL = Hallucination; AGI = Agitation; DEP Depression; ANX = Anxiety; EUP = Euphoria; APA = Apathy; DIS = Disinhibition; IRR = Irritability; AMB = Aberrant Motor Behaviors; NIG = Nighttime Behaviors; APP = Appetite Changes; †Chi^2 p-value for comparison of NPS prevalence between women and men <.10; **p < .01. **NOTE: all 3 radar figures have different scales**.

impact cognitive functions such as working memory in different ways (Levy and Dubois, 2006; Radakovic and Abrahams, 2018). However, most studies do not consider these subtypes of apathy and demonstrate, that in normal aging, mild cognitive impairment and Alzheimer's disease, frontal/dysexecutive disorders in association with apathy (Drijgers et al., 2011; Montoya-Murillo et al., 2019; Ready et al., 2003; Robert et al., 2006). Also, some pharmacological and non-pharmacological treatments of apathy have been shown to improve cognitive performance in Alzheimer's disease (van Dyck et al., 2021). However, these data were not considered in this study. By contrast, previous results reported associations between anxiety and accelerated memory decline and greater executive dysfunction (Gulpers et al., 2016; Ready et al., 2003; Robert et al., 2006). We didn't find any association with anxiety and cognitive performances.

Finally, in the AD group, depression had a different impact on women and men's performance on semantic fluency and focused attention. Specifically, women with depression performed better on semantic fluency and had a quicker response time on focused attention, while in men the pattern was reversed. When men were not depressed, they performed better on semantic fluency and showed a better focused attention. This contradicts some of the previous literature which showed that women with AD tend to show poorer executive performance when depression is present (Nakaaki et al., 2008; Sun et al., 2008). Nevertheless, other studies also showed broader associations of depression with executive function, memory and language (Kuzis et al., 1999; Ready et al., 2003).

4.1. Strengths and perspectives

To our knowledge, this is the first study to consider a broader field of cognitive evaluations to investigate associations with NPS as a function of sex. In addition, the inclusion of two large databases, ADNI and NACC, allowed the accumulation of a large population of more than 1200 participants, HC, MCI and AD.

Interestingly, most studies on sex differences in NPS and cognitive decline have focused on Alzheimer's disease or amnestic MCI (Inamura et al., 2020; Tao et al., 2018; Xing et al., 2015). To our knowledge, few studies have examined these differences in normal cognitive aging (i.e. in HC participants). Specifically, Kassem et al. (2017; 2018) and Ng et al. (2009) showed that NPS at baseline (anxiety and depression) have a different longitudinal effect on cognitive decline in women and men. This might imply that longitudinal and comparative analyses of neuropsychiatric profiles could be of interest between clinically progressing participants (HC who convert to MCI, MCI who convert to AD e.g.) and those who do not progress. Considering that our results show that women have less NPS than men, and that those with NPS showed better cognitive performance than those without NPS (even in cognitively normal women), one could think that these women need less treatment or cognitive management, which could delay the implementation of these treatments compared to men. Also, it has been argued that women are more protected than men in the prodromal stages and have accelerated cognitive and cerebral decline in later stages (Ferretti et al., 2018). Our results should therefore encourage consideration of sex in the effectiveness of treatments (e.g. rivastigmine treatment delaying conversion from MCI to AD in women (Ferris et al., 2009); or intranasal

Table 3
ANCOVA results with main effect of sex, NPS and interaction between them for each clinical group on cognitive performances.

	HC				MCI				AD			
Effect of sex												
Cognitive variables	**Women**	**Men**	**F**	**p**	**Women**	**Men**	**F**	**p**	**Women**	**Men**	**F**	**p**
Semantic fluency (vegetable fluency)	16.60	12.63	4.423	**0.004***	11.08	10.49	0.955	0.380	8.35	6.77	4.274	**0.011***
Working memory (digit span backward)	6.69	6.48	0.006	0.937	7.11	6.06	7.558	**0.006**	5.17	4.54	1.762	0.061
Oral naming (BNT)	26.98	27.74	0.358	0.996	23.37	26.05	12.850	**<0.001***	20.76	22.06	2.158	0.264
Effect of NPS												
	No-Agi	**Agi**	**F**	**p**	**No-Apa**	**Apa**	**F**	**p**	**No-Dep**	**Dep**	**F**	**p**
Processing speed (digit symbol)	47.05	44.50	0.684	0.523	37.44	36.98	0.018	0.823	30.57	25.35	4.35	**0.030***
					No-Irr	**Irr**	**F**	**p**	**No-Irr**	**Irr**	**F**	**p**
					37.30	37.14	0.026	0.937	28.15	27.94	0.007	0.928
Interaction Sex and NPS												
					Women No-Apa	**Men No-Apa**	**Men Apa**	**F**	**p**	**Women No-Dep**	**Women Dep**	**Men No-Dep**	**Men Dep**	**F**	**p**
Semantic fluency (Animals Fluency)					14.89	15.97	16.27	2.199	0.139	10.71	12.90	13.58	10.71	5.373	**0.021***
Working memory (digit span backward)					6.49	6.31	5.80	5.321	**0.022***	5.26	5.08	4.83	4.21	<0.001	0.988
Focused attention (TMTA)					41.58	43.59	42.99	1.545	0.215	61.05	56.55	56.15	87.86	6.011	**0.015***

Legend: HC = Healthy Controls; MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease; F = ANCOVA statistical value; p = p-value; BNT = Boston Naming Test; NPS = neuropsychiatric symptom; No-Agi/Agi = Absence/presence of agitation; No-Apa/Apa = Absence/presence of apathy; No-Irr/Irr = Absence/presence of irritability; No-Dep/Dep = Absence/presence of depression; TMTA = Trail Making Test version A.

insulin having better cognitive effects on delayed memory in men (Claxton et al., 2013)). Furthermore, this also supports the need to consider both sex and NPS in models for predicting cognitive performance or clinical conversion (e.g., MCI to AD), both for anticipating risk of decline and for establishing norms for neuropsychological assessments (stratification of standardized norms by sex).

5. Limitations

(1) A particular limitation includes potential comorbidities between NPS, especially in patients with MCI or AD, since several NPS may be present in the same individual. From this perspective, taking into consideration the NPS as co-occurring rather than independently, might allow a better understanding of their impact on cognitive performance; (2) It should be noted that the NPI scale does not attempt to determine the origin of NPS or distinguish the triggers of the behaviors, whether they are due to the physical (new location) or psychosocial (interactions or care) environment (Lai, 2014). (3) Furthermore, the lack of consideration of the amyloid status of participants. This parameter, when controlled, could show different results, as demonstrated in the study of Xing et al. (2015). (4) We should also mention the gender-specific biases that impact NPS′ evaluation. Previous studies reported that gender-related social expectations such as communication in women or impulsivity in men, introduce biases in NPS evaluations performed by relatives, and the sex of the patient rather than the informant is the strongest predictor of sex differences in behavior (Ott et al., 1996). (5) Finally, a potential hormonal impact on NPS was not considered in our study. A positive relationship was found between plasma testosterone levels and physical aggression in men with dementia (Orengo et al., 1997). On the other hand, estrogen levels were positively associated with affective symptoms (emotional lability) in women with Alzheimer's disease but not in men (Fillit, 1994).

6. Conclusion

In order to explore the effect of sex and NPS on cognitive performance at different stages of cognitive decline, we compared different cognitive functions in women and men at different clinical cognitive groups (HC/MCI/AD) with and without NPS. Our results showed essentially cognitive differences due to sex, where women performed better overall in semantic fluency (HC and AD groups), and oral naming (MCI group), as well as in working memory (MCI group) than men. Some differences were due to NPS: apathy influenced working memory in Women with MCI and depression had an impact on semantic fluency in Women with AD and Men with AD, as well as an impact on focused attention in Men with AD. These results might suggest (1) that some NPS might have a potential compensatory effect on cognitive performance, (2) some NPS have a detrimental effect, and (3) some NPS must be considered in light of sex when assessing their impact on cognitive performance.

Conflict of interest/disclosure statement

All authors declared no conflict of interest.

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All data are available on the ADNI and NACC websites upon demand (http://adni.loni.usc.edu/data-samples/access-data/ & https://naccdata.org/requesting-data/submit-data-request).

Authors' roles

Research project: AH, LR; Data extraction and processing: LR, AH; Statistical analysis: LR; Manuscript: LR, AH, OM.

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