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REVIEW

Sex differences in cognitive impairment in Alzheimer's disease

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Abstract

Sex differences in neurocognitive abilities have been extensively explored both in the healthy population and in many disorders. Until recently, however, little work has examined such differences in people with Alzheimer's disease (AD). This is despite clear evidence that AD is more prevalent in women, and converging lines of evidence from brain imaging, post-mortem analyses, hormone therapy and genetics suggesting that AD affects men and women differently. We provide an overview of evidence attesting to the poorer cognitive profiles in women than in men at the same stage of AD. Indeed, men significantly outperform women in several cognitive domains, including: Language and semantic abilities, visuospatial abilities and episodic memory. These differences do not appear to be attributable to any differences in age, education, or dementia severity. Reasons posited for this female disadvantage include a reduction of estrogen in postmenopausal women, greater cognitive reserve in men, and the influence of the apolipoprotein E ε4 allele. Assessment of cognitive abilities contributes to the diagnosis of the condition and thus, it is crucial to identify the role of sex differences if potentially more accurate diagnoses and treatments are to emerge.

Key words: Dementia; Gender; Sex differences; Cognition

Core tip: This review assesses evidence that women with Alzheimer's disease (AD) show greater cognitive impairment than men. The evidence shows that female AD patients are outperformed by males in multiple cognitive domains including visuospatial, verbal processing, semantic and episodic memory. This disadvantage is not attributable to sex differences in age, education level, or dementia severity. Possible explanations include estrogen loss in women or a greater cognitive reserve in men, which may provide protection against the disease process. Such findings have implications for tailoring more specific gender-based treatments.

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INTRODUCTION

"Biomedical research in general, and neuroscience in particular, has been built on a false assumption that one may safely ignore potential sex influences"[1].

Alzheimer's disease (AD) is the most common neurodegenerative disease associated with aging, with worldwide estimates of 30 million people with dementia, 4.6 million new cases annually, and one new case every 7 s[2]. The prevalence and the incidence of AD are greater amongst women than men and this discrepancy increases with advanced age[3-5].

A meta-analysis of 13 population studies from across United States, Europe, and Asia indicates that women are at significantly greater risk of developing AD, though not other dementias[6]. The neurocognitive profiles of male and female AD patients, however, are less well-described. These profiles require far greater examination as sex differences in the pattern of cognitive decline may yield vital information about differential risk factors, pathogenesis and most importantly, treatment of AD in men and women. In order to make sense of any sex differences that emerge under AD neuropathology, we first need to have a clear understanding of those sex differences that may already exist in the normal population, and specifically the healthy elderly population.

SEX DIFFERENCES IN THE GENERAL POPULATION

Sex differences in cognitive abilities receive consistent, extensive discussion in the "normal" literature, with the prevailing view being that women tend to have better verbal abilities[7,8], while men display a visuospatial advantage[8,9].

VERBAL ABILITIES

Tasks measuring verbal ability generally rely on rapid access to semantic and phonological information. Category fluency requires a person to name as many exemplars of a category (*e.g.*, tools) as possible, usually within one minute, while lexical fluency involves listing as many words beginning with a given letter (typically, F, A and S). In confrontation naming, the respondent must produce names for a series of visually presented items, usually but not exclusively line drawings. This task is regarded as a measure of core semantic memory function, though performance depends also on visual acuity and retrieval of phonological information.

In their meta-analysis of sex differences in almost 1.5 million participants, Hyde *et al*[7] found a small, but reliable female advantage in verbal ability with a *Cohen's d* = 0.11 (Cohen's *d* is calculated from: Mean of group A - Mean of group B/pooled standard deviation of A and B); and effect sizes are traditionally viewed as small (*d* = 0.2), medium (*d* = 0.5) or large (*d* = 0.7+). The small effect size reflects the mixed findings, with 44 studies (27%) reporting females outperformed males, 109 (66%) found no significant difference, and in 12 (7%) males outperformed females. Recent evidence suggests that sex differences in verbal ability are not universal but task-dependent. For lexical fluency, a female advantage has emerged in some studies[10,11], but not others[12,13]. Category fluency tasks do not elicit reliable sex differences[14] although differences may emerge for specific categories; for example, a female advantage for fruits and a male advantage for tools[15]. Confrontation naming, by contrast, has shown a male advantage in the few published papers examining sex differences[16]. In summary, sex differences in verbal abilities in the general population may be smaller than once believed[17].

VISUOSPATIAL ABILITIES

Linn *et al*[18] partitioned visuospatial tasks into three groups: Mental rotation, spatial perception (spatial working memory) and spatial visualisation (navigation). Mental rotation involves the ability to mentally rotate a two or three-dimensional figure rapidly and accurately. Spatial perception tasks are those where participants are required to determine spatial relationships with respect to the orientation of their own bodies in spite of distracting information. Spatial visualisation involves complicated multi-stage manipulations of spatially presented information (*e.g.*, the embedded figures test).

Sex differences in normative visuospatial processing are more robust than those documented for verbal processing. Voyer *et al*[9] meta-analysed 286 studies spanning 50 years, finding that men significantly outperformed women on most visuospatial tasks. Within Cohen's[19] nomenclature, the effect sizes were large for mental rotation (*d* = 0.73), medium for spatial perception (*d* = 0.44), and small for spatial visualization (*d* = 0.13). A later review by Li *et al*[20] examined 16 studies comparing men and women on spatial rotation and 11 on spatial navigation, and all 27 pointed to a male advantage.

AGE RELATED COGNITIVE DECLINE

As expected, many aspects of cognitive performance do decline with age[21-24]. Although not typically apparent for category fluency[25] and spatial perception[26], age-related deficits are seen in lexical fluency[27] and block design tasks[28] - underscoring how the precise requirements of the verbal and spatial tasks are crucial.

Greater age-related cognitive decline in healthy

men than women has been established not only in cross-sectional studies, but also crucially in longitudinal studies[29-34]. For example, Wiederholt *et al*[33] assessed 1692 participants aged 55-94 years finding that performance on all cognitive tests decreased progressively with age, but that the decline was slower in women. More recently, using internet testing, Maylor *et al*[23] examined sex differences and age-by-sex differences on various cognitive tasks in a very large sample of healthy individuals (109612 men and 88509 women). Importantly, and consistent with other studies, men showed greater age-related decline than women, irrespective of whether the task was one on which they were better. Of course, such large samples are sufficiently powered to detect even the most trivial differences and although the age by gender interactions described in this study are highly significant, they account for just 0.1% of the variance in cognitive performance.

As part of the Whitehall Ⅱ cohort study, Singh-Manoux *et al*[35] assessed 5198 male, and 2192 female, civil servants, aged 45-70, monitoring their cognitive performance (memory, vocabulary, reasoning and verbal fluency) over 10-years. Their results suggest that cognitive performance may decline earlier than previously thought. For example, reasoning scores decreased by 3.6% for men and women aged 45-49, and 9.6% and 7.4% respectively for those aged 65-70. The authors also noted the much larger cross-sectional than longitudinal age-related decline in women, which they attributed to cohort differences in education, with older women tending to be less well educated.

Based on neurocognitive and behavioural data, some have proposed that "age is kinder to women"[36]; however, any such female advantages are quite small and contentious. Meinz and Salthouse[36] meta-analysed 25 studies (5201 individuals aged 18-64) investigating sex differences in the patterns of age-cognition relations across a wide range of tasks. They concluded that "large (12%-25% of the total variance) effects related to age, small (at most 3% of the variance) effects associated with gender, and small to non-existent (less than 1%) effects associated with interactions of age and gender on measures of cognitive performance" (p 63). Only a minority of measures (speed and reasoning) revealed significant age by sex interactions: Men had smaller age-related declines. Although the age-related differences across sex were quite small, favouring women (only spatial abilities demonstrated a large sex gap favouring men), the confidence intervals for estimated effect sizes were small, suggesting the results are reliable.

Other research, however, suggests that men and women decline at similar rates[22,27,37,38]. Gerstorf *et al*[22] examined 368 participants aged 70-100 over a 13-year period, finding that for all cognitive tests men and women declined in parallel. Proust-Lima *et al*[38] however, found that after adjusting for vascular status, sex differences in cognitive decline did emerge, but only at the oldest age, with women showing a steeper decline than men do. Similarly, in a sample of 647 twin pairs (both dizygotic and monozygotic) aged between 65 and 98 years, Read *et al*[24] described larger sex differences in working memory and perceptual speed deficits at later ages, with women faring worse.

Therefore, although age-related cognitive decline is evident on many tasks, the weight of evidence points to similar levels of impact in men and women until the very oldest age, when women suffer a faster decline. We might then expect to find that sex differences in the younger population persist in the elderly. Furthermore, any sex effects in AD patients that differ from that seen in the healthy population are likely to be due to the disease process rather than aging *per se*.

SEX DIFFERENCES IN THE ELDERLY

Research suggests that typical sex differences in cognitive performance may persist into old age, with better visuospatial and language skills in males and females respectively[11,23].

VERBAL ABILITIES

The pattern of sex differences in category fluency of the healthy elderly is far from consistent, with some finding a female advantage[11,39-44], others no sex differences at all[22,25,45-48] and at least one report of a male advantage[33]. The presence of an effect may depend upon the specific category examined, with reports of both a female advantage and an absence of sex differences[49] or both a female advantage and a male advantage[41] or all three possibilities depending upon the specific semantic category examined[15].

A picture naming advantage in elderly males has been documented[16,50-53] mirroring the advantage often seen in young adults, although not in all studies of the elderly[16,39,43-46,54-59]. In a longitudinal study by Connor *et al*[16], the rate of decline in naming was comparable for men and women.

VISUOSPATIAL ABILITIES

Corresponding to the findings in the healthy young, elderly men outperform elderly women on mental rotation[60] and spatial perception tasks[39]. For spatial visualisation tasks, the findings are variable and task-specific. A male advantage was reported by some[11,24] although equivalent male and female performance was observed by others including on the block design task[11] and figure copying[39], mirroring the conflicting patterns seen in the young.

MEMORY

Little evidence supports an unambiguous sex difference in memory function for the healthy elderly. Some report women being better at immediate word learning[47],

Table 1 Sex differences in studies assessing fluency and naming in the elderly

Ref.	Sample size		MMSE		Tasks	Finding
	M	F	M	F		
Marra *et al*[41]	85	168	19.1	17.6	CF (fu)	NS
					CF (b)	M > F
Monsch *et al*[42]	43	46			LF (F, A, S)	NS
					CF (s, *n*)	NS
					CF (a + f + ve)	F > M
Beinhoff *et al*[45]	26	23	25.6	24.7	CF (a)	NS
					CN	NS
Henderson *et al*[46]	22	24			CN	M > F
Henderson *et al*[46]	270	377	17.5	17.3	CF (a)	M > F
					CN	M > F
Moreno-Martinez *et al*[49]	28	33	21.2	18.9	CF (I, tr, v, t, mi)	M > F
					CF (a, fl, f, fu, k, c, bg, bp)	NS
Randolph *et al*[53]	129	196			CN	M > F
Buckwalter *et al*[55]	72	87	17.8	16.5	CN	M > F
McPherson *et al*[77]	23	36	23.3	22.2	LF (F, A, S)	NS
					CF (a)	NS
					CN	M > F
Ripich *et al*[78]	29	31			LF (F, A, S)	NS
					CN	M > F
Bayles *et al*[79]	30	33	15.2	15.9	LF (A, S)	NS
					CF (a, f)	NS
					CN	NS
Perneczky *et al*[81]	50	43	23.9	23.0	CF (a)	NS
					CN	M > F
Henderson *et al*[136]	26	27	13.8	11.8	LF (F, A, S)	NS
					CF (a)	NS
					CN	NS

F: Female; M: Male; NS: Not significant; MMSE: Mini mental state examination; CF: Category fluency; CN: Confrontation naming; LF: Lexical fluency; CF: Categories; a: Animals; b: Birds; bg: Buildings; bp: Body parts; c: Clothing; f: Fruit; fl: Flowers; fu: Furniture; i: Insects; k: Kitchen utensils; mi: Musical instruments; n: First names; s: Supermarket items; t: Tools, tr: Trees; v: Vehicles; ve: Vegetables.

verbal memory and episodic memory[22], while others have found no sex differences in verbal memory[61] or for delayed word learning[47,50]. Some evidence also documents that elderly men have better visual memory[38], working memory and episodic memory[24]. In summary, sex-differences in the memory ability of the healthy elderly where described, appear to be significantly dependent upon the specific task.

We have reviewed the evidence for sex and age-related differences in cognitive tasks within the normal population and principally within the healthy elderly population. It is important to have a clear understanding of such patterns, and the extent to which they are well-replicated, if we are to make sense of any sex differences in cognitive abilities that may emerge after the onset of AD.

VERBAL ABILITIES IN AD

Semantic memory impairments emerge early in AD neuropathology[62]. Category fluency deficits may be apparent as much as five years prior to diagnosis[63] and mild AD patients are more impaired than those with Mild Cognitive Impairment (MCI) and elderly controls on category fluency[64,65]. Two meta-analyses[66,67] have highlighted large significant category fluency deficits in people with AD compared to healthy elderly controls, with Laws *et al*[67] calculating an extremely large effect size in 92 studies (d = 2.10).

The pattern with regard to lexical fluency deficits, however, is more varied with some finding no impairment[68,69], but others a worsening of performance[70]. Nonetheless, meta-analytic studies[66,67] confirm a reliable AD deficit in lexical fluency, with[67] estimating a large effect size (d = 1.46).

Compared to the healthy elderly, AD patients also have far greater difficulties on confrontation naming tasks[64,69,71-75]. A meta-analysis of 56 naming studies assessing 2607 AD patients and 2285 healthy controls by Laws *et al*[67] obtained a large effect size deficit in AD patients (d = 1.54).

SEX DIFFERENCES IN VERBAL ABILITIES IN AD

While AD is characterised by decline in the verbal and semantic domains, does any evidence suggest that the relative performance of men and women differs from the pattern in the healthy elderly? A search of the literature reveals a modest number of relevant studies (Table 1).

Several studies in the 1990s reported that, compared to men with equivalent AD severity, women manifest a more profound impairment of semantic memory[46,76-78].

Table 2 Studies assessing sex differences in visuospatial abilities for Alzheimer's disease patients

Ref.	Sample size		MMSE		Tasks	Finding
	M	F	M	F		
Beinhoff *et al*[45]	26	23	25.6	24.7	FC	M > F
Henderson *et al*[46]	22	24	Not given		FC	NS
Henderson *et al*[46]	270	377	17.5	17.3	FC	NS
Buckwalter *et al*[55]	72	87	17.8	16.5	BD	NS
					FC	NS
Perneczky *et al*[81]	50	43	23.9	23.0	FC	NS
Cushman *et al*[90]	22	12	24.03		JLO	NS
Heun *et al*[101]	171	267	15.5	16.3	FC	M > F
Millet *et al*[102]	20	20			Corsi,	NS
					Corsi (b),	M > F
					VPT	
Henderson *et al*[136]	26	27	13.8	11.8	FC	NS

M: Male; F: Female; NS: Not significant; MMSE: Mini mental state examination; BD: Block design; Corsi: Corsi block tapping; Corsi (b): Corsi block tapping (backwards); FC: Figure copying; JLO: Judgment of line orientation; VPT: Vecchi's pathway task.

In particular, female AD patients name fewer items correctly in confrontation naming tasks[46,55,77,78]. Others have reported higher naming scores by men, but no significant sex differences[45,79]. Crucially, the significant sex differences in AD patients remain after controlling for the effects of age, education, and duration of illness[46,55,76,78]. In their meta-analysis, Laws *et al*[67] confirmed a male naming advantage by showing larger effect sizes in studies containing a greater proportion of female AD patients.

Several studies have reported no sex differences in lexical fluency performance in AD patients[42,77-80] but a more ambiguous profile has emerged with category fluency tasks and may reflect the specific choices of categories. Perhaps surprisingly, men with AD significantly out-perform women on the most commonly used category of animals[46] as well as for insects, trees, tools, musical instruments, vehicles[49] and birds[41]. Nevertheless, others have found no significant sex differences for: Animals[45,46,49,77,79,81], fruits[49,79], furniture[41,49] supermarket items or first names[42]. Only one study[42] has asserted a female semantic fluency advantage, though this was for the total of animals, fruits and vegetables combined.

VISUOSPATIAL ABILITIES IN AD

While verbal and memory problems in AD are widely acknowledged, the prevalence of visuospatial deficits has been relatively underplayed, and may be important given the link between visuospatial abilities and functional competence in healthy older individuals[82] as well as those with dementia[83]. Some evidence also intimates that visuospatial tests may be useful in staging the disease process, differentiating mild from moderate dementia in AD[84].

People with AD fare worse than the healthy elderly on visuospatial tasks, including, for example, tests of mental rotation[85-88]. Lineweaver *et al*[88] posited that since mental rotation involves the parietal cortex, and AD results in extensive damage to this region, AD patients would be impaired at this task. This was indeed the case when compared with healthy elderly controls[88].

Salmon *et al*[89] claimed that the visuospatial deficits associated with AD are usually evident in visuoconstructional tasks (*e.g.*, block design) and visuoperceptual tasks [*e.g.*, judgement of line orientation (JLO) task]. In line with this, several studies show that AD patients are worse than elderly controls on the JLO task[88,90-92], although Finton *et al's*[93] AD patients presented with no problems on this task. Impairments have been reported both for block design[91,94] and for figure copying[95,96]. Even participants with mild AD score lower than elderly controls on a figure-copying task[97,98] and on drawing a complex figure from memory[98].

Visuospatial deficits are also apparent for some years prior to AD diagnosis. Backman *et al*[99] found that healthy elderly individuals, who were later diagnosed with AD, performed worse on visuospatial tasks than those who remained free of dementia at follow-up. In a related vein, Laukka *et al*[100] identified an increase in the rate of visuospatial decline in elderly participants up to 10 years prior to AD diagnosis.

SEX DIFFERENCES IN VISUOSPATIAL ABILITIES IN AD

Although AD reduces performance on a range of visuospatial tasks, does the performance on these tasks differ between men and women? If AD affected men and women equivalently, then we might expect to see a continuing male advantage on most visuospatial tasks, as an extension of the typical healthy elderly profile.

Of 16 studies that have considered sex differences in AD patient cognition, nine included at least one visuospatial ability task (Table 2). Only one used a spatial perception task[90], which was primarily concerned with navigation (they also included the JLO task) and no significant sex differences emerged. All other papers examined spatial visualisation tasks where, as already discussed, findings in the general population are variable and seem to be contingent on the specific task used. Buckwalter *et al*[55] found no differences between male and female AD patients on block design. Beinhoff *et al*[45], however, reported that AD males outperformed AD females at a drawing task measuring visuospatial episodic memory. These findings were unlikely to reflect a generalised visuospatial skill advantage as no sex differences emerged for visuospatial memory span. Most other researchers, however, have failed to discern any difference between AD men and AD women at copying a geometric figure[46,55,80,81,101]. Heun *et al*[101] did report a male superiority on visuoconstructive tests that involved copying geometrical figures such as cubes, but this did not reach significance.

In summary, the visuospatial abilities of men and women with AD do not parallel the male-female divergence seen in the healthy population. To date however, no paper has examined mental rotation performance in AD patients, which as discussed earlier, is the most sensitive visuospatial task to sex differences in the general population. Given the complexity of rotation tasks, researchers may feel they are less useful with AD patients. As noted, Lineweaver *et al*[88] did use a simplified rotation task, but they did not report male and female performance separately.

By contrast, some studies suggest that sex-based cognitive differences may disappear or even reverse in AD. For example, Perneczky *et al*[81] reported no significant sex differences in patients with mild AD on either verbal or visuospatial tests. One possible interpretation is that a proportionally greater deterioration of verbal and visuospatial ability occurs, respectively, for women and men. However, some contend that the male visuospatial advantage remains in AD sufferers, possibly on tasks that tasks requiring active manipulation of visuospatial information[102]. And Beinhoff *et al*[45] reported that AD males were superior at learning and retaining visuospatial information, though no sex differences in visuospatial memory span emerged. Turning to verbal abilities, Chapman *et al*[103] found greater accuracy in AD men on the Logical Memory test, which assesses verbal episodic memory, and this was a reversal of the profile in their healthy elderly controls. Surprisingly perhaps, male AD patients are also superior on naming tasks[46,55,77], and verbal fluency[55]. It is evident then that findings relating to sex differences in AD patient cognition are somewhat inconsistent, and the results of individual studies may even be misleading on this issue. Moreover, a failure to find significant sex differences in some studies may reflect insufficient statistical power; and thus, meta-analysis is a useful approach in this area.

Surprisingly few studies present neurocognitive data separately on males and females with AD. Irvine *et al*[104] identified just 15 published studies presenting data from a total of 828 men and 1238 women with AD. Unsurprisingly, AD studies contained more female than male patients (60% *vs* 40%) and although most researchers test both male and female patients, they do not routinely report between-sex comparisons, and so any differences have gone unnoticed. In earlier work, we tried to circumvent this methodological drawback by assessing the "proportion" of male participants per study as a moderator of effect sizes. This approach showed that picture-naming effect sizes increase in AD patients as the proportion of female patients increase[67]. Similarly, our meta-analysis[67] of 92 studies examining semantic and 96 examining phonemic fluency in over 4500 and 3000 AD patients respectively, found that the proportion of females significantly predicted both effect sizes. In other words, as most studies of AD patients have more females, studies will tend to significantly inflate effects, and differences in the proportions of male and female participants will increase variability in findings across studies.

Irvine et al[104] *meta-analysis*

The meta-analysis by Irvine *et al*[104] uncovered small, but significant male advantages across each of five cognitive domains examined (Cohen's *d*, 95%CIs, Table 3): Episodic memory (*d* = - 0.17, 95%CI: -0.33 to -0.01) semantic memory (*d* = -0.25, 95%CI: -0.42 to -0.07) verbal (*d* = -0.27, 95%CI: -0.37 to -0.16), non-semantic (*d* = -0.14, 95%CI: -0.26 to -0.02) and visuospatial (*d* = -0.24, 95%CI: -0.43 to -0.05). In terms of consistency, 49 of 52 (94%) effect sizes calculated by Irvine *et al*[104] were in the direction of worse female performance across varied cognitive domains. Furthermore, moderator regression analyses revealed that these deficits were not predicted by differences in age, education or overall dementia severity (as measured by MMSE). Hence, the worse cognitive performance of women with AD is not attributable to obvious demographic confounds.

What are the possible reasons for AD affecting the cognitive abilities in women more than in men?

One reason for the more pronounced decline in women might relate to men having greater cognitive reserve. Cognitive reserve has been defined as the amount of brain damage an individual can tolerate before reaching a clinical threshold for impairment[105]. Individuals with greater reserve are hypothesized to sustain more AD-related neuronal damage before onset of symptoms and clinical diagnosis. Consistent with this hypothesis, several recent neuroimaging studies have reported differences in brain function for male and female AD patients who are at the same disease stage. In accord with the greater age related cognitive decline in men, corresponding brain imaging evidence points to greater age-related brain deterioration in males than females[36,106]. Magnetic resonance imaging has detected greater age-related brain atrophy (as indicated by increased cerebrospinal fluid volume) in males than females[108]. In terms of specific regions and structures, greater age-related frontal and temporal lobe volume reductions have been described in males[109], while others[110] have reported a more specific reduction in hippocampal volume across early adulthood in males but not in females. A more recent and novel study using diffusion tensor imaging[111] assessed patterns of white matter connectivity - the connectome - in a large sample of males (*n* = 428) and females (*n* = 521) aged from 8 to 22, finding that females displayed stronger interhemispheric connections, while intrahemispheric connections seemed stronger in males. Although the study found no age-by-sex interaction, suggesting no sex differences in the developmental trajectory of connectivity, the duration covered was relatively limited.

In their post mortem analyses of 141 brains from the religious orders study, Barnes *et al*[21] found the association between AD pathology and clinical AD was significantly more likely to be expressed in women than

Table 3 Cohen's *d* effect sizes (95%CI) in different cognitive domains

Ref.	Sample size			Semantic	Non-semantic	Verbal	Visual-spatial	Memory
	M	F	Total	*d*	*d*	*d*	*d*	*d*
Marra *et al*[41]	85	168	253	-0.23		-0.23		
Beinhoff *et al*[45]	26	23	49	-0.07	-0.44	-0.22	-0.60	-0.37
Hendersen *et al*[46]	22	24	46	-0.37	-0.37	-0.37	-0.18	
Hendersen *et al*[46]	270	377	647	-0.30	-0.12	-0.30	-0.11	-0.12
Moreno-Martinez *et al*[50]	28	33	61	-0.42		-0.42		
Buckwalter *et al*[55]	72	87	159	-0.46	-0.24	-0.46	-0.24	
McPherson *et al*[71]	23	36	59	-0.24	-0.54	-0.35		-0.71
Ripich *et al*[78]	29	31	60	-0.74		-0.74		
Bayles *et al*[79]	30	33	63	-0.10		-0.10		
Perneczky *et al*[81]	50	43	93	-0.24	-0.12	-0.20	0.02	-0.17
Heun *et al*[101]	17	76	93		-0.18		-0.62	-0.04
Millet *et al*[102]	20	20	40		-0.40	0.08	-0.63	-0.40
Laiacona *et al*[107]	11	15	26	-0.29		-0.29		
Hendersen *et al*[136]	26	27	53	-0.26	-0.22	-0.09	-0.44	-0.15
Hebert *et al*[137]	119	245	364	-0.23	0.04	-0.09		
Total	828	1238	2066	-0.25 (-0.42 to -0.07)	-0.14 (-0.26 to -0.02)	-0.27 (-0.37 to -0.16)	-0.24 (-0.43 to -0.05)	-0.17 (-0.33 to 0.01)

Negative effect sizes favour men and positive effect sizes favour women; numbers in parenthesis are 95%CIs. M: Male; F: Female.

in men. Indeed, each unit of AD pathology (based on neuritic plaques, diffuse plaques, and neurofibrillary tangles in areas sampled from four cortical regions) increased the odds of clinical AD by more than 20 times in women compared with a 3-fold increase in men. Furthermore, with each additional unit of AD pathology, the cognitive function scores for episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability were significantly more reduced in women than in men.

Although male and female AD patients show some commonalities in functional imaging studies, differences in regional cerebral blood flow (rCBF) emerge, with women showing a more severe decrease of rCBF in the medial temporal region and frontal lobe[112]. Neuroimaging studies reporting sex differences in brain function for males and females at the same stage of the disease are consistent with a reserve hypothesis. Perneczky *et al*[81,113] found that despite being at the same disease stage; and showing no significant cognitive differences, men with AD had more pronounced and extensive pathology affecting the frontal, temporal and insular cortex, as well as the hippocampus in the right hemisphere. Moreover, women were more likely to clinically express reductions of regional cerebral metabolic rate as dementia. The authors suggest that this could be because the brain reserve capacity serves as a stronger counterweight to neurodegeneration in men than in women.

Early neuropathological progression appears to be independent of sex, but female MCI patients show an increased vulnerability to cognitive impairment earlier in the illness course; and women with AD show greater cognitive impairment than men, despite an apparent equivalence in brain atrophy[114]. Perneczky *et al*[113] reported more pronounced and extensive AD pathology for men than women in the frontal, temporal and insular cortices as well as the right hippocampus, despite being at the same disease stage and showing no significant differences in general cognitive abilities.

The apolipoprotein E (APOE) ε4 allele is an established genetic risk factor for AD[115]. Although estimates vary somewhat across studies and ethnicity, the *APOE ε4* allele is present in > 50% of AD patients and approximately only 15% of healthy elderly controls[116]. Crucially, *APOE ε4* affects the probability of developing AD more in women than men[117-120]. This common polymorphism increases the risk of clinical conversion more in women than in men both in the conversion from healthy aging to MCI/AD and in the conversion from MCI to AD[120]. Lin *et al*[121] have recently examined longitudinal rates of change over eight years in a large sample of 398 MCI subjects (141 females and 257 males), finding faster rates of cognitive and functional decline in women than men and this effect was greater in female *APOE ε4* carriers. In the healthy population, the impact of APOE ε4 on cognitive performance is more pronounced in women[122,123], and has been specifically linked to hippocampal atrophy in female MCI sufferers[124]. A large post mortem study (n = 729) established that AD-related abnormalities such as neurofibrillary tangles and senile plaques are affected by a complex interaction between the aging process, sex, and genetic (*APOE ε4*) risk factors[125]. These findings are consistent with a relatively greater semantic and verbal impairment in female AD sufferers that differs from, and is greater than, any pre-existing sex differences in cognition[101].

Estrogen has been implicated in the pathobiology of AD[126]. Indeed, findings suggest that verbal sex differences in AD may arise *via* an estrogen deficiency in women. Further evidence shows that Estrogen therapy prevents the decrease in verbal memory when administered immediately following the surgical

removal of both ovaries in premenopausal women[127]. Women with AD who receive estrogen hormonal therapy perform as well on naming and verbal short-term memory tasks as men and significantly better than AD women not receiving such therapy. Further evidence suggests that duration of estrogen use is related to the rate of global cognitive decline and visuospatial ability in non-demented elderly women, although not to semantic or episodic memory[37]. Loss of estrogen alone cannot fully explain the poorer cognitive performance of women with AD; otherwise we would expect the same deficits seen in women with AD (for verbal fluency and verbal episodic memory) to be evident in the healthy elderly and this is not the case.

Following the menopause, cognitive abilities in healthy elderly women may be adversely affected by estrogen loss, albeit primarily on verbal tasks[127-130]. Indeed, women show significant changes in cognitive function during pregnancy and the postpartum period, principally in verbal free-recall and working memory[131,132], word fluency and word list learning[133]. Recent evidence suggests that during the third trimester and the early postpartum period, verbal recall deteriorates in pregnant women[134]. Furthermore, a longitudinal study of pregnant women showed they performed worse than non-pregnant controls on two tests of verbal memory, a visuospatial task, and on a task of processing speed[135]. These findings support the view that changes in sex hormone production within the physiological range that occur during reproductive events modify performance on a variety of cognitive functions - but principally on verbal tasks.

CONCLUSION

Although not unanimous, the evidence presented in this review converges on the multiple cognitive abilities being more adversely affected by AD in women than in men. This conclusion is strengthened by our own recent meta-analyses consistently affirming that men with AD outperform women with AD across a range of cognitive domains.

The literature on verbal abilities in the elderly reveals either an advantage for women or no sex difference - crucially, not one paper documents a male advantage in this domain. Findings are somewhat inconsistent in studies of cognitive decline under normal aging, suggesting something specific about AD neuropathology that disadvantages females. Some limited evidence suggests that females deteriorate faster than males in the earlier stages of the disease. Possible explanations are for a hormonal influence, possibly due to estrogen loss in women or a greater cognitive reserve in males, which provides protection against the disease process. Future studies which examine sex differences on a longitudinal basis, may provide greater clarity on these issues.

The unequivocal finding from the Irvine *et al*[104] meta-analysis of AD patients is that men modestly but significantly outperform women in all of the five cognitive domains assessed. Moreover, most papers report better male performance within every domain (only three had a female superiority in any single domain and the effect sizes were close to zero). Neither any differences in age nor dementia severity (as measured by MMSE) could account for the male advantage. Overall, the findings indicate that in women with AD, multiple cognitive functions are affected both more severely and more widely than men.

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