Published in final edited form as:

Aging health. 2012 ; 8(6): 625–632. doi:10.2217/ahe.12.66.

Language performance in postmenopausal women with and without hormone therapy and men

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Abstract

Aims—In the current study, we explored the potential effects of hormone therapy (HT) on language functioning in healthy, postmenopausal women and compared them with men of similar ages.

Materials & methods—Language functioning on tasks of verbal fluency and object naming was examined in 100 participants (mean age: 61.9 years; 33 HT users, 15 HT non-users and 52 men) at baseline and follow-up (mean follow-up time period: 2.6 years).

Results—At baseline, men had higher composite language scores than HT users. However, HT users demonstrated more improvement over time compared with men, whereas HT non-users performed similarly to men, with no improvement over time. Longer duration of HT use was not associated with improved performance on language tests.

Conclusion—These results suggest an association between HT use and better language ability in postmenopausal women.

Keywords

cognitive decline; estrogen; hormone therapy; language functioning; postmenopausal women

Prior research suggests a role for estrogen in several physiological and neurological mechanisms associated with cognitive functioning [1–4], and estrogen deficiency associated with menopause may contribute to the cognitive declines experienced by postmenopausal

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Financial & competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

women [5]. This connection between estrogen and cognition has been supported by the observation that postmenopausal women who experience a rapid decline in estrogen levels have a higher risk of developing Alzheimer's disease (AD) compared with men of the same age [6,7], who have a more stable, intrinsic supply of estrogen, even in older adulthood [8]. The use of hormone therapy (HT) may counteract or mediate the effects of estrogen deficiency on cognitive functioning and prevent or delay cognitive decline in postmenopausal women.

Previous research investigating the effect of HT on cognitive functioning has yielded mixed findings. However, the effect of HT may be better understood within specific domains of cognitive functioning. Past studies have mainly found evidence of a beneficial effect of HT use, particularly in the domains of verbal abilities, including verbal memory and language [9–11].

In terms of language, the most support for a beneficial effect of HT has been found on measures of semantic fluency. In a study of postmenopausal women by Grodstein *et al.*, women who were currently using HT demonstrated a significantly better performance than women who had never used HT on a semantic fluency task [12]. Other investigations also found that HT users had higher mean scores on semantic fluency measures than non-users [10,13,14]. In one of the few longitudinal studies examining the effect of HT use over time, Rice *et al.* found that women using HT demonstrated an improvement in category naming scores over time compared with women given a placebo [15]. Taken together, these findings seem to provide significant support for a protective and perhaps even beneficial effect of HT use on semantic fluency in postmenopausal women.

Researchers comparing the performances of HT users with HT non-users on tasks of phonemic verbal fluency and object naming have found less support for an effect of HT. Although Szklo *et al.* found that HT users performed better than non-users on a verbal fluency task [16], several other researchers were unable to find an association between HT use and test performance [13,14,17]. In terms of object naming, Henderson, Watt and Buckwalter found that HT users had significantly higher scores than HT non-users [18], but others found no significant differences [14,17].

Given the variability of results from past studies, it is not difficult to see why the effect of HT use has been a controversial topic and why it continues to be the focus of ongoing research. Although there does seem to be some support for a protective effect of HT on the cognitive functioning of non-demented postmenopausal women in the area of language, particularly in semantic fluency, investigations of other cognitive domains, such as executive functioning, visual-spatial skills, attention and working memory, have yielded less evidence for a protective effect of HT use.

Prior cross-sectional research has compared the cognitive performances of HT users with HT non-users. Fewer studies have been conducted to examine the longitudinal effect of HT on the relative decline in cognitive functioning across time. However, the effect of HT use on cognitive functioning has been suggested to be modulated by the duration of use. Paganini-Hill and Henderson found that the risk for AD in women decreased significantly

with longer duration of HT use [19,20]. Ryan *et al.* also found that longer duration of HT use appeared to be more cognitively beneficial [11]. Furthermore, Grodstein *et al.* found a trend of increasing scores on a semantic fluency task with increasing duration of HT use, and that the relationship between HT use and performance on this task was greater for women who had five or more years of HT use [12]. If the effect of HT use is also related to the duration of use, then perhaps further investigation of the long-term effect of HT use over time is needed to gain a better understanding of the exact nature of its role on cognitive functioning.

The current study was designed to investigate the effects of HT use on language abilities in healthy, non-demented postmenopausal women. Specifically, the differences between the performance of women who were currently using HT and women who had never used HT on measures of language were examined. The longitudinal effects of HT on the relative decline in language functioning over time were also investigated. In addition to comparisons between HT users and HT non-users, both groups were also compared with males as a control group, which is an approach that has been documented before [10]. HT users were expected to demonstrate better language performance than HT non-users and men at baseline, and less decline at follow-up.

Method

Participants

A total of 104 participants with baseline and follow-up evaluations conducted at least 1 year apart were retrospectively identified from archival data collected at the University of California, Los Angeles (UCLA) Semel Institute for Neuroscience and Human Behavior (CA, USA). Four of those participants did not have language scores for at least one of the evaluations and, therefore, were excluded from the present study. The mean age at baseline was 61.90 years (standard deviation [SD]: 9.97), and the mean level of education was 16.17 years (SD: 3.07). Participants were screened for any major medical, psychiatric or neurological conditions, such as major depressive disorder or Parkinson's disease, and volunteers with a significant history were excluded from the study. In addition, those who met criteria for dementia at either baseline or follow-up were excluded from the current study, as the focus of this investigation was the effect of HT on normal aging. Women who were pre- or peri-menopausal were also excluded from the present study.

Measures & procedures

Each participant received a baseline neuropsychological evaluation, as well as a follow-up evaluation using the same protocol approximately 1–2 years later. The mean number of years between participants' baseline and follow-up scores was 2.59 years (SD: 1.67). Each participant completed the Boston Naming Test (BNT) [21] and the Controlled Oral Word Association Test (COWAT) [22] as part of a full neuropsychological evaluation covering multiple cognitive domains. The present study focused particularly on language tasks. The BNT is a measure of object naming in which participants are asked to name objects pictured in 60 drawings. The COWAT is a measure of verbal fluency that includes both a phonemic fluency task (FAS), where participants are asked to generate as many words as possible that

begin with a particular letter ('F,' 'A' or 'S') in three 60-s trials, and a semantic fluency task (Animals) in which participants are asked to generate the names of as many different animals as possible within 60 s.

In addition to language tests, the evaluation also included the Mini-Mental State Examination (MMSE) [23] and measures of attention and processing speed (WAIS-III Digit Span, WAIS-III Digit Symbol, Trail-Making Test Part A, Stroop Color Naming, Stroop Word Reading) [24–26], verbal memory (WMS-III Logical Memory II, WMS-III Verbal Paired Associates II, Buschke–Fuld Delayed Recall) [27,28], executive functioning (Trail-Making Test Part B, Stroop Color-Word Interference, Wisconsin Card Sorting Test – Perseverative Errors) [25,26,29] and visuospatial skills (Rey–Osterrieth Complex Figure Test – Copy, WAIS-III Block Design) [24,30]. All participants took part in a clinical interview, and female participants completed a questionnaire regarding lifetime estrogen exposure through menarche therapy and HT.

Data analyses

Participants were divided into three groups: male subjects ($n = 52$), postmenopausal women who had never used HT (HT non-users, $n = 15$), and postmenopausal women who reported one or more years of HT use (HT users, $n = 33$). Of the HT users, 14 reported using estrogen only, 16 reported using a combination of estrogen plus progesterone and three participants did not specify the type of HT used. There were no significant differences in age, education or years of HT use between the estrogen-only HT users and estrogen plus progesterone HT users.

The association between HT use and performance on measures of language was examined by comparing the groups' baseline and follow-up raw scores using multivariate analysis of variance (ANOVA) tests (Wilks' λ). Additionally, standardized z-scores were computed for each test using age- and education-based normative data, and a composite language score was calculated for each participant by averaging the z-scores of the BNT, FAS and Animals. Group differences in composite language scores were assessed at baseline and follow-up using ANOVA analyses.

In order to examine the longitudinal effect of HT use on the relative decline in cognitive functioning over time, the baseline and follow-up scores were analyzed using a repeated measures ANOVA. In addition, difference scores were calculated by subtracting participants' baseline scores from their follow-up scores to provide an estimate of the relative change in scores over time. Difference scores were calculated for individual subtest raw scores, as well as the composite language score.

Results

Demographic characteristics

Demographic characteristics of the study sample are presented in **TABLE 1**. There were no significant differences between groups in age, years of education or years between baseline and follow-up evaluations. The HT users and non-users did not differ in years of menstruation. Within the HT group, there were no significant differences between estrogen-

only users and estrogen plus progesterone users in age, years of education, years between baseline and follow-up or test performance, with the exception of significant differences for follow-up BNT scores, with estrogen-only users outperforming estrogen plus progesterone users ($F_{2,97} = 4.22$; $p = 0.05$).

Language performance

Group means and SDs of language test raw scores at baseline and follow-up are presented in **TABLE 2**. Multivariate ANOVA tests did not reveal a significant overall group difference in FAS, Animals and BNT raw scores at either baseline ($F_{6,190} = 1.77$; $p = 0.11$) or follow-up ($F_{6,190} = 1.67$; $p = 0.13$). However, there was a significant group difference in the composite language score at baseline ($F_{2,97} = 3.20$; $p < 0.05$), but not at follow-up ($F_{2,97} = 0.69$; $p = 0.50$). *Post-hoc* Bonferroni tests revealed that HT users had significantly lower baseline composite language scores than men ($p = 0.04$), but performed similar to men at follow-up.

Means and SDs of the relative change in scores across time are also presented in **TABLE 2**. A repeated measures ANOVA of baseline and follow-up raw scores on FAS, Animals and BNT revealed no significant overall group effect over time ($F_{6,190} = 1.14$; $p = 0.34$). However, a repeated measures ANOVA of the composite language scores at baseline and follow-up revealed a significant difference between groups over time ($F_{2,97} = 3.28$; $p = 0.04$). Specifically, *post-hoc* Bonferroni tests revealed that HT users (mean change = 0.24; SD: 0.55) demonstrated more improvement in composite language scores from baseline to follow-up than men (mean change = -0.03; SD: 0.53; $p = 0.04$), who seemed to demonstrate relatively little change across time. Notably, HT non-users performed similarly to men and did not demonstrate an overall improvement in language scores over time (mean change = -0.08; SD: 0.45). No significant group differences were found on individual subtest scores.

In order to investigate the specificity of the group differences on language performance, we also examined participants' performance in other cognitive domains. Measures of gross cognitive functioning (MMSE) and composite domain scores for measures of attention/processing speed, verbal memory, executive functioning and visuospatial skills were compared between groups using repeated measures ANOVAs. There were no significant group differences across time in MMSE or any other cognitive domain. Group means and SDs of MMSE and composite domain scores are reported in **TABLE 3**.

Duration of HT use

Within the HT users, the relationship between language performance and duration of HT use was analyzed with partial correlations, controlling for age and years of education (**TABLE 4**). There was no association between duration of HT use and longitudinal change in performance across all language subtests.

Discussion

The present study suggests that HT use may provide some longitudinal benefit in improving the language abilities of postmenopausal women. Although there were no significant differences between HT users and non-users, HT users demonstrated significantly more

improvement compared with men in language scores between baseline and follow-up approximately 2.5 years later, whereas the HT non-users performed similarly to men and did not demonstrate significant improvement in language scores over time. These findings offer some preliminary support for a possible long-term benefit of HT use on language functioning.

Deficits in language functioning, particularly tasks involving object naming and semantic fluency, have been identified as early, preclinical markers for AD [31]. Past studies have found that individuals in the early stages of AD display prominent deficits in these areas [32,33], and even individuals who are clinically asymptomatic but have a genetic risk for AD demonstrate worse performance on these tasks compared with those without any genetic risk [31]. Thus, semantic knowledge may be an area of cognition that declines relatively early in the disease process, and therefore might be particularly sensitive to variations in physiological processes such as fluctuating hormone levels. Consequently, language functioning may be an area of cognition in which postmenopausal women might stand to gain the most benefit from the use of HT. Accordingly, language was the only domain in which HT users demonstrated more improvement over time, with no group differences found on MMSE or in other cognitive domains.

Although the mechanism by which HT specifically affects language functioning has yet to be clearly established, there are potentially multiple biological mechanisms that may underlie the effect of estrogen on cognitive functioning. Estrogen has several neuroprotective and neurotrophic effects, including promoting dendritic growth [34]. HT can also enhance neurotransmitter functions, including cholinergic activity, through increased activation of estrogen receptors [35], which are found in higher concentrations intraneuronally in the basal forebrain, frontal lobe and locus coeruleus [36]. Accordingly, HT has been associated with increased brain activation and cerebral blood flow in multiple cortical regions [36–38], including those involved in semantic learning and retrieval.

Findings from the current study are consistent with many other observational studies that found that estrogen replacement served a neuroprotective role against AD [19,39–41]. However, findings are inconsistent with some randomized clinical trials of HT, particularly the Women's Health Initiative Memory Study (WHIMS), the largest prospective study on HT to date, which found higher rates of dementia and more significant cognitive decline in HT users compared with placebo groups [42,43]. However, Dye and colleagues emphasized that limitations of the WHIMS could account for the negative findings [39]. First, participants in the WHIMS treatment group were at high risk for cerebrovascular and cardiovascular disease, which could have contributed to the increased rates of dementia. Second, WHIMS researchers did not differentiate between dementia types (i.e., AD vs vascular dementia), which significantly limits the ability to interpret the results as the underlying neurobiological and pathological mechanisms would vary. Third, participants did not complete baseline cognitive testing; thus, reported cognitive impairments in HT users may have been present even before the HT trial began. Furthermore, participants were all aged 65 years or older, thus beginning HT at least a decade after the average age of menopause and outside the hypothesized 'critical period' of optimal benefit.

Previous evidence supports a critical period hypothesis that HT begun at the time of menopause could protect against cognitive impairment, but HT initiated years after menopause could have a negative or neutral effect on cognition [7,44,45]. Furthermore, according to the 'healthy-cell bias' hypothesis, healthy neurons seem to benefit from estrogen exposure, while unhealthy or compromised neurons exposed to estrogen tend to degenerate [46]. Estrogen-induced signaling pathways in hippocampal and cortical neurons, which play a role in semantic networks, may be particularly vulnerable to neurodegenerative processes [47]. Thus, HT may benefit recent postmenopausal, healthy women without cognitive impairment, before neurodegenerative processes have had a chance to progress. The women in our study were healthy, cognitively intact and relatively younger than the mean age of participants in other observational studies. However, due to the use of archival data, information regarding the age at which HT users initiated treatment was unavailable.

Another factor that may mediate the effect of HT use on cognition is the type of estrogen formulary taken. Specifically, a recent review found that some formularies, such as 17 β -estradiol, are associated with more cognitive benefits than others, particularly those that include progesterone compounds [39]. However, other studies failed to find a significant difference between women taking estrogen-only HT compared with those taking a combination of estrogen plus progesterone [48,49]. In the current study, HT users were relatively evenly divided between estrogen-only HT and estrogen plus progesterone HT, and *post-hoc* analysis did not find any significant differences in language performance between these two groups. However, the limited sample size precluded a rigorous examination of a potentially mediating effect of the specific type of HT in the overall analysis.

Another limitation of the current study was that the archival data did not include information regarding who was using HT at the time of evaluation and who had used HT in the past, which limited our ability to separately examine current versus past HT users. Additionally, the small size of the HT non-user group compared with the other groups may have resulted in inadequate statistical power to detect group differences. Statistical analyses were able to detect significant differences between the HT user group and the men, both of which had a larger participant number, but were unable to detect significant differences between HT users and non-users, even in cases where the differences were visibly larger than the statistically significant differences between HT users and men. Still, given the limited power provided by the small HT non-user group and the associated lack of significant differences found between this group and the HT user group, our findings should be interpreted with caution and further analyses with a larger sample size and more statistical power are needed to further build upon these findings.

Despite these limitations, by using a longitudinal design, the findings of the current study offer preliminary support for a possible cognitive benefit of HT on improving language functioning over time in healthy, cognitively intact postmenopausal women. Prior studies investigating the effects of HT on cognition, including the WHIMS study, have mostly been cross-sectional. However, the benefit of HT use may be a long-term effect that can only be seen across the span of several years. In the current study, the improvement in language functioning over time seen in HT users would not have been detected with a cross-sectional analysis, as HT users were similar to non-users and worse than men at baseline, and similar

to both groups at follow-up. Therefore, further research using longitudinal designs that also take into account other mediating variables, such as genetic risk factors and variability in HT use, can further our understanding of the long-term effect of HT on language and other areas of cognition.

Conclusion

HT use may provide some longitudinal benefit in the language abilities of healthy, cognitively intact postmenopausal women. Evidence suggests that initiating HT use at the time of menopause, and prior to the onset of significant cognitive impairment, could be a critical factor in determining potential cognitive benefit from HT use. Cognitive benefits are also likely to be observed only after a period of time. Therefore, longitudinal studies are able to offer a deeper understanding of the relationship between HT use and cognitive change over time.

Future perspective

The effect of HT use on cognition is confounded by a number of factors, including the time of initiation of HT, the specific formulary used and the duration of use. Future research investigating these and other factors will be important in clarifying the potential benefit or harm of HT use in postmenopausal women.

Acknowledgments

The work was supported by an NIH NRSA 1F31AG035438-01 to GW Small and colleagues and by NIH grants P01-AG025831, AG13308, P50 AG 16570, MH/AG58156, MH52453; AG10123; M01-RR00865, the Department of Energy (DOE contract DE-FC03-87-ER60615); General Clinical Research Centers Program; the Fran and Ray Stark Foundation Fund for Alzheimer's Disease Research; and the Ahmanson Foundation. GW Small reports having served as a consultant and/or having received lecture fees from Dakim, Lilly and Novartis. GW Small also reports having received stock options from Dakim, Inc. KJ Miller reports having received grant funding and having served as a consultant for Dakim, Inc.

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Executive summary

Language performance

- We found that hormone therapy (HT) users demonstrated an overall improvement in language abilities over time, whereas HT non-users and men, on average, did not demonstrate significant improvement over time.

Duration of HT use

- The overall improvement in language performance of HT users did not appear to be affected by the duration (i.e., number of years) of HT use.

Conclusion

- Cognitive benefits are likely to appear over time, which suggests that future research examining the effect of HT use should utilize a longitudinal design.

Table 1

Demographic characteristics for hormone therapy users, hormone therapy non-users and males.

	HT users [†] (n = 33)	HT non-users [†] (n = 15)	Males [†] (n = 52)		
<i>Demographic variables</i>				<i>F_{2,97}</i>	<i>p</i>
Age at baseline (years)	61.79 (8.14)	58.80 (12.43)	62.87 (10.25)	0.97	0.38
Years between baseline and follow-up	2.53 (1.95)	2.34 (1.23)	2.71 (1.61)	0.31	0.73
Years of education	15.83 (2.65)	15.07 (2.87)	16.69 (3.31)	1.95	0.15
<i>Estrogen exposure</i>				<i>F_{1,43}</i>	<i>p</i>
Years of menstruation	33.55 (8.00)	37.36 (3.41)		2.91	0.10
Years of HT use	12.82 (10.86)				

Group differences were assessed using one-way analysis of variance.

HT: Hormone therapy.

[†]Mean (standard deviation).

Table 2

Language composite scores and subtest raw scores at baseline and follow-up[†].

	HT users [‡]	HT non-users [‡]	Males [‡]
Baseline			
Language composite	−0.11 (0.76) *	0.07 (1.10)	0.32 (0.67) *
FAS	39.12 (11.85)	42.27 (14.59)	42.06 (12.05)
Animals	19.76 (4.30)	21.00 (4.80)	21.06 (4.83)
BNT	55.06 (4.89)	54.00 (5.86)	57.12 (2.84)
Follow-up			
Language composite	0.13 (0.86)	−0.01 (1.37)	0.29 (0.82)
FAS	42.70 (12.31)	44.20 (16.98)	41.79 (11.61)
Animals	20.70 (4.77)	20.00 (5.93)	20.62 (5.82)
BNT	55.27 (3.68)	53.73 (6.78)	57.02 (3.69)
Relative change in scores from baseline to follow-up			
Language composite	0.24 (0.55) *	−0.08 (0.45)	−0.03 (0.53) *
FAS	3.58 (9.62)	1.93 (8.65)	−0.27 (8.13)
Animals	0.94 (4.34)	−1.00 (2.00)	−0.44 (4.50)
BNT	0.21 (2.10)	−0.27 (2.49)	−0.10 (2.44)

Animals: Semantic fluency task; BNT: Boston Naming Test; FAS: Phonemic fluency task; HT: Hormone therapy.

[†] Group means and standard deviations of language composite scores and individual subtest raw scores at baseline and follow-up, as well as relative change in scores between baseline and follow-up are presented. Group differences in baseline and follow-up scores were assessed using one-way analysis of variance. Group differences in relative change over time were assessed using a repeated measures analysis of variance.

[‡] Mean (standard deviation).

* Groups differ by $p < 0.05$.

Table 3Domain composite scores[†].

	HT users [‡]	HT non-users [‡]	Males [‡]		
MMSE	n = 33	n = 15	n = 51	F_{2,96} = 0.45	p = 0.64
Baseline	29.18 (1.04)	29.00 (0.93)	29.10 (0.94)		
Follow-up	28.70 (1.26)	28.80 (1.47)	28.55 (1.30)		
Relative change	−0.48 (1.18)	−0.20 (1.01)	−0.55 (1.36)		
Attention/processing speed	n = 29	n = 15	n = 41	F_{2,82} = 1.12	p = 0.33
Baseline	0.31 (0.52)	0.04 (0.79)	0.16 (0.64)		
Follow-up	0.45 (0.57)	0.19 (0.74)	0.15 (0.84)		
Relative change	0.14 (0.45)	0.15 (0.34)	−0.01 (0.54)		
Verbal memory	n = 28	n = 14	n = 37	F_{2,76} = 0.80	p = 0.45
Baseline	0.17 (0.83)	0.13 (1.20)	0.42 (0.82)		
Follow-up	0.38 (0.94)	0.28 (1.03)	0.45 (0.92)		
Relative change	0.21 (0.66)	0.15 (0.47)	0.03 (0.56)		
Executive functioning	n = 18	n = 11	n = 24	F_{2,50} = 0.01	p = 0.99
Baseline	0.22 (0.77)	−0.07 (0.98)	0.29 (0.66)		
Follow-up	0.35 (0.95)	0.06 (0.88)	0.44 (0.60)		
Relative change	0.13 (0.75)	0.12 (0.75)	0.16 (0.38)		
Visuospatial skills	n = 31	n = 15	n = 49	F_{2,92} = 0.13	p = 0.88
Baseline	−0.05 (0.91)	−0.12 (0.95)	0.40 (0.73)		
Follow-up	−0.19 (0.92)	−0.23 (1.45)	0.20 (0.92)		
Relative change	−0.14 (0.71)	−0.11 (1.08)	−0.20 (0.63)		

HT: Hormone therapy; MMSE: Mini-Mental State Examination.

[†] Group means and standard deviations of composite domain scores at baseline and follow-up, as well as relative change in scores between baseline and follow-up are presented. Group differences in baseline and follow-up scores over time were assessed using a repeated measures analysis of variance.

[‡] Mean (standard deviation).

Table 4

Correlations between years of hormone therapy use and relative change in language scores from baseline to follow-up in hormone therapy users[†].

Relative change scores	Correlation coefficient (r)
Language composite	0.12
FAS	-0.12
Animals	0.11
BNT	0.07

Animals: Semantic fluency task; BNT: Boston Naming Test; FAS: Phonemic fluency task.

[†]Partial correlations controlled for age and years of education are reported. Note that no correlations were significant at the 0.05 level.