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Interactive effects of fitness and hormone treatment on brain health in postmenopausal women

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Abstract

Recent research in rodents suggests that extended and chronic hormone therapy can exacerbate memory impairments and irreversibly damage cells. However, aerobic fitness regimens have been shown to spare brain tissue and cognitive function. In addition, interactions between estrogen treatment and exercise have been reported in rodents. However, whether aerobic fitness and hormone treatments show interactive effects on human brain tissue and cognition has yet to be determined. Here we report two unique and important results: (a) HRT treatment up to 10 years in duration spares gray matter in prefrontal cortex and is associated with better performance on measures of executive function, whereas HRT treatment beyond 10 years in duration increases the degree of prefrontal deterioration and amplifies the decline on measures of executive functioning (b) higher fitness levels augment the effects of shorter durations of hormone treatment and ameliorate the declines associated with prolonged hormone treatment.
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1. Introduction

The projected population increase in people over 60 years of age has heightened research and public interest in interventions that reduce or reverse age-related neurocognitive decline. Both aerobic fitness and hormone replacement therapy treatments have emerged as two potential interventions that can improve the cognitive and brain vitality of older adults. Aerobic fitness regimens have been shown to reduce cognitive decline and alter cortical structure and function [5–8]. Similarly, hormone replacement therapy has been shown to reduce age-related cognitive decline [4,27], delay the onset of dementia [34], and spare gray and white matter in prefrontal, parietal, and temporal cortices [10,23].

However, recent research with rodents [19,20], monkeys [12], and humans [15,17] suggests that the efficacy of hormone therapy decreases, and sometimes reverses, with extended and chronic therapy regimens. For example, rodent studies suggest that long-term and chronic estrogen treatment can exacerbate memory impairments due to heightened neuroinflammation and/or reduce the efficacy of estrogen receptors [19,20]. Recent evidence also suggests that long-term chronic administration of estrogen can irreversibly damage cells in the hypothalamus and negatively affect microglial cells important in regulating immune system responses [19]. In addition, longitudinal studies conducted through the Women's Health Initiative (WHI) report that estrogen treatment may actually increase the risk for dementia [29].

Human studies rarely assess the impact of duration of hormone treatment on cognitive and brain health [35]. However, studies that have examined the effect of duration have reported inconsistent results. Some studies have reported a

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benefit of longer durations on cognition and brain tissue [4,10], whereas others report escalated inflammation and risk for neurodegenerative disorders [15,17]. One potential explanation for this inconsistency is that duration of hormone use may be interacting with other lifestyle variables, such as aerobic fitness levels. An interaction between duration of HRT and aerobic fitness would suggest that the effect of extended HRT regimens is dependent on the fitness levels of the participants.

Both estrogen and aerobic fitness are thought to have some similar mechanisms of action such as increased production of neurotrophic growth factors and enhanced vascularization [8]. Moreover, exercise and estrogen modulate biochemical markers associated with neuroprotection, angiogenesis, and neuronal growth and function alone, and interactively [3,8]. For example, brain derived neurotrophic factor (BDNF) gene expression and protein levels in the hippocampus are affected by an interaction between estrogen treatment and exercise [3]. Importantly, humans show the greatest concentration of BDNF receptors (trkB) in prefrontal cortical regions and show little changes in receptor concentration with age [25]. Thus, it is likely that the prefrontal cortex responds to BDNF-related manipulations even later in life, with the greatest improvements following interventions that increase levels of BDNF, such as estrogen and exercise. The sum of these findings suggests that interactive sparing effects of estrogen and exercise may be evident in human brain tissue and cognition. In addition, recent research on chronic and long-term administration of estrogen suggests that the neuroprotective mechanisms of estrogen and exercise may change over time.

In this study, we examined the potential for interactions between HRT and aerobic fitness on the sparing of cognitive function and brain tissue volume in 54 postmenopausal elderly women. Specifically, we predicted that short-term HRT would be beneficial to brain and behavior, but extended therapy regimens would be detrimental to cognitive and brain health. Furthermore, we predicted that aerobic fitness levels would interact with HRT treatment and reduce the deficits associated with long durations of hormone therapy and augment the beneficial effects of short-term HRT treatment.

2. Methods

2.1. Participants

Participants were recruited for this study through the use of University fliers and newspaper advertisements. Fifty-four postmenopausal women (mean age = 69.61; range = 58–80) agreed to participate in the study and signed a consent form approved by the Institutional Review Board at the University of Illinois (Table 1). Hormone status and duration were assessed via self-report. Participants were excluded from participating if they reported any neurological defects or psychiatric illness. In addition, participants were excluded if their personal physician suggested they not participate because of potential health complications or if the MRI environment posed any type of health risk. Finally, participants were excluded from the study if they scored below 51 on the Modified Mini-Mental State Examination (MMSE; high score of 57) [31].

2.2. Fitness and MRI measures

Participants were required to obtain consent from their personal physician before physical fitness testing was conducted. Aerobic fitness (VO_2 peak) was assessed by graded maximal exercise testing on a motor-driven treadmill with continuous monitoring of respiration, heart rate, and blood pressure by a cardiologist and nurse.

High-resolution T1 Magnetic Resonance Imaging (MRI) scans (1 mm × 1 mm × 1.3 mm) were collected on a Siemens 3-Tesla head-only magnet on all participants and were analyzed via an optimized voxel-based morphometry technique (VBM) [1,10,13].

2.3. VBM analyses

VBM provides a means to estimate tissue atrophy in a point-by-point fashion throughout the brain with reasonably high spatial resolution. This allows regionally specific conclusions about the variables of interest on changes in brain

Table 1
Demographic information and ANOVA results for NEVER (0 years), SHORT (1–10 years), MID (11–15 years), and LONG (16+ years) durations of hormone treatment

	NEVER	SHORT	MID	LONG	ANOVA
SES	1.88	1.77	1.75	1.83	$F = .14$ ($p < .93$)
Education	16.08	16.00	15.71	16.33	$F = .08$ ($p < .97$)
MMSE	54.71	54.84	55.41	54.08	$F = 1.21$ ($p < .31$)
K-BIT	114.53	115.23	114.25	113.08	$F = .36$ ($p < .78$)
Age	71.82	66.84	68.41	70.66	$F = 2.11$ ($p < .11$)
Age at menopause	49.17	46.76	50.08	43.00	$F = 1.83$ ($p < .15$)
HRT status	0 Users	5 Current	6 Current	8 Current	$F = 33.27$ ($p < .001$)
VO_2	22.27	25.59	22.45	21.24	$F = 1.87$ ($p < .14$)

Socio-economic status (SES) was determined by asking participants which taxable income bracket they fell into (if single (1) <30,000, (2) 30–60,000, (3) 60–135,000, (4) >135,000. If married (1) <45,000, (2) 45–100,000, (3) 100–160,000, (4) >160,000). The ANOVA column presents results from a one-way ANOVA for each of the variables as a function of HRT duration. The only significant effect was HRT status. Pairwise comparisons revealed no differences in the status of the three groups actually using hormone replacement suggesting that the effect was entirely driven by the NEVER group.

matter. Detailed methodology for this technique has previously been published [1,10,13].

In short, the MRI images of participants' brains were extracted from the skull [30], segmented into 3D maps representing the structure of the gray and white brain matters [36], and then registered into a common, study-specific, spatial coordinate system using a 12-parameter affine registration algorithm [16]. These maps were then filtered with a 12 mm 3D Gaussian kernel to precondition the data for statistical analysis. A priori probability density maps were obtained from the original data and used as seeds for re-segmentation of the images into gray and white matter maps. The resulting maps were then interrogated for systematic variation in gray and white matter structure using duration of hormone treatment, VO_2 peak, age, education, socioeconomic status (SES), and age at menopause as continuous variables within a multiple regression model. SES was determined by asking participants which taxable income bracket they fell into (if single (1) <30,000, (2) 30–60,000, (3) 60–135,000, (4) >135,000. If married (1) <45,000, (2) 45–100,000, (3) 100–160,000, (4) >160,000). Because of the possibility that certain demographic variables were related to the effects of hormone duration or fitness levels, we used age, education, SES, and age at menopause as covariates to isolate the variance associated with duration of hormone treatment, fitness level, and the interaction between hormone treatment duration and fitness. Statistical maps were thresholded at a $Z > 3.1$ uncorrected for multiple comparisons. FSL 3.1 (http://www.fmrib.ox.ac.uk/fsl/) was used for all analyses.

Partial volume estimate values from each of the four significant brain regions for the main effect of duration were extracted from each individual participant and analyzed by splitting the data into four separate groups (see below).

2.4. Cognitive measures

Executive function was assessed by the number of perseverative errors on a computerized version of the Wisconsin Card Sort Test (WCST), assessing working memory, inhibition, and switching processes [21]. Importantly, the volume of prefrontal gray matter tissue has previously been shown to mediate age-related declines in performance on the WCST [14]. In a separate analysis to assess whether duration of hormone treatment has any effects on general cognitive functioning we also analyzed the results from the modified MMSE.

We analyzed the WCST and MMSE scores (and regional VBM analysis, see above) by dividing participants into four groups: (a) (NEVER) users ($N = 16$), (b) users of hormones for up to 10 years in duration (SHORT) ($N = 13$), (c) users of hormones from 11 to 15 years in duration (MID) ($N = 13$), (d) users of hormones of 16+ years in duration (LONG) ($N = 12$). This split allowed for an approximately equal number of hormone-taking participants in each group. The type of treatment (unopposed estrogen versus opposed estrogen) varied equally between the hormone groups. In order to assess the effects of aerobic fitness we used a median split (Median = 22.0), to divide the participants into higher fit (Mean $VO_2 = 26.48$; S.D. = 4.21) and lower fit (Mean $VO_2 = 19.01$; S.D. = 2.11) groups.

The data from the WCST, MMSE, and regional VBM measures were then interrogated by an ANOVA for main effects of HRT Duration and Fitness and an interaction between HRT Duration and Fitness using SES, age, age at menopause, and years of education as covariates within the model. Post hoc tests were then conducted to determine specific differences between the groups. In addition, we conducted a correlation between VBM measures and the number of perseverative errors in the WCST.

3. Results

We found a significant main effect of duration ($F(3,42) = 11.63$; $p < .001$), a significant main effect of VO_2 ($F(1,42) = 16.14$; $p < .001$), and a significant interaction between hormone treatment duration and VO_2 ($F(3,42) = 4.12$; $p < .012$) on the number of perseverative errors in the Wisconsin Card Sort Test. Importantly, Fig. 1 shows that the significant $VO_2 \times$ Duration interaction resulted from higher VO_2 reliably reducing the deficits associated with long durations of hormone therapy (Fig. 1). Pairwise comparisons revealed significant differences between the SHORT group and MID ($p < .005$), LONG ($p < .000$), and NEVER ($p < .001$) groups such that short-term users of 10 years or less had significantly fewer perseverative errors than the other groups. In addition, the MID ($p < .035$) but not the LONG ($p < .523$) groups had significantly fewer perseverative errors than the NEVER group. The MID and LONG groups also differed in the number of perseverative errors ($p < .021$), such that people in the MID group had fewer perseverative errors. All of these effects have been adjusted

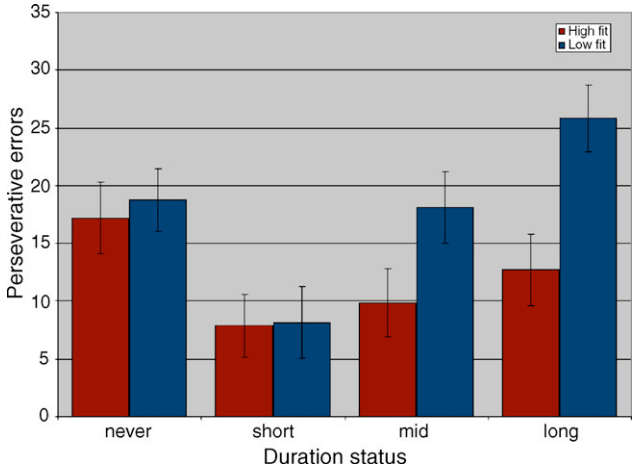

Fig. 1. Adjusted mean and standard errors for perseverative errors on the Wisconsin Card Sort Test for all four hormone groups and high fit and low fit participants after controlling for age, SES, age at menopause, and education.

for potentially confounding demographic variables (see Section 2). Importantly, SES ($F(1,42) = .326$; $p < .571$), age ($F(1,42) = .106$; $p < .746$), age at menopause ($F(1,42) = 2.47$; $p < .124$), and education ($F(1,42) = .599$; $p < .443$) were statistically unrelated to perseverative errors and were not significantly different between the four groups.

In addition, post hoc *t*-tests revealed that the high fit SHORT ($t(1,10) = 4.43$; $p < .001$) and high-fit MID ($t(1,10) = 2.94$; $p < .01$) users performed reliably better than the high fit NEVER users (a trend for the high-fit LONG users at $p < .09$). However, this was not the case for the low-fit group which showed a crossover between better performance for the low-fit SHORT users ($t(1,10) = 3.28$; $p < .002$) and worse performance for the low-fit LONG users ($t(1,10) = 2.51$; $p < .03$) compared to the NEVER users.

We also assessed the effects of duration of hormone treatment and fitness levels on the modified MMSE scores to assess whether similar effects would occur on a global measure of cognitive function. We found no main effect of duration ($F(3,42) = .259$; $p < .854$), no main effect of fitness ($F(1,42) = 2.24$; $p < .14$), and no interaction between Duration and Fitness ($F(3,42) = .56$; $p < .64$) on MMSE scores. Therefore, our results suggest that the effects of Duration of hormone treatment and fitness do not affect measures of global cognitive function as assessed by the MMSE, but might be specific to particular cognitive processes (e.g. executive functions).

Brain volume was assessed by voxel-based morphometry (VBM) on high-resolution magnetic resonance images (see Section 2) [1]. The results from the VBM analysis showed four regions in gray matter that varied with duration of hormone treatment: left and right prefrontal cortex, left parahippocampal gyrus, and left subgenual cortex (Fig. 2). Analyses indicated that longer hormone durations were associated with significantly less tissue volume in these regions. A main effect of VO_2 was found in parietal and superior frontal cortex, left and right prefrontal cortex, and subgenual cortex. Higher VO_2 scores were associated with significantly greater tissue volume in these regions. This finding replicates a previous report that found higher fitness levels to be related to more tissue in similar cortical regions [5]. The $VO_2 \times$ Duration interaction indicated that higher VO_2 scores significantly reduced the decline in tissue volume that accompanied long durations of hormone therapy. There were no significant effects of hormone duration on white matter and no significant $VO_2 \times$ Duration interactions in white matter. However, there was a main effect of VO_2 in prefrontal white matter tracts and in the genu of the corpus callosum that showed greater tissue volume in higher fit participants. Given the well-documented reduction in white matter volume with age and its detrimental influence on cognition [22] this is an interesting and potentially important finding.

Critically, the tissue volume measures in all four gray matter regions revealed that high fitness levels were associated with a more modest decline in regional brain volume than low fitness levels with increasing durations of hormone therapy (Fig. 3). High fitness levels also were associated with a significant sparing of the neural tissue of women not receiving hormone replacement therapy. Additionally, short durations of therapy (<10 years) showed enhanced tissue volume compared to all other groups and decline in tissue volume only began at MID durations (11–15 years). Thus, high levels of fitness was associated with the sparing of selective regions of neural tissue for all groups, augmenting the effects of shorter durations of hormone therapy, and offsetting negative effects of long durations of hormone therapy.

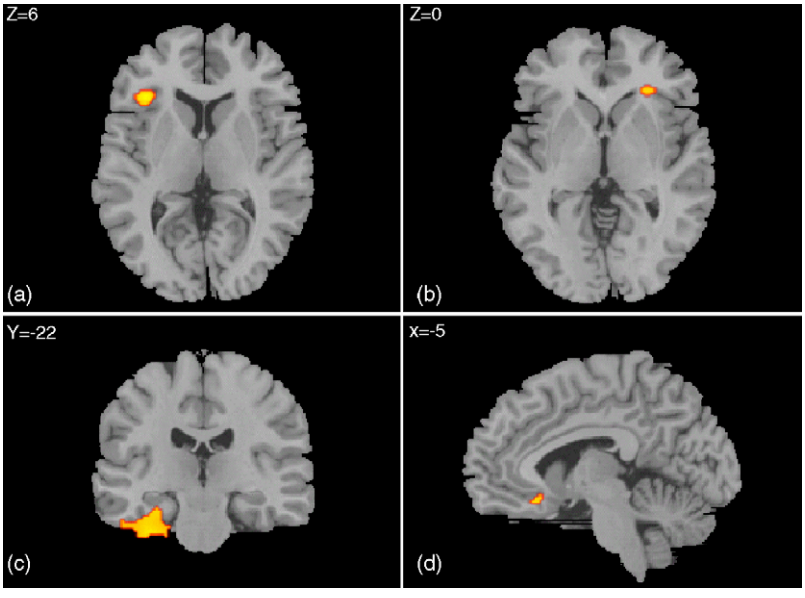

Fig. 2. Main effects of duration on gray matter volume measures using age, age at menopause, education, and SES as covariates. (a) Left inferior frontal gyrus, (b) right insula and inferior frontal gyrus, (c) left parahippocampal gyrus, and (d) subgenual cortex. All statistical maps are thresholded at a *Z*-score of 3.1 ($p < .001$) uncorrected for multiple comparisons.

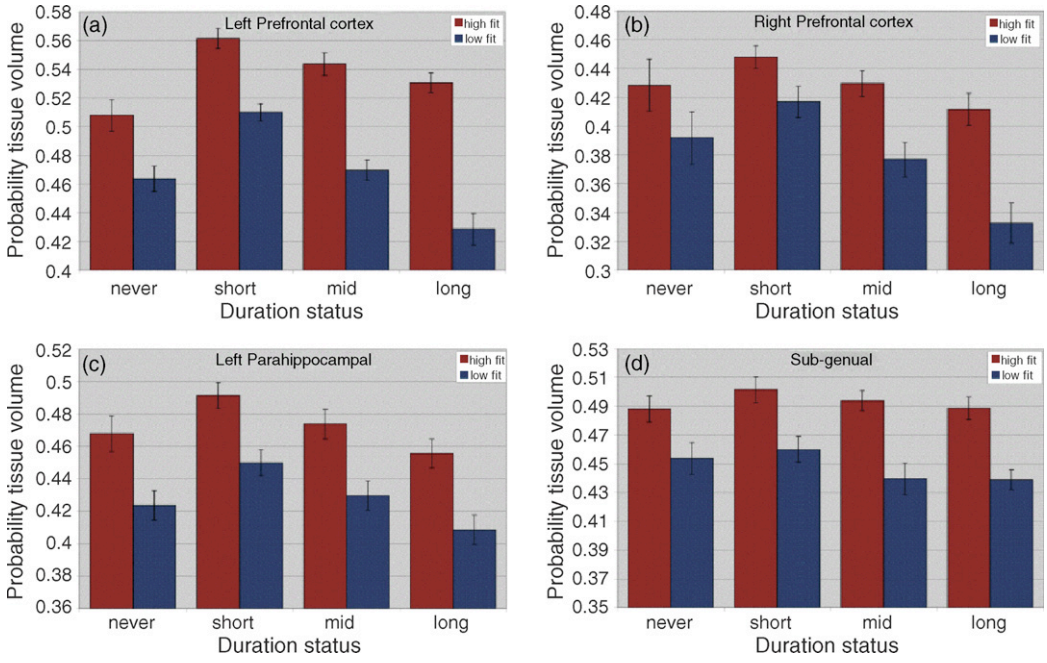

Fig. 3. Mean volume measures in (a) the left prefrontal cortex, (b) right prefrontal cortex, (c) left parahippocampal gyrus, and (d) subgenual cortex for never users, SHORT-term users, MID-term users, and LONG-term users of hormone therapy. The red bars represent high fit participants and blue bars represent low fit participants. Main effects were found in all four regions for duration of treatment and VO_2. The left and right prefrontal cortex and subgenual cortex showed significant interactions between duration of hormone therapy and fitness levels. In addition, the left prefrontal and right prefrontal tissue volume measures were significantly correlated with perseverative errors on the WCST.

Interestingly, the pattern of these effects closely resembled the effects found for perseverative errors on the WCST. A correlation analysis between the tissue volume measures and perseverative errors revealed that the amount of tissue in both the left ($r = -.391$; $p < .003$) and right ($r = -.275$; $p < .044$) prefrontal regions was negatively correlated with the number of errors. Neither the parahippocampal region ($r = -.13$; $p < .34$) nor the subgenual region ($r = -.11$; $p < .43$) was significantly related to WCST performance. These correlations argue that the effects of fitness and hormone therapy on brain tissue have an observable and potentially important relationship with cognitive health and function.

4. Discussion

We report the first known evidence that the benefit of hormone therapy on a component of executive function (i.e. the ability to discard or inhibit previously effective rules when they are no longer effective) and neural tissue in postmenopausal women is transient. These results converge with recent animal research reporting that long-term and chronic estrogen administration has negative effects on neural tissue and behavior [12,15,17,19,20]. However, we also find that higher fitness levels appear to offset the risks associated with longer durations of hormone replacement treatment. Whereas rodent studies suggest that the benefits of exercise depends on the presence of estrogen [3], we find that the largest sparing of neural tissue was related to the combinatory effect of high fitness and shorter durations of hormone therapy and that the benefits of exercise was not dependent on the presence of estrogen. This apparently conflicting result may be related to the different measures (brain volume versus BDNF) or may be related to the population studied (humans versus rats) or some other factor. In any case, the mechanisms underlying short-term neuroprotection may not be the same mechanisms at work after longer hormone treatment durations or with concomitant exercise—more research is needed to appropriately address this question.

Also, consistent with previous studies, we find that the sparing effects associated with short durations of hormone therapy and higher fitness levels were specific to regions most sensitive to age-related atrophy [5]. Regions of prefrontal and temporal cortex showed the most substantial effects of HRT and fitness. This selectivity of hormones and fitness on neural tissue argues that not all cognitive processes or brain regions will be sensitive to these interventions, at least within the age range of the participants in the present study. Consistent with this view, we find that the effects were limited to executive function measures and not global measures of cognitive function as assessed by the MMSE. Therefore, studies that have limited cognitive measures to only MMSE scores may have overlooked potential cognitive effects associated with HRT or duration of HRT.

The present results fit well with an expanding literature which is examining the factors that enhance cognitive and cortical plasticity of older adults. For example, there are now a number of studies that have found that engagement

in cognitively stimulating activities such as reading, participation in discussion groups, attending theatrical and musical performances, and learning new skills can reduce cognitive decline and even the rate of transition to Alzheimer's dementia [26,32]. Older adults also show benefits from formal cognitive training of abilities such as inductive reasoning, short-term memory, and the ability to concurrently perform multiple tasks and these training benefits can be retained for a number of years [2,18]. Indeed, in some cases the benefits of cognitive training transfer to real-world skills such as driving [24]. The present results suggest that a combination of HRT and exercise may also serve to enhance both cognition and brain structure of older women.

It should be noted that because of the cross-sectional nature of the study we cannot entirely rule out the possible confounding effects of certain demographic characteristics. However, we were able to minimize these effects within our sample and statistically remove the variability associated with potentially confounding demographic factors. More specifically, although the women within the LONG duration sample were slightly older than the women in the other groups, they were not statistically so; likewise, although the women in the LONG duration group experienced menopausal symptoms at an earlier age than the women in the other groups, they did not statistically differ from the other groups. Based on this, we can be reasonably certain that the effects represent the role of duration of hormone treatment rather than an effect associated with other factors such as an older sample or an earlier age of menopause for the LONG group.

Another important limitation of our study was that despite the positive results, we had a relatively small sample size ($n = 54$) for the assessment of the interaction between duration of estrogen treatment. Therefore, it is important for future research to replicate and extend our findings to a larger sample of women for a better generalization of these results. Ideally, such replications would take place in randomized clinical trials.

Our results are also important in relation to recent results from large randomized controlled studies that suggest that hormone replacement therapy could increase the chances for dementia and mild cognitive impairment [29]. Although the WHI studies did not examine duration of therapy or interactions with physical fitness levels, the general summary of the WHI results seem to be in conflict with our results [10]. One potential source of this discrepancy is that the women participating in the current study began taking HRT during menopause in order to control menopausal symptoms, whereas the women participating in the WHI studies were randomly assigned to a therapy regimen that may have been many years post-menopause [9,28,33]. Recent reviews have suggested that this may be one explanation for the apparent discrepancies within the current literature on estrogen research [9,28,33]. Our result also offers additional factors – duration of therapy and physical fitness – that are infrequently assessed in human estrogen research but may be contributing to the inconsistencies reported.

In sum, our results reveal that age-related neural atrophy is not an inevitable consequence of aging and there are multiple methods in which neural decline may be reduced, or even reversed, in old age. Although more research conducted in the context of randomized clinical trials is needed to determine the mechanisms of estrogen and fitness in humans (e.g. BDNF), our results provide a promising direction in determining the limits, efficacy, and interactions of aging interventions and treatments. Further research examining whether the combination of these interventions, and others such as a diet high in anti-oxidants [11] and cognitive training, delays the onset or reduces the severity of certain age-related pathologies is warranted.

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References

[1] Ashburner JA, Friston KJ. Voxel-based morphometry—the methods. Neuroimage 2000;11:805–21.
[2] Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, et al. Effects of cognitive training interventions with older adults—a randomized controlled trial. JAMA 2002;288(18):2271–81.
[3] Berchtold NC, et al. Estrogen and exercise interact to regulate brain-derived neurotrophic factor mRNA and protein expression in the hippocampus. Eur J Neurosci 2001;14:1992–2002.
[4] Carlson MC, et al. Hormone replacement therapy and reduced cognitive decline in older women. Neurology 2001;57:2210–6.
[5] Colcombe SJ, Erickson KI, Raz N, Webb AG, Cohen NJ, McAuley E, et al. Aerobic fitness reduces brain tissue loss in aging humans. J Gerontol: Biol Med Sci 2003;53:176–80.
[6] Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psych Sci 2003;14:125–30.
[7] Colcombe S, Kramer AF, Erickson KI, Scalf PE, McAuley E, Cohen NJ, et al. Cardiovascular fitness, cortical plasticity, and aging. PNAS 2004;101(9):3316–21.
[8] Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci 2002;25(6):295–301.
[9] Craig MC, Maki PM, Murphy DGM. The Women's Health Initiative Memory Study: findings and implications for treatment. Lancet Neurol 2005;4:190–4.
[10] Erickson KI, Colcombe SJ, Raz N, Korol DL, Scalf P, Webb AG, et al. Selective sparing of brain tissue in postmenopausal women receiving hormone replacement therapy. Neurobiol Aging 2005;26:1205–13.
[11] Galli RL, Shukitt-Hale B, Youdim KA, Joseph JA. Fruit polyphenolics and brain aging: nutritional interventions targeting age-related neuronal and behavioral deficits. In: Denham H, editor. Increasing healthy life span: conventional measures and slowing the innate aging process, vol. 959. New York, NY, US: Annals of the New York Academy of Science, New York Academy of Sciences; 2002. p. 128–32.

[12] Golub MS, Germann SL, Hogrefe CE. Endocrine disruption and cognitive function in adolescent female rhesus monkeys. Neurotoicol Teratol 2004:799–809.
[13] Good CD, Johnsrude I, Ashburner J, Henson RN, Friston KJ, Frackowiak RSJ. Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. Neuroimage 2001;14:685–700.
[14] Gunning-Dixon FM, Raz N. Neuroanatomical correlates of selected executive functions in middle-aged and older adults: a prospective MRI study. Neuropsychologia 2003;41:1929–41.
[15] Hogervorst E, Williams J, Budge M, Riedel W, Jolles J. The nature of the effect of female gonadal hormone replacement therapy on cognitive function in post-menopausal women: a meta-analysis. Neuroscience 2000;101:485–512.
[16] Jenkinson M, Bannister PR, Brady JM, Smith SM. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 2002;17(2):825–41.
[17] Kang JH, Weuve J, Grodstein F. Postmenopausal hormone therapy and risk of cognitive decline in community-dwelling aging women. Neurology 2004;63:101–7.
[18] Kramer AF, Willis SL. Enhancing the cognitive vitality of older adults. Curr Dir Psychol Sci 2002;11:173–6.
[19] Marriott LK, et al. Long-term estrogen therapy worsens the behavioral and neuropathological consequences of chronic brain inflammation. Behav Neurosci 2002;16:902–11.
[20] Marriott LK, Wenk GL. Neurobiological consequences of long-term estrogen therapy. Curr Dir Psychol Sci 2004;13:173–6.
[21] Milner B. Effects of different brain lesions on card sorting. Arch Neurol 1963;9:90–100.
[22] O'Sullivan M, Jones DK, Summers PE, Morris RG, Williams SCR, Markus HS. Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. Neurology 2001;57:632–8.
[23] Raz N, et al. Hormone replacement therapy and age-related brain shrinkage: regional effects. NeuroReport 2004;15(16):2531–4.
[24] Roenker DL, Cissell GL, Ball K, Wadley VG, Edwards JD. Speed of processing and driving simulator training result in improved driving performance. Hum Factors 2003;45:218–32.
[25] Romanczyk TB, Weickert CS, Webster MJ, Herman MM, Akil M, Klienman JE. Alterations in trkB mRNA in the human prefrontal cortex throughout the lifespan. Eur J Neurosci 2002;15:269–80.
[26] Schooler C, Mulatu MS. The reciprocal effects of leisure time activities and intellectual functioning in older people: a longitudinal analysis. Psychol Aging 2001;16(3):466–82.
[27] Sherwin BB. Estrogen and cognitive functioning in women. Endocr Rev 2003;24:133–51.
[28] Sherwin BB. Estrogen and memory in women: how can we reconcile the findings? Horm Behav 2005;47:371–5.
[29] Shumaker SA, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women. JAMA 2004;291(24):2947–58.
[30] Smith SM. Fast robust automated brain extraction. Hum Brain Mapp 2002;17(3):143–55.
[31] Stern Y, Sano M, Paulson J, Mayeaux R. Modified mini-mental state examination: validity and reliability. Neurology 1987;37:179.
[32] Wilson RS, Mendes de Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA, et al. Participation in cognitive stimulating activities and risk of incident Alzheimer disease. JAMA 2002;287:742–8.
[33] Wise PM, Dubal DB, Rau SW, Brown CM, Suzuki S. Are estrogens protective or risk factors in brain injury and neurodegeneration? Reevaluation after the Women's Health Initiative. Endocr Rev 2005;26:308–12.
[34] Zandi PP, Carlson MC, Plassman BL, Welsh-Bohmer KA, Mayer LS, Steffens DC, et al. Hormone replacement therapy and the incidence of Alzheimer disease in older women. JAMA 2002;228:2123–9.
[35] Zek RF, Trivedi MA. The effects of estrogen replacement therapy on neuropsychological functioning in post-menopausal women with and without dementia: A critical and theoretical review. Neuropsych Rev 2002;12:65–109.
[36] Zhang Y, Brady M, Smith SM. Segmentation of brain MR images through a hidden Markov random field model and the expectation maximization algorithm. IEEE Trans Med Imaging 2001;20(1):45–57.