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Hormone Effects on fMRI and Cognitive Measures of Encoding: Importance of Hormone Preparation

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Abstract

This exploratory and retrospective analysis compared fMRI and cognitive data from nine HT-naïve women to data from women exposed to either opposed CEE (N=10) or opposed estradiol (N=4). These preliminary data suggested that exposure to either form of HT was associated with healthier fMRI response; however, CEE-exposed women exhibited poorer memory performance than either HT-naïve or estradiol-exposed subjects. These preliminary findings emphasize the urgency to characterize differential neural effects of various HTs.

INTRODUCTION

Findings from an ancillary study of the WHI, the WHI Memory Study (WHIMS),^{1, 2} revealed a potential cognitive harm associated with a common postmenopausal hormone therapy (HT), opposed conjugated equine estrogen (CEE). These findings were in sharp contrast to extensive data suggesting estrogen's neuroprotective and neurotropic effects.³ The discrepancy between the findings of basic science and the WHIMS highlighted the many unanswered questions concerning the effects of HT and menopause upon the human CNS.

One post-WHIMS theory proposes that various HT formulations exhibit differential neuroefficacy. This exploratory report examined the effect of exposure to one of two forms of HT, opposed CEE or opposed estradiol, versus no exposure to HT. Specifically this study explored the effect of long-term HT, initiated at menopause on cerebral response during an fMRI verbal encoding task, and performance on verbal memory in a group of nonhysterectomized, postmenopausal women.

METHODS

PARTICIPANTS

Subjects came from a pool of 42 women, enrolled as controls for a study examining the effects of parental history on risk for developing AD. The 23 (54.8%) eligible subjects had intact

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ovaries and uterus, and were postmenopausal. Mean age was 58.5 years (SD 4.7). At the time of scan, two women were on opposed CEE and two on opposed estradiol. The HT regimens used by participants were standard therapies, initiated around menopause. All participants provided written informed consent. Exclusions for this study are described elsewhere.^{4, 5}

INDEPENDENT VARIABLES

A three-level HT-status variable was created for exploratory analyses. Ten women were exposed to opposed CEE and four to opposed estradiol preparations. Nine women were naïve to HT.

FMRI TASK AND ANALYSES

The fMRI task is described in detail elsewhere.^{4, 5} Briefly, subjects were presented with novel and previously learned line-drawings. Response to novel items was compared to activation to previously learned pictures. This difference in activation to novel versus previously learned items was the condition of interest in this study. The fMRI scanning procedures and individual subject image analysis are described in a previous publication.^{4, 5}

Between groups comparisons were constrained to a region of interest (ROI), based on normative activation on this same fMRI task in 77 healthy young and middle-aged adults.⁴ Supplementary Figure E depicts this mask. The variables of years of exposure and HT-status are inter-related for these analyses. Thus, nonparametric Wilcoxon score general linear models⁶ were employed to detect an effect of either HT-status and/or years of use simultaneously.

COGNITIVE TASK AND ANALYSES

Subjects underwent a battery of neuropsychological tests, including a verbal memory test, the Auditory Verbal Learning test (AVLT).⁷ This test is similar to our fMRI task, as such was selected for analysis. In this test, participants were read a list of fifteen words five times and asked to recall the words after each presentation, and again after short and long delays. Age-corrected scores were obtained using published normative data.⁷ As with fMRI data, nonparametric Wilcoxon score general linear models⁶ were used to examine the effect of HT-status and/or length of exposure for the three groups.

RESULTS

The accompanying Table describes subjects' demographic, genetic, behavioral and laboratory data. The table provides information for the three groups, HT-naïve, CEE-, and Estradiol-exposed). The groups did not differ on any subject characteristic variable.

IMAGING RESULTS

The fMRI task evoked hippocampal and inferior temporal lobe activation bilaterally to novel items compared to previously-learned items for all participants.

To compare the three groups of women, we used a nonparametric general linear model, combining HT-status and years of exposure to estimate activation. Within our ROI, an effect of HT-exposure, either CEE or estradiol-exposure was evident bilaterally in the medial temporal lobes. Global maxima for the right was located in the body of the hippocampus ($F=6.76$, $p=0.003$; $x,y,z: 26,-20,-16$; cluster size=372). For the left, global maxima was in the ventral posterior temporal lobe ($F=8.10$, $p=0.001$; $x,y,z: -36,-38,-20$, cluster size=143). A 2mm radius cluster around the global maxima in the right hippocampus was selected to represent the activation patterns for the three groups and is depicted in Figure 1. This

representation of activation suggested that the estradiol and CEE-exposed groups exhibited the greater neural response than the HT-naïve group.

COGNITIVE RESULTS

Age-corrected AVLT variables for the three groups were subjected to nonparametric general linear modeling, incorporating both HT-status and years of exposure. The overall model was significant for two of the five AVLT variables examined: the age-corrected standard scores for the total of the learning trials and the long-delay free recall. Estimates of model-implied expected values for each group suggested that the estradiol-exposed group exhibited the best performance, the CEE-exposed group the worst, with the HT-naïve group intermediate to the two. [Total of the Learning Trials $F(3,19)=8.07$, $p=0.001$; Long-Delay Free Recall $F(3,19)=6.63$, $p=0.003$]

DISCUSSION

The mechanistic basis for estrogen's neurobiological effects in the brain is well established (see review³). In contrast, the WHIMS findings^{1, 2} revealed an increased risk for cognitive decline and dementia with opposed CEE therapy. These surprising findings justify the need to characterize the *in vivo* neurobiological actions of estrogen. To date, only one study has examined the effects of estrogen intervention on brain activation with fMRI, finding short-term estrogen treatment enhanced activation of the neural network underlying working memory.⁸

Our comparison of women either naïve or exposed to one of two forms of HT revealed a difference in signal change bilaterally in the medial temporal lobes, including the right hippocampus (see Figure 1), suggesting that both forms of HT enhanced the neuronal response. It is possible that HT-exposed women may be evidencing a compensatory increased activation;⁹ however, our previous findings using this simple encoding task found increased hippocampal signal change reflected a healthy state.^{4, 5}

On the other hand, cognitive analyses suggested that despite their 'healthy' fMRI response, women exposed to opposed CEE demonstrated worse cognitive performance compared to women naïve to HT and those exposed to opposed estradiol. To our knowledge, these are the first data to support the WHIMS findings of detrimental cognitive effects associated with opposed CEE therapy. It may be that CEE is associated with hippocampal neuroprotection; however, other cumulative effects of CEE may be detrimental. Further study with larger samples is needed to elucidate the CNS effects of HT.

The foremost limitation with our study is the small sample size, especially for women exposed to opposed estradiol. Furthermore, this is not a randomized trial. We were unable to control for length of exposure to HT or other factors that may influence estrogen's effects. Notably, four women were on active treatment at the time of the scan, a factor that could have affected their BOLD signal. However, excluding the four women on HT revealed a similar pattern of neuronal activation in a more general comparison of HT-naïve and HT-exposed groups. In total, these factors may compromise the comparability of groups and generalizability of the data. Nonetheless, we present these data primarily to prompt further inquiry and emphasize the urgency to clarify the differential effectiveness of various HT preparations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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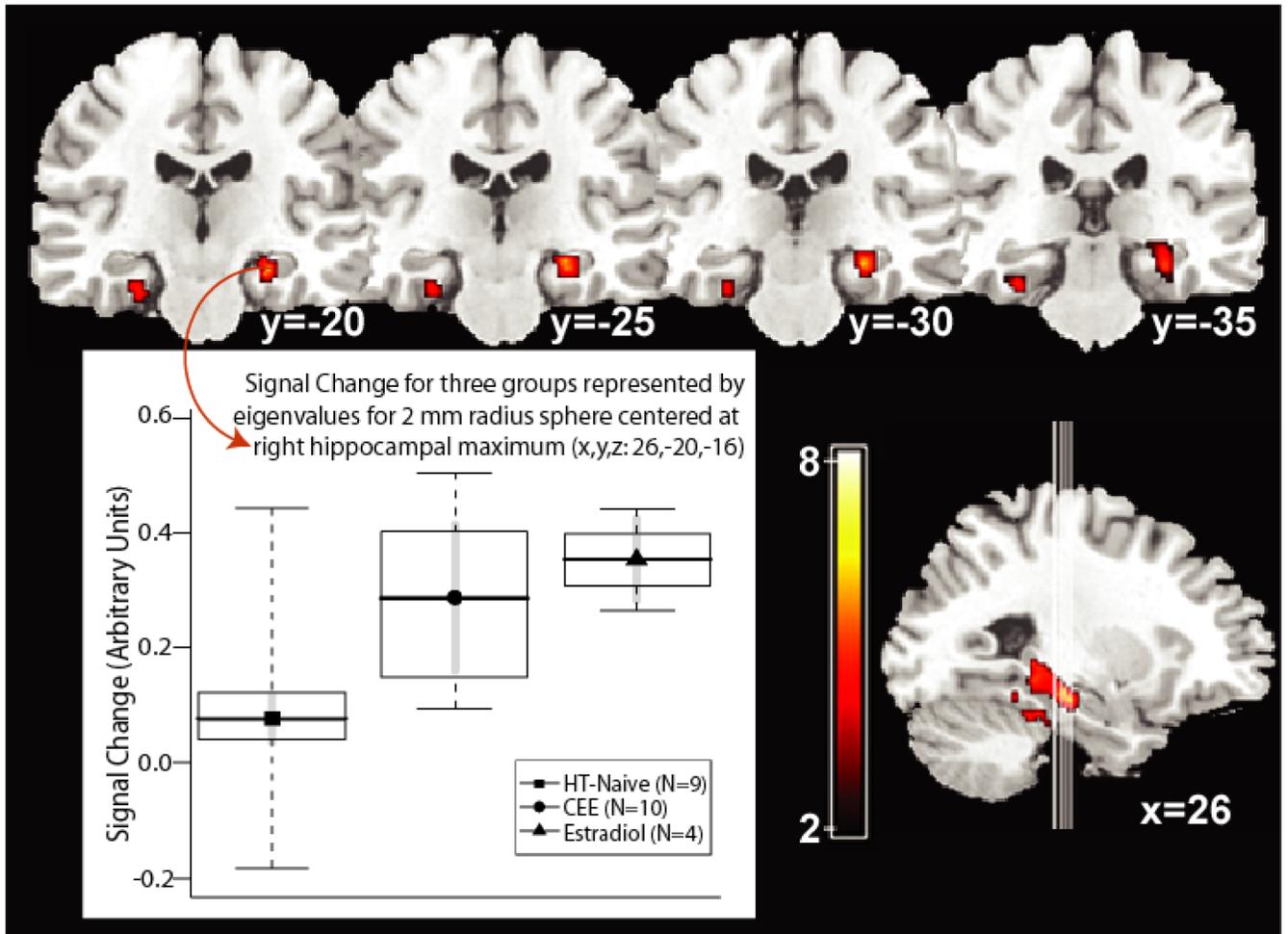


Figure 1.

Area in ROI showing differential activation between three groups. Plots of cluster activation at global maxima suggest that Estradiol and CEE-exposed groups exhibit greater signal change than HT-naïve group. The statistical comparison is overlaid on a template brain. Orientation for coronal slices located at y coordinates -20 to -5 ; the left side of the brain is on the left side of the image. Orientation for sagittal slice is at x coordinate = 26. Smaller figure depicts activation for three groups of women (HT-naïve, or Estradiol or CEE-exposed) represented by eigenvalues from a 2mm radius cluster centered at maximum of right hippocampal cluster (x,y,z: 26, -20 , -16). Displayed are boxplots (min, 25th percentile, median, 75th percentile, max, in black) superimposed on 95% confidence intervals of the medians (grey).

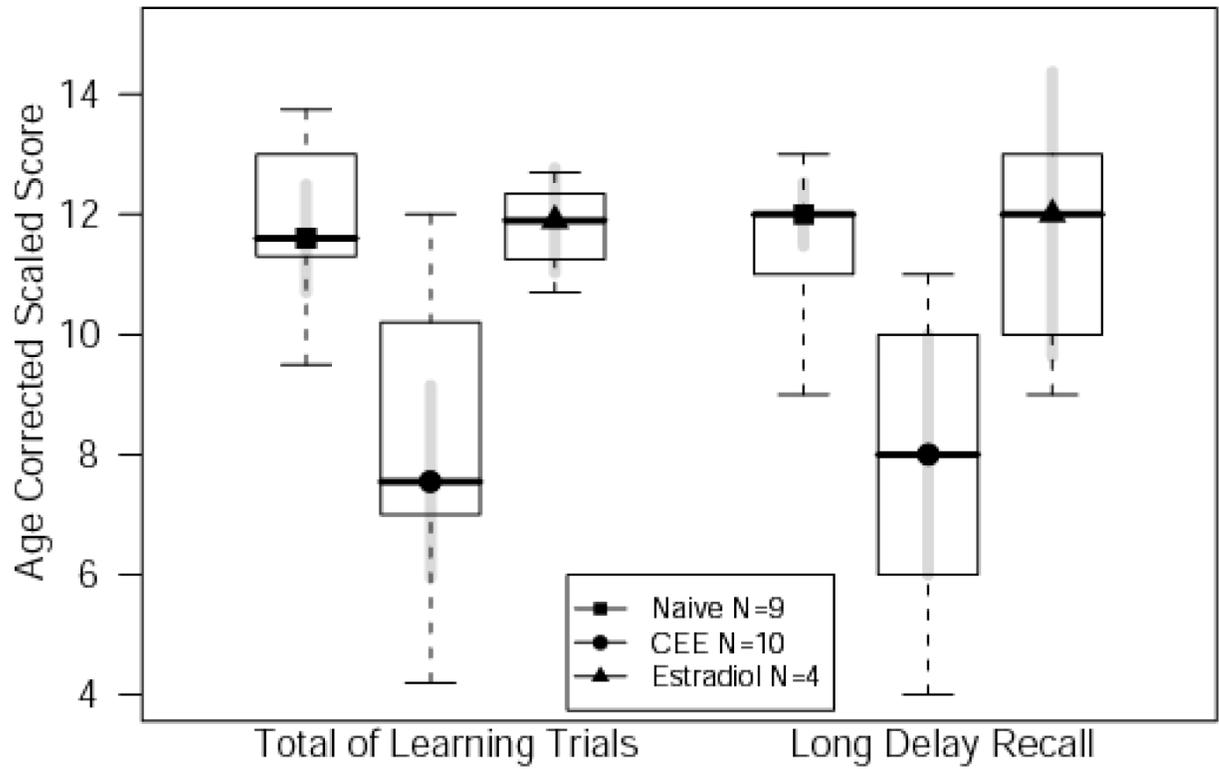


Figure 2. Verbal Learning and Recall scores (AVLT) for women who are either HT-naïve, or Estradiol or CEE-exposed. Displayed are boxplots (min, 25th percentile, median, 75th percentile, max, in black) superimposed on 95% confidence intervals of the medians (grey).

Table

Subject Characteristics

	HT Naïve (N=9)	Opposed CEE (N=10)	Opposed Estradiol (N=4)
Age (SD) years	58.7 (4.8)	59.9 (4.0)	54.5 (4.7)
Education (SD) years	15.9 (3.0)	16.9 (2.9)	14.5 (3.0)
BMI (SD) cm/kg	27.7 (5.6)	26.1 (6.0)	22.2 (3.1)
%ApoE 4 positive [*]	20.0% (1 subject)	20.0% (2 subjects)	0% (0 subjects)
fMRI Reaction time (SD) ms	0.8 (0.13)	0.8 (0.06)	0.7 (0.04)
fMRI Accuracy (SD) % correct	98.9 (2.2)	98.9 (2.0)	98.2 (2.3)
Systolic BP (SD) mmHG ^{**}	130.1 (17.3)	130.6 (15.4)	121.0 (17.1)
Diastolic BP (SD) mmHG ^{**}	81.9 (7.6)	75.6 (7.0)	77.0 (7.7)
Hemoglobin (SD) gm/dl	13.3 (1.0)	13.6 (0.6)	13.9 (1.1)
Hematocrit (SD) %RBC	39.6 (2.7)	40.6 (2.2)	40.8 (2.8)
Age initiated HT ^{***}	NA	50.6 (2.1)	47.0 (7.1)
Years used HT ^{***}	NA	6.8 (4.9)	3.5 (3.5)

* Two subjects from HT-naïve group did not consent to ApoE testing

** One subject's blood pressure data were missing

*** Data on age initiated and years used HT were unavailable for 3 participants