Effects of Hormone Therapy on Brain Volumes Changes of Postmenopausal Women Revealed by Optimally-Discriminative Voxel-Based Morphometry

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Purpose
Women’s Health Initiative Memory Study (WHIMS) trials provided a unique opportunity for researchers to examine the critical questions about the cognitive effects of hormone therapy (HT) among older postmenopausal women. The associated results [1-2] have indicated that conjugated estrogens (CEE) and CEE plus medroxyprogesterone acetate (MPA) therapy increase dementia risk and have adverse effects on cognition in women aged 65 and over. Recently, based on the MRI techniques, Resnick et al. [3] investigated whether a set of regions of interests (ROIs) including total brain, hippocampus, and frontal lobe, have significantly different amount of brain volumes between women randomly assigned to HT or placebo. The results suggest that HT-treated women had slightly lower volumes in some specific regions than those with placebo. However, the ROI-based analysis actually has limited statistical power since it doesn’t take into account the complex and anisotropic structural information inside the brain ROIs. In this study, we aimed to find evidence of structural differences between groups associated with HT and placebo from WHIMS, based on optimally-discriminative voxel-based morphometric analysis (ODVBA [4]), a recently-developed framework of group analysis, which has been shown to achieve optimal sensitivity and specificity to locate the underlying regional patterns of volume changes in brain MRI.

Methods
This study has totally 1,365 women subjects (ages from 71 to 88), including 254 active and 256 placebo in the CEE Alone trial, and 420 active and 435 placebo in the CEE+MPA trial, total up to 674 HT and 691 placebo. The T1-weighted images were preprocessed according to a number of steps including 1) Alignment of the brain with the AC-PC plane; 2) Removal of extra-cranial material; 3) Tissue segmentation into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF); 4) High-dimensional image warping to a standard MNI space, resulting in the mass-preserved tissue density maps, i.e., RAVENS; 5) Correction for the effects of i) Intracranial volume (ICV), ii) age, iii) clinical site, and iv) time from randomization to scan. Group comparisons were performed via voxel-based statistical analysis of the volumetric measurements by using ODVBA. ODVBA conducts regional discriminative analyses with the non-negativity constraint, as a spatially adaptive filtering, to optimally detect a group difference while clearly delineate the region, thereby transcending the limitations of the conventional smoothing approaches. We used 2,000 permutations to derive statistical significance maps.

Results
HT, CEE Alone, CEE+MPA < Placebo: Women assigned to HT showed significant (p<0.05, FWE corrected) GM losses compared to those assigned to take placebo in the prefrontal cortex including the bilateral medial frontal gyrus, the bilateral anterior cingulate cortex, and the area in the ventromedial prefrontal cortex (vmPFC) including the bilateral orbitofrontal cortex and the bilateral rectus. The comparison between CEE-Alone treated women and placebo-treated women revealed significantly (p<0.05, FWE corrected) lower GM volumes in the CEE-Alone group, which were predominantly located in the bilateral medial frontal gyrus and the bilateral anterior cingulate cortex. The CEE+MPA group didn’t have significantly reduced GM volumes with FWE correction relative to the matched placebo, but demonstrated trends toward significance with a more liberal significance level, especially in the area in the prefrontal cortex (p<0.05, uncorrected), which are in accordance with the significant regions detected by the previous two comparisons. It’s worth noting that all the above three comparisons agree on the trends (HT < placebo: p<0.005, uncorrected; CEE Alone < placebo: p<0.005, uncorrected; CEE+MPA < placebo: p<0.05, uncorrected) around inferior/medial temporal lobe including the left inferior temporal gyrus, the left fusiform, and the left parahippocampal gyrus.

HT, CEE Alone, CEE+MPA > Placebo: There were no significant differences surviving the multiple comparison correction, while all three comparisons showed the trends (p<0.05, uncorrected) around the parietal/occipital area including the bilateral posterior cingulate cortex, the bilateral precuneus, and the right middle occipital gyrus.

Conclusions
The ODVBA morphometric analysis on the WHIMS-MRI data revealed the significant gray matter volume reductions associated with the hormone therapy mainly in the prefrontal cortex, and also demonstrated relatively strong trends around the inferior/medial temporal lobe.

References
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