

Estrogen Increases Hippocampal Activity and Functional Connectivity in Postmenopausal Women

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Introduction

Estrogen replacement therapy (ERT) has been increasingly applied clinically to prevent perimenopausal symptoms, osteoporosis, and colon cancer. Recent researches also demonstrated ERT may have the benefit to improve the cognitive function and prevent hippocampus atrophy^[1,2]. Less is known, however, what the brain responses to estrogen would be in imaging domain. To better understand the neuronal protective mechanisms of estrogen, here we investigated the BOLD and functional connectivity responses induced by acute estrogen administration in postmenopausal women.

Materials and Methods

Subject materials: Six healthy normal weighted postmenopausal female subjects (age averaged at 56.2, ranging from 50 to 63 years old) participated in this study. All subjects have averaged postmenopausal history of 6.8, ranging from 3 to 9 years. None of them has received any ERT treatment in life. All subjects underwent series of MRI scans with respiration, heart rate, blood pressure, finger tip blood O₂ saturation level continually monitored. **MRI methods:** A GE 1.5T Signa HDx scanner. Imaging datasets included whole-brain anatomical dataset and first 6-min resting-state BOLD-fMRI dataset, 15-min BOLD-fMRI scan with saline injection at the 5th minute, and finally a 30-min BOLD-fMRI scan with IV injection of 0.1mg/kg estrogen at 5th min into the scan. For anatomical images, T1-weighted three-dimensional Spoiled Gradient Recalled Acquisition, SPGR sequence (TR = 25 ms, TE = 5 ms; flip angle = 30°; FOV = 24x24 cm; slice thickness = 1.5 mm; NEX = 1; matrix size = 256 × 192) was used to obtain 124 images covering the entire brain. For all BOLD-fMRI scans, gradient-echo echo-planar (EPI) sequence (TR=2000 ms, TE=50 ms, 90° flip angle, 20 transverse sections, slice thickness = 4 mm, 1-mm intersection gap, FOV=24x24 cm, matrix size= 64x64) was used. **Data Analysis:** AFNI v2.0 software was used for data processing and analysis procedures. BOLD time-courses with estrogen/ saline injection were motion-corrected and fitted with differential-exponential model to get the area under curve (AUC%). Paired t-test was used to get the estrogen induced brain activation maps comparing the voxel-wise AUC% values of two injections ($P < 0.05$ after correction). The last 6 minute dataset of the 30-min scan was also used to evaluate the functional connectivity after estrogen injection. For functional connectivity analysis, time-course data was motion-corrected, detrended, and frequency filtered (with low-pass filter of 0.1 Hz) before the connectivity computation. For each subject, functional connectivity between the hippocampus and the rest of brain region was obtained with cross-correlation of the spontaneous low-frequency fluctuations in each 6-min dataset. Group analysis was then performed using one-sample student t-test to determine the significant hippocampal functional connectivity in the whole brain. The functional connectivity significant regions were identified using a threshold at $P < 0.05$ after Bonferroni correction.

Results

Compared to saline injection, acute estrogen injection induced brain activations in hippocampus, amygdala, caudate putamen, and thalamus (as in Fig. 1). Before estrogen injection, subjects demonstrated normal hippocampal functional connectivity. After estrogen injection there was increased functional connectivity with hippocampus especially in the dorsal lateral prefrontal cortex (DLPFC), bilateral posterior cingulate cortex (PCC) and middle temporal gyrus (MTG) (as in Fig 2).

Discussion and Conclusion:

Previous researches have shown estrogen is neuroprotective in both human subjects and animal models of stroke and Alzheimer's disease. Our results demonstrated the acute estrogen injection increases hippocampal BOLD responses as well as the hippocampal functional connectivity with some other cognitive highly associated brain regions. Those brain regions with significant increased hippocampal functional connectivity locate in mainly the striatum and thalamus, rich in capillary and neuronal nucleus. Increased hippocampal activity as well as connectivity with cognitive network may account to some degree for the mechanisms of neuroprotective property of estrogen as well as ERT. Postmenopausal Women may be especially sensitive to estrogen stimuli. Future investigations on the differential responses of estrogen in postmenopausal and non-menopausal women may be desired to provide more details on the neuroprotective effectiveness of endogenous and exogenous estrogen.

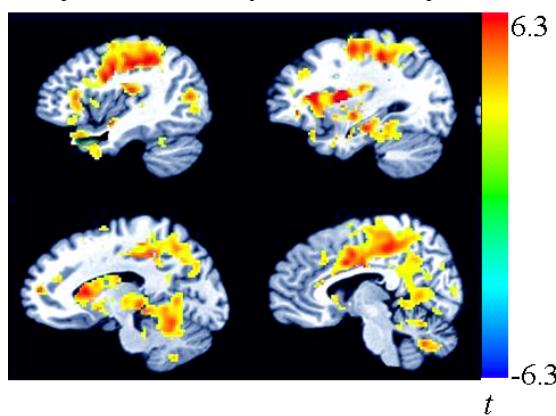


Fig. 1 Acute estrogen injection induced brain activation.

References:

1. Schreiber DA, Redmond L. *Neuroscience*. 2008 Oct 10.
2. Simpkins JW, Singh M. *Alzheimers Dement*. 2008 Jan;4(1 Suppl 1):S131-6. Epub 2007 Dec 21.

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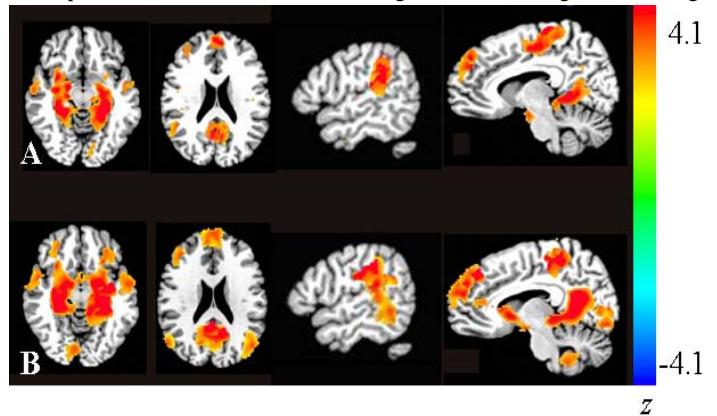


Fig. 2 Hippocampal functional connectivity maps overlaid on SPGR images. Row A shows maps before estrogen injection; Row B shows maps after estrogen injection.