

## Increases in CBF by Donepezil treatment Enhance Cingulate Functional Network activity in Mild Alzheimer's Disease

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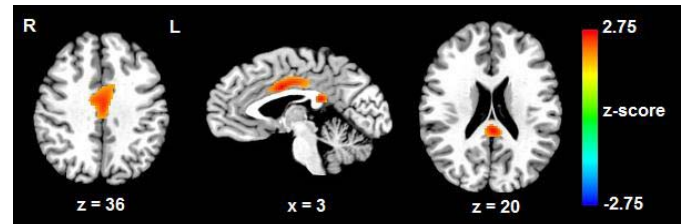
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**Introduction:** Cholinergic inhibitor (Aricept®) has been shown to improve cognitive function in adults with Alzheimer's disease (AD) [1]. Also, it has an effect on improving the cerebral blood flow (CBF) perfusion detected by PET technology [2]. Previously we have found increased CBF in cingulate and posterior cingulate regions using a Pseudo-Continuous Arterial Spin Labeling (pCASL) MR technique [3]. It is hypothesized that the increase in CBF after treatment could alter functional connectivity in related neural networks. The aim of the current study is to determine the changes in the functional connectivity in networks with significantly increased CBF after the drug treatment.

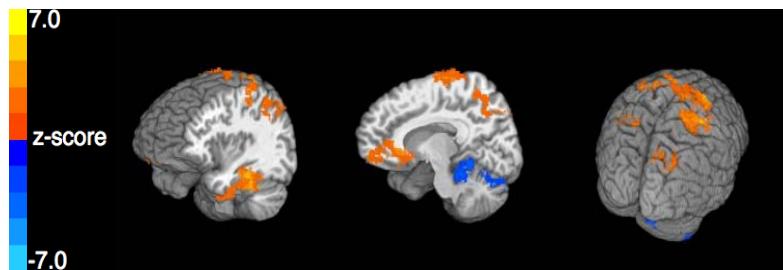
**Methods:** A total of 14 patients (age  $77.57 \pm 6.57$  yrs) with newly diagnosed Alzheimer's disease were enrolled in a 3-month follow-up drug treatment study. Magnetic resonance images were taken both before and after the patients were given donepezil hydrochloride (Aricept®) treatment. **MRI Protocol:** All MRI scans were performed on a GE 3T Signa LX scanner. Anatomical images were acquired using 3D spoiled gradient echo (SPGR) sequence with 144 continuous axial slices. pCASL pulse sequence was used for the functional perfusion measurements [3, 4]. The labeling pulse repeated the saturation/slab-selective pulse at the beginning of the sequence (time zero). A slab-selective inversion pulse was applied

1s later and then immediately followed by a 1.5 s long pseudo-continuous labeling pulse that labeled the moving blood spins. The EPI sequence (FOV/matrix/TR/TE/TI<sub>1</sub>/TI<sub>2</sub> = 24cm/64×64/4s/25ms/1.5s/1.75s) was used to acquire twelve axial slices with 7 mm thickness and 1 mm gap between each slice. Resting-state functional MR images were obtained using a single-shot EPI sequence (TR/TE/FA/thickness/matrix size = 2s/25ms/90°/5mm/64×64) with 36 sagittal slices. **Data Analysis:** AFNI software was used to process all images. A 6-direction motion correction was performed to correct artifacts from motion during the resting scan. Using the regions with significant increase in CBF from our previous results as the seed region (Fig. 1), functional connectivity between the dorsal cingulate and the entire brain was obtained with cross-correlation of the spontaneous low-frequency fluctuations in the resting-state fMRI. The images were then transformed to the Talairach space with a  $2 \times 2 \times 2$  mm<sup>3</sup> interpolation. Finally, a paired two-sample *t*-test compared the connectivity changes before and after 3-month Aricept® treatment.



**Fig. 1** Increased regional CBF in bilateral dorsal cingulate cortex (BA 24) and bilateral posterior cingulate cortex (PCC) after the cholinergic inhibitor (Aricept) treatment.

**Results and Discussion:** Significantly increased regional CBF was found in the regions such as bilateral dorsal cingulate cortex (BA 24) [3]. PET and SPECT studies using subjects in the resting condition also demonstrated that the hypoperfusion in the early stage of development of AD was most prominent in the parietal associative cortices and cingulate gyri [5]. Therefore, increased CBF in regions such as cingulate gyrus may directly relate to the changes in the functional network between itself and the entire brain.



**Fig. 2** Increased FC in prefrontal cortex (BA 11), anterior cingulate (BA 12, 32), precuneus (BA 7), left parahippocampus, and precentral cortex. Decreased FC in the cerebella regions such as culman and pyramis ( $p < 0.05$ , corrected for cluster size  $> 4048$  mm<sup>3</sup>).

Using the dorsal cingulate as the seed region, it was found that, as showed in Fig. 2, functional connectivity was increased in prefrontal cortex (BA 11), anterior cingulate (BA 12, 32), precancerous (BA 7), left parahippocampus, and precentral cortex ( $p < 0.05$ , corrected). Especially, anterior part of the brain, including BA 11 and 12, are closely associated with cognition. Parahippocampus and precuneus are related to learning and memory [6]. Therefore, we conclude that donepezil increases CBF in cingulate regions and also rekindle the connections in the immediate functional network of cingulate gyrus, which includes brain regions that are closely associated with human cognition and memory.

**References:** 1. Kircher TT. et al. Am J Geriatr Psychiatry 2005. 2. Ushijima Y. et al. Ann Nucl Med 2006. 3. Li W. et al. ISMRM 2009. 4. Garcia DM. et al. ISMRM 2005. 5. Mielke R. et al. J. Neural Transm 1998. 6. Aguirre et al. Cerebral Cortex 2006.

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