Effect of Antiepileptic Treatment on Hippocampal Activity in Alzheimer's Disease measured by ASL

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Introduction

Increased hippocampal perfusion has been reported in early AD (1,2,3). Recent evidence from animal studies has raised the intriguing possibility that epilepsy plays a more central role in the pathophysiology of AD. Epileptic activity directly damages the hippocampus via hypoxia and ischemia (4). Ischemia in turn increases amyloid deposition (5). Our hypothesis is that similar epileptiform activity and seizures occurs in the hippocampus of humans with AD and that suppression of epileptiform activity will improve memory deficits. If increased hippocampal perfusion in AD is caused by epileptiform activity, then an antiepileptic drug, Levetiracetam, should lead to decreased rCBF in the hippocampus.

Methods

Nine AD subjects were imaged on a GE 3 Tesla scanner using an 8-channel head coil receive array. Each subject received 3 study drug regimens at 3 different days. The 3 drug regimens were Placebo, Low dose levetiracetam (2.5 mg/kg), High dose levetiracetam (7.5mg/kg). After drug administration, Both resting-state pulsed-continuous arterial spin labeling (PCASL) (6) and BOLD acquisitions were performed. PCASL images were acquired with a 3D stack of spirals RARE sequence. Resting state BOLD images were acquired with gradient-echo EPI sequence.

Both ASL and BOLD image time series were head-motion corrected using SPM8. ASL perfusion images for each drug state of each subject were quantified using the averaged perfusion difference image over its time series and the reference image. ASL perfusion images were normalized to the standard template space. ASL perfusion images were then compared using SPM8 across 3 drug states using within-subject ANOVA with voxel-level threshold 0.01 and cluster-level corrected threshold 0.05. Resting state ASL and BOLD data analysis are still in progress.

Results and Discussion

We observed significant perfusion decrease in the posterior cingulate gyrus extending to precuneus and occipital cortex for low dose/high dose levetiracetam compared to placebo (Fig. 1a and 1b), significant perfusion decrease in right hippocampus, putamen, insular, middle and superior temporal cortex for low dose levetiracetam compared to high dose levetiracetam (Fig. 1c). We also observed perfusion increase in both hippocampi, caudate, putamen, amygdala and middle temporal regions for low dose levetiracetam compared to placebo (Fig 2a), and perfusion increase in both hippocampi, caudate, putamen, amygdala, anterior cingulate for high dose levetiracetam compared to placebo (Fig 2b). Our results demonstrate changes in the hippocampus with levetiracetam but with a different sign than anticipated. These findings suggest a more complex behavior of drug and epileptic activity effects in AD. Further work will probe the differential effect on AD compared to controls.

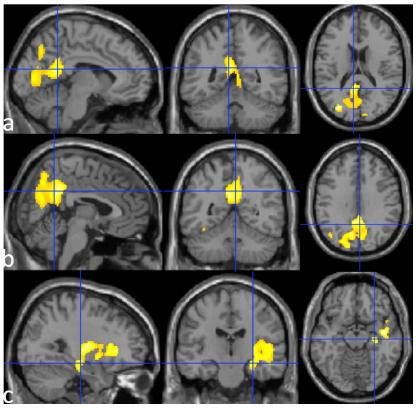

Fig.1. (Left) Significant Perfusion change of (a) Placebo> 2.5 mg/kg levetiracetam, (b) Placebo> 7.5 mg/kg levetiracetam, and (c) 2.5 mg/kg> 7.5 mg/kg levetiracetam overlaid on an anatomical image.

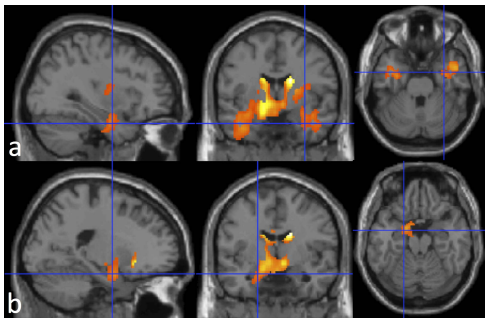

Fig.2. (Right) Significant Perfusion change of (a) 2.5 mg/kg levetiracetam >Placebo and (b) 7.5 mg/kg levetiracetam> Placebo overlaid on an anatomical image.

References: 1. Alsop et al, Neuroimage 2008;42:1267-1274. 2. Dai et al, Radiology 2009;250:856-866. 3. Fleisher et al, Neurobiol Aging 2009;30:1737-1748. 4. Thom et al, J Neuropathol Exp Neurol 2009;68:928-938. 5. Guglielmotto et al, J Neurochem 2009;108:1045-1056. 6. Dai et al, Magn Reson Med 2008;60(6):1488-97.