Normalization of fMRI activation patterns in HIV positive individuals with cognitive impairment after treatment with Lithium

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Background: HIV-associated cognitive impairment is associated with psychomotor slowing, impaired information retrieval, and poor performance on tasks involving attention, concentration, and working memory. Our group has shown that HIV-1 associated neurotoxins PAF and Tat activate glycogen synthase kinase (GSK-3β) and lithium (a potent inhibitor of GSK-3β) protects neurons against Tat- and PAF- induced cell death in vitro. Additional data in the HIVE-SCID mouse model suggest that lithium protects against neuronal loss and dendritic simplification. This rationale has led to a pilot trial of lithium in HIV-infected subjects with cognitive impairment. Here we report data using fMRI as a neuroimaging biomarker to investigate neuroprotection in the context of a clinical trial.

Methods: *Subjects:* Fifteen HIV positive subjects with impaired cognitive functioning (HIV+ CI) were enrolled in a ten-week open-label study to assess the effects of lithium 300mg twice daily on HIV-associated cognitive impairment. Subjects were predominantly male (66.67%) 60% Caucasian and 40% African American, with a mean age of 47 ±5.54. Cognitive impairment was defined as scores at least one standard deviation below age- and education- based norms on two or more independent neuropsychological tests, or at least two standard deviations below the norm on one or more independent tests, using a standard neuropsychological test battery(1). Participants completed functional magnetic resonance imaging (fMRI) at both baseline, and after 10 weeks of treatment with lithium. An additional seven HIV positive subjects without cognitive impairment (HIV+), mean age 52 ±8.12, 86% male, were evaluated using the same neuropsychological test battery and imaging protocol at a single time point. *FMRI task:* Participants were administered a task based on Garavan et al. (2), designed to isolate the central executive system via increasing attention demands. The task consisted of three trials, during which a series of large and small squares was visually presented in random order. Subjects were asked to keep a running count of number of large squares and number of small squares presented during each trial. At the end of each trial, subjects were asked to respond whether they had seen more large or small squares during the trial. Number of "switches" from large to small squares during each trial was varied, while the total number of squares presented was held constant. Order of trial runs was counterbalanced among subjects. *Imaging:* All MR images were acquired on a Siemens 3T Trio system with an 8-channel head coil. Contiguous 4mm axial slices were obtained during task performance using the following parameters: GRE EPI pulse sequence with TR/TE= 2000/30ms, 4x4x4mm voxel size, 64x64 matrix. *FMRI Analyses:* FMRI data was processed using the AFNI (3) and FSL (4) software packages. All images underwent preprocessing steps for slice timing and motion correction as well as Gaussian spatial smoothing (FWHM = 8mm). Non-brain signal removal was performed using FSL's BET program, and the FSL FLIRT (FMRIB's Linear Image Registration Tool) program was used to achieve spatial normalization to the standard MNI152/ICBM template. Activation maps were obtained with AFNI using multiple regression analysis. An ideal hemodynamic response function was created for each stimulus time series. Modeling included only performance during the counting portion of each trial; rest periods were treated as baseline, and signal acquired while each subject responded was excluded from functional analyses. Calculated beta coefficients were scaled to represent percent signal change relative to the average signal during rest periods during the entire run. These steps yielded maps revealing brain regions activated for each trial type (1, 2, and 3 "switches") as well as areas that differed as a function of switching frequency (3 vs. 2 switches, 3 vs. 1 switch and 2 vs. 1 switch). To identify regions that differed in activation across groups of patients for all types of trials and switching frequency, a 3 way ANOVA was performed using the 3dANOVA3 program in AFNI. Trials 1-3 were pooled for each group for between-group comparisons.

Results: *NP changes:* There were no significant cognitive changes in this 10-week trial; the overall cognitive performance showed minimal improvement. *FMRI changes:* Differences in activation patterns between groups are shown below in Figures 1-3. Voxels with uncorrected $p<0.01$ were considered significant. Compared to HIV+ subjects without cognitive impairment, HIV+CI subjects at baseline demonstrated significantly less activation in areas including the prefrontal cortex, insular cortex, caudate, and anterior cingulate. Following treatment, HIV+CI subjects demonstrated significantly greater activation in areas including the bilateral insular cortex and prefrontal cortex, as well as the anterior cingulate relative to baseline. When compared again to HIV+ subjects without impairment, differences in activation in these areas were greatly reduced in HIV+CI subjects post-treatment.

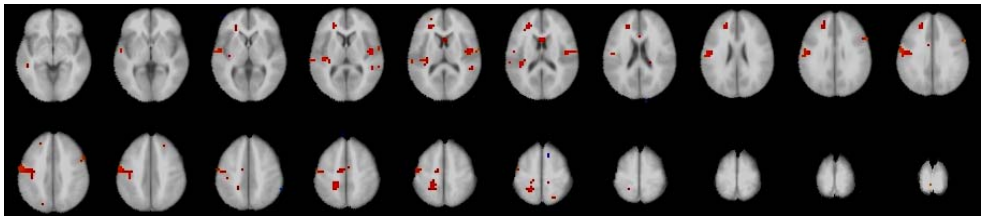

Figure 1. HIV+ vs. HIV+CI pre treatment.
Red= greater activation HIV+ Blue= greater activation HIV+CI pre treatment

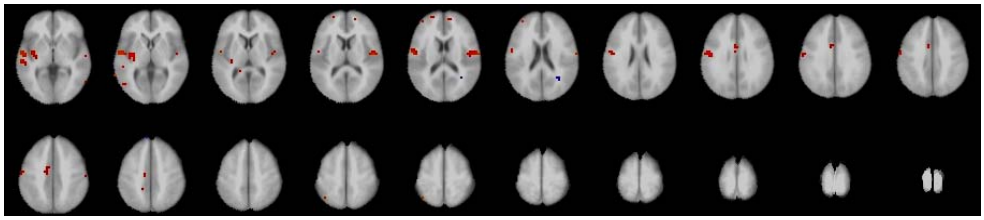

Figure 2. HIV+CI pre treatment vs. HIV+CI post treatment.
Red= greater activation post-treatment Blue= greater activation pre-treatment

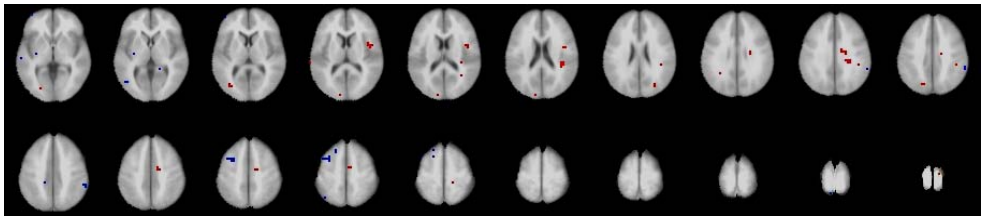

Figure 3. HIV+CI post treatment vs. HIV+
Red= greater activation HIV+ Blue= greater activation HIV+CI post treatment

Conclusion: Our preliminary data suggest that lithium at the dose of 300mg twice daily normalizes the brain activation pattern in HIV+CI individuals. Specifically, relative to HIV+CI individuals before treatment, the pattern of activation in HIV+CI individuals following 10 weeks of treatment with lithium more closely resembles the activation seen in HIV+ individuals without cognitive impairment during this attention-switching task. Although no significant clinical changes were observed in this short trial, the fMRI results encourage further clinical investigations of lithium as a disease-modifying agent in HIV-associated cognitive impairment.

References: (1) Marder K, Albert SM, McDermott MP, et al. Inter-rater reliability of a clinical staging of HIV-associated cognitive impairment. Neurol 2003; 60:1467-73. (2) Garavan H, Ross TJ, Li SJ, Stein EA. A parametric manipulation of central executive functioning. Cereb Cortex 2000; 10:585-92. (3) Cox RW: AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. Computers and Biomedical Research 1996; 29:162-73. (4) Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage 2004; 23(S1): 208-19.