Cerebral Blood Flow and Metabolism Are Elevated in the Lenticular Nuclei of Unimpaired HIV+ Subjects

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Abstract

Background: Blood oxygenation level dependent functional magnetic resonance imaging (BOLD-fMRI) can non-invasively assess the effects of HIV in the brain. Quantitative fMRI extends these principles by simultaneously acquiring BOLD and cerebral blood flow (CBF) changes during functional activation and hypercapnia in order to determine cerebral metabolic rate of oxygen consumption ($CMRO_2$), a closer approximation of synaptic transmission. We hypothesized that unimpaired HIV+ patients have elevated changes in CBF and $CMRO_2$ due to derangements in presynaptic glutamate recycling within the lenticular nuclei (LN), a subcortical structure often affected by HIV.

Methods: Seronegative controls (n=12) and HIV+ unimpaired patients (n= 12) were studied at 3 Tesla GE MRI scanner. All subjects viewed a fixed number pattern in the center of a screen which corresponded to finger taps on a 4-button box. The LN was manually drawn for each subject with clusters of active voxels chosen using an overall significance threshold of $p = 0.05$ (Figure 2). Paired t-tests for BOLD, ΔCBF, and $\Delta CMRO_2$ were performed with p values significant if $p < 0.05$. In addition, correlation coefficients were obtained between these quantitative fMRI measures and laboratory values (log plasma and cerebral spinal fluid (CSF) HIV viral loads and CD4 levels).

Results: Unimpaired HIV+ patients were predominantly male (92%) with more than half (67%) taking anti-retroviral (ARV) medications. Median CD4 at time of imaging was 446 (IQR 275-589) with most having good virological control within the plasma (log plasma viral load 2.79 (1.69-3.49) and CSF (log CSF viral load 1.89 (1.69-2.31) (Table 1). Functional changes in BOLD, CBF, and $CMRO_2$ were significantly greater for unimpaired HIV+ patients compared to seronegative controls (Figure 3). No significant correlation existed between quantitative fMRI values and laboratory values (Figure 4).

Conclusions: Quantitative fMRI demonstrates significant differences in functional changes in CBF , BOLD, and $CMRO_2$ prior to neuropsychologically measured changes in HIV+ patients. These differences may reflect relative derangements in presynaptic recycling of glutamate in unimpaired HIV+ patients compared to controls. Observed differences do not correlate with existing laboratory markers of HIV disease and may reflect ongoing inflammation and oxidative stress even in unimpaired HIV+ subjects with good virologic control due to ARVs. Quantitative fMRI could assess the effects of early initiation of neuroprotective therapies for unimpaired HIV+ patients.

Introduction

• Human immunodeficiency virus (HIV) induces structural and metabolic brain changes leading to HIV-associated neurocognitive impairment (HNCI) (1-4).

• The lenticular nuclei (LN) can be affected causing psychomotor slowing on neuropsychological performance (NP) testing.

• Quantitative functional magnetic resonance imaging (fMRI) using blood oxygen level dependent (BOLD) and cerebral blood flow (CBF) (5) during a functional task and calibration condition of mild hypercapnia can determine cerebral metabolic rate of oxygen consumption ($CMRO_2$), a marker of neuronal function.

AIM: To determine if quantitative fMRI measures can detect the effects of HIV in the brain prior to typically measured neuropsychological performance measures.

Methods

Subjects

• Seronegative (n=12) and HIV+ unimpaired subjects (n=12)

• Imaging performed at 3T GE scanner at UCSD

• HIV+ subjects had NP testing and laboratory testing performed within 2 months of their scan (*Table 1*).

Table 1: Demographics of Subjects

	Seronegative Controls (n=12)	Unimpaired HIV+ (n=12)
Age (in years) (SE)	40 (4)	42 (3)
Sex (% male)	83	92
% taking ARVs	Not Applicable	67
Median CD4 cell count (cells/μL)	Not Applicable	446 (275-589)
Median log plasma viral load (IQRs)	Not Applicable	2.79 (1.69-3.49)
Median log CSF viral load (IQRs)	Not Applicable	1.89 (1.69-2.31)
Global Deficit Score (GDS) (SE)	Not Applicable	0.16 (0.03)

Hypercapnic Calibration

Figure 1A. Non-rebreathing mask set-up B. Physiological monitoring in 3T scanner.

Quantitative fMRI Parameters

PICORE QUIPSS II sequence (TR=2.5s, TI1=700 ms, TI2=1500 ms, 20-cm tag width, and a 1-cm tag-slice gap) used with a dual-echo gradient echo readout and spiral acquisition of k-space (TE1=9.4 ms, TE2=30ms, flip angle=90°, FOV 24 cm, 64 x 64 matrix) acquired over four 7 mm-thick axial slices that included the LN.

Stimuli

Numbers in center of screen indicated which key to press on a 4-button response box (*Figure 2*).

Figure 2. LN functional activation map for fingertapping task using 4 button response box.

Statistical Analysis

• Within anatomical region of interest (LN), CBF activated voxels were cluster-thresholded ($p < 0.05$). In functional/anatomical region, $CMRO_2$ calculated by:

$$\frac{\Delta S}{S_0} = M\left(1 - f^{\alpha-\beta} r^{\beta}\right)$$

• $\Delta S/S_0$ measures fractional BOLD signal changes, f measures fractional changes in CBF, M is a baseline LN scaling factor, resulting in r as calculated fractional changes in $CMRO_2$ (6).

• Paired t-tests were performed between controls and unimpaired HIV+ patients for CBF, $CMRO_2$, and BOLD ($\alpha = 0.05$) within the functional/anatomical defined region.

• Pearson correlations were calculated for laboratory values and quantitative fMRI measures in unimpaired HIV+ patients.

Results

Greater functional changes in CBF and $CMRO_2$ in LN for unimpaired HIV+ subjects versus controls.

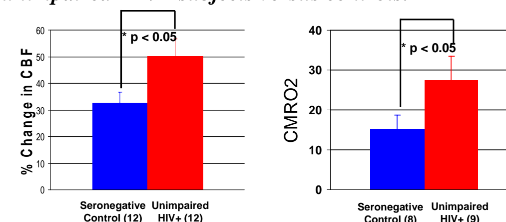

Figure 3. Significant increases in both CBF and $CMRO_2$ were seen in unimpaired HIV+ patients compared to controls. Similar results were seen for BOLD (data not shown).

No significant correlations were observed between quantitative fMRI measures and laboratory values.

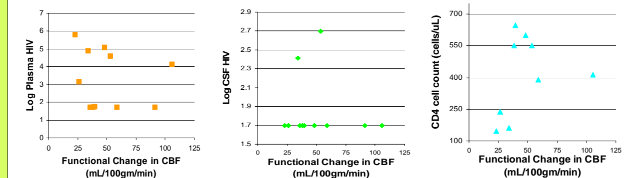

Figure 4. No correlation was observed between laboratory values of log plasma viral load, log CSF viral load, CD4, and CBF. Similar results were seen for $CMRO_2$ and BOLD.

Conclusions

1.) Quantitative fMRI measures of CBF, BOLD, and $CMRO_2$ demonstrate significant increases prior to typically measured neuropsychological performance testing measures in HIV+ patients.

2.) Increased functional metabolic demands occur in unimpaired HIV+ subjects with good virological control on ARVs. These differences may reflect ongoing inflammation and oxidative stress with subsequent decreased recycling of glutamate (8,9).

3.) Observed differences in quantitative fMRI measures of BOLD, CBF, and $CMRO_2$ for unimpaired HIV+ patients do not correlate with existing laboratory markers of HIV disease.

4.) Quantitative fMRI should be considered in the evaluation of even unimpaired HIV+ patients. Early neuroprotective therapies could be considered for unimpaired HIV+ patients.

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