Longitudinal Progression of Cortical Atrophy in HIV Patients on Stable Treatment

Michael R. Nowak[1], Bradford Navia[2], Jaroslaw Harezlak[3], Constantin Yiannoutsos[3], Charles Guttmann[4], Elyse Singer[5], Thomas Campbell[6], Eric Daar[5], Giovanni Schifitto[7], David Tate[8]

[1]Texas A&M University, Department of Computer Science and Engineering, College Station, TX, [2]Tufts University Medical School, Boston, MA, [3]Indiana University School of Medicine, Indianapolis, IN, [4]Brigham and Women's Hospital, Boston, MA, [5]University of California Los Angeles, Los Angeles, CA, [6]University of Colorado, Denver, CO, [7]University of Rochester Medical Center, Rochester, NY, [8]HJF for the Advancement of Military Medicine, San Antonio, TX.

BACKGROUND

- Modern therapies have greatly reduced the occurrence of severe HIV-associated neurocognitive disorder (HAND) symptoms in HIV-positive patients.

- However, the overall incidence of HAND syndromes is increasing as individuals with the disease are living longer (Lindl et al., 2010).

- Such impairments are relatively mild, but are still constitute a negative effect on quality of life (citation). While the clinical features of such cognitive dysfunctions have been well documented, the underlying pathology of the neurodegenerative nature of HIV is not clear (Dash et al., 2011).

- The HIV Neuroimaging Consortium (HIVNC) was formed to prospectively study the effects of chronic HIV infection on brain metabolites and structure as measured by magnetic resonance imaging (MRI) in a cohort of patients on stable combined antiretroviral therapy (cART).

- Analyses from HIVNC have helped identify regions in the brain - subcortical gray matter structures and central white matter (Navia et al., 2010; Cohen et al., 2010; Tate et al., 2010) primarily affected by HIV. A low nadir CD4 has been show to be an important predictor of atrophy in these regions.

- These cross sectional investigations and other research (Kallianpur et al., 2011; Thompson et al., 2005; Chiang et al., 2007), show that chronically infected HIV patients on effective cART are susceptible to neuronal damage.

- In this study we examined the longitudinal progression of cortical atrophy and its relationship to nadir CD4 count.

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METHODS

- Magnetic resonance imaging (MRI) data and relevant clinical variables were obtained from the NIH-funded HIVNC cohort, for a small subsample of 18 HIV-infected patients, across three timepoints (initial scan, six month, one year).

- Inclusion criteria were a nadir CD4 count < 200 cells/mm3, on stable regimen with any FDA-approved antiretroviral therapy for at >12 consecutive weeks prior to study screening, hemoglobin > 9.0 gm/dL, serum creatinine ≤ 3 x ULN (upper limits of normal), AST, ALT, and alkaline phosphatase all ≤ 3 x ULN.

- Exclusion criteria included severe premorbid or comorbid psychiatric disorders, confounding neurologic disorders, brain infection, active alcohol and drug abuse or related medical complications within 6 months of study;

- A standardized monitored structural imaging protocol was followed that included a spoiled gradient (SPGR) T1 weighted volumetric scan with the following parameters: TR/TE=16/600; FOV=20 cm; Slice thickness=1.3 mm; Matrix size=256 × 128, with 1 NEX.

- To extract consistent volume and thickness evaluations, MRI data were automatically processed with the longitudinal stream as described by Reuter et al. (2012) in FreeSurfer v.5.1.1 (Martinos Institute, Harvard University, Boston, MA) on a local computer cluster running Macintosh OS X 10.7.

- The longitudinal rate of cortical thickness change was calculated as a symmetrized percent change (spec), with respect to the temporal average (thickness at midpoint of linear fit): spec = rate/avg.

- Post-processing statistics were performed in the single-binary application QDEC (acronym for Query, Design, Estimate, Contrast) included in the FreeSurfer software distribution to perform inter-subject/group averaging and inference on morphometry data produced by the application's processing stream.

RESULTS

Age	48.4 ± 6.41 years
Nadir CD4 Cell Count	32.8 ± 24.62 cells/mm^3
Baseline CD4 Cell Count	319.8 ± 179.55 cells/mm^3
Duration with HIV	11.6 ± 7.72 years
Time between Imaging Sessions	6.6 ± 0.61 months

Table 1. *Subject Characteristics*

Anatomical Location	Hemisphere	Mean Cortical Thickness (mm)
Anterior cingulate gyrus	R	2.9314 ± .29829
Anterior middle frontal gyrus	R	2.3792 ± .20262
Fusiform gyrus	L, R	2.5547 ± .13777, 2.5259 ± .12816
Inferior parietal lobule	R	2.4705 ± .13914
Insula	L	3.0835 ± .13238
Isthmus of cingulate gyrus	L	2.4028 ± .17634
Lateral occipital gyrus	L, R	2.2328 ± .11263, 2.2507 ± .12214
Lateral orbital gyrus	L	2.7144 ± .16741
Lingual gyrus	L, R	1.9342 ± .14428, 2.0127 ± .12584
Medial orbital gyrus	L, R	2.5741 ± .21110, 2.5307 ± .22057
Middle temporal gyrus	L, R	2.7670 ± .17145, 2.8411 ± .21066
Paracentral lobule	L	2.3298 ± .11028
Pars opercularis	L, R	2.5561 ± .14651, 2.5834 ± .15471
Posterior cingulate gyrus	R	2.5871 ± .14766
Posterior middle frontal gyrus	R	2.5810 ± .14490
Precentral gyrus	L, R	2.4660 ± .17267, 2.4867 ± .12538
Precuneus	L	2.3263 ± .15075
Superior frontal gyrus	R	2.7167 ± .15950
Superior parietal lobule	L, R	2.2000 ± .12845, 2.1831 ± .13246
Superior temporal gyrus	R	2.7313 ± .19768
Supramarginal gyrus	R	2.5227 ± .11800

Table 2. *The locations of statistically significant cortical thinning, as a symmetrized percent change to temporal averages, in various brain regions (P < 0.05). The mean cortical thickness (mm) measurement has been derived from the average of the respective structure from each subject time point. Some areas of cortical thinning are seen bilaterally while others are unilateral.*

Anatomical Location	Hemisphere	p-value
Anterior middle frontal gyrus	R	0.012
Fusiform	R	0.002
Inferior parietal lobule	R	0.018
Lateral occipital gyrus	R	0.027
Insula	L	0.035
Lateral occipital gyrus	L	0.030
Posterior cingulate	L	0.048
Lingual gyrus	L, R	<0.010, 0.001
Medial orbital gyrus	R	0.006
Middle temporal gyrus	R	0.022
Paracentral lobule	L, R	0.017, 0.047
Pars opercularis	R	0.300
Postcentral gyrus	L, R	0.016, 0.046
Posterior cingulate gyrus	R	0.029
Posterior middle frontal gyrus	R	0.015
Precentral gyrus	L, R	0.017, 0.011
Precuneus	L	0.014
Superior frontal gyrus	L, R	0.043, 0.047
Superior parietal lobule	L, R	<0.010, 0.005
Superior temporal gyrus	R	0.04
Supramarginal gyrus	R	0.17

Table 3. *The locations of statistically significant correlation between the symmetrized percent changes of cortical thinning and nadir CD4 concentration. Some areas of cortical thinning are seen bilaterally while others are unilateral.*

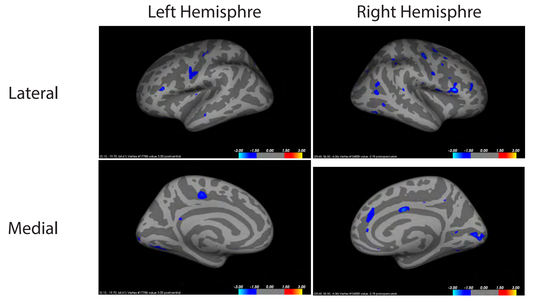


Figure 1. *Parametric maps were calculated on the null hypothesis of no significant difference between the symmetrized percent changes of cortical thinning with respect to the temporal average using a lower threshold of P < 0.05 and a saturation point of P < 0.001.*

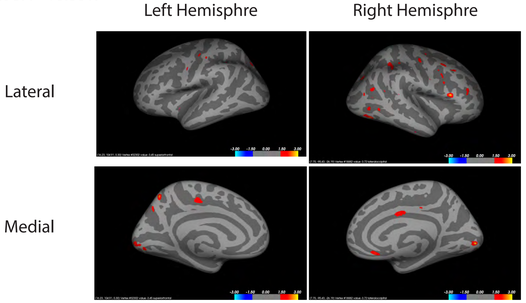


Figure 3. *Parametric maps calculated on the null hypothesis of no significant correlation between the symmetrized percent changes of cortical thinning and nadir CD4 concentration using a lower threshold of P < 0.05 and a saturation point of P < 0.001.*

CONCLUSIONS

This is among one of the first studies to use a validated measurement of cortical thickness to demonstrate progressive selective cortical atrophy that is correlated with an individual's historic nadir CD4 count even though they may be immunologically stable and receiving cART. Further research is needed to elucidate HIV brain neuropathology, including its neurodegenerative and neurocognitive effects over time and the benefit of minimizing a patient's nadir CD4 count. Our group is conducting further analyses to assess the generalizability and functional relevance of these findings and determine the factors that contribute to brain tissue loss in the setting of stable and chronic HIV disease.