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Diffusion tensor imaging of subcortical brain injury in patients infected with human immunodeficiency virus

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Diffusion tensor imaging (DTI) was used to derive *in vivo* tissue status measurements of subcortical brain regions that are vulnerable to injury in human immunodeficiency virus (HIV)-infected patients. Quantitative measurements, including the mean diffusivity (MD) and fractional anisotropy (FA), were determined in lateralized basal ganglia (caudate and putamen) and centrum semiovale in 11 well-characterized HIV patients and in 11 control subjects. DTI measurements were examined for patterns of relationship with markers of clinical and cognitive progression. DTI measures acquired in subcortical regions were significantly correlated with loss of function in specific cognitive domains. Significant relationships were identified between measures for putamen and verbal memory (MD), visual memory (FA), working memory (FA), and overall cognitive impairment (MD). Measures for caudate (FA) were significantly correlated with visual memory. Measures for centrum semiovale were significantly correlated with visual memory deficits (MD) and visuoconstruction (FA). Relationships between anisotropy measures and anemia (basal ganglia) and CD4 counts (centrum semiovale) were also observed. Findings from this investigation indicate that DTI is a sensitive tool for correlating neuroanatomic pathologic features with specific cognitive deficits in patients with HIV infection. *Journal of NeuroVirology* (2005) **11,** 292–298.

Keywords: basal ganglia; HIV dementia; quantitative MR

Introduction

Patients infected with the human immunodeficiency virus (HIV) are at risk for cognitive deterioration and progression to dementia (HIV-D). Cognitive decline is usually marked by losses involving psychomotor speed, memory, motor skills, and learning capacity with relative sparing of language, judgment, perceptual processes, and capacity for abstraction (Lipton and Gendelman, 1995). This pattern of deficits is consistent with a subcortical process. Autopsy studies of HIV-Dementia patients indicate extensive neuropathology in basal ganglia and deep white matter (for a review see Bell, 1998) and findings in these regions bear a relation to the degree of antemortem neurocognitive dysfunction (Cherner *et al*, 2002). Less is known, however, about changes in these regions over the course of infection and the significance of localized subcortical injury to the specific cognitive sequelae of HIV infection.

Diffusion tension imaging (DTI) can be used to acquire *in vivo* measurements of the diffusion characteristics of protons in interrogated brain regions (Basser and Pierpaoli, 1996). This noninvasive approach can be used to obtain measures that

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confer information concerning tissue status, including the overall (the mean diffusivity or MD) and the direction-dependent (fractional anisotropy or FA) diffusion of water molecules in brain regions of interest (ROIs). DTI abnormalities have been identified in HIV patients (Filippi *et al*, 2001; Pomara *et al*, 2001). DTI measures summarized for whole brain have been found to be significantly associated with dementia severity and with psychomotor loss, a sensitive early marker of brain injury and cognitive deterioration (Ragin *et al*, 2004a, 2004b). Limited DTI data are available, however, for the subcortical brain regions that have been implicated in HIV-D and the relationship of these measurements to specific cognitive sequelae. In order to evaluate the validity of DTI measures as potential imaging biomarkers in the setting of HIV infection, it is important to establish whether there is a relationship with cognitive outcomes of interest (Filippi and Grossman, 2002; Smith *et al*, 2003).

In this investigation DTI measurements were acquired in specific brain regions known to be sites of HIV-induced pathology. Tissue status measurements were determined for lateralized regions of basal ganglia, including caudate head and putamen, and of centrum semiovale (deep white matter) and examined for patterns of relationship with cognitive functions that are vulnerable to deterioration in HIV-infected patients. The *in vivo* measurements were correlated with measures of impairment in attention, memory, constructional, motor, and executive functions. Patterns of relationship with factors that have been identified as potential determinants of dementia progression (e.g., CD4 and plasma viral load) were also examined.

Results

To evaluate differences between the HIV and control groups, the MD and FA measures were submitted to separate repeated measures analysis of variance. In these analyses, measurements for the three different subcortical regions (centrum semiovale, caudate, and putamen) were considered simultaneously with age treated as a covariate. FA values were generally reduced and MD values were generally elevated in the HIV patients, however differences between the groups were not significant.

Tables 1 and 2 present correlations between the DTI measures and cognitive functions. Significant relationships were identified between increased MD in putamen and verbal memory deficits ($r = -.44$, $P = .04$). Anisotropy (FA) measurements in the basal ganglia were significantly correlated with visual memory (caudate: $r = .41$, $P = .05$; putamen: $r = .42$; $P = .05$) and working memory deficits (putamen: $r = .56$, $P = .015$). FA measures for putamen ($r = .43$, $P = .048$) were also significantly correlated with overall degree of impairment (the average of all measured cognitive functions). Examination of DTI measures for centrum semiovale indicated significant correlations between MD and visual memory deficits ($r = -.49$, $P = .02$); anisotropy measures were inversely correlated with visuoconstruction ($r = -.52$, $P = .013$). A consistent pattern of findings was obtained when these significant cognitive correlates were further examined separately for left and right hemispheres.

Table 1 Cognitive correlates of MD measurements

Cognitive function	*CSEM*	*Caudate*	*Putamen*
Working memory	−.36	−.34	−.21
Verbal memory	−.21	−.29	−.44*
Visual memory	−.49*	−.32	−.15
Constructional	.15	.33	.33
Psychomotor	.07	.04	.11
Motor speed	−.17	−.14	−.16
Frontal executive	−.28	−.15	−.17
Overall average	−.32	−.25	−.22

CSEM: centrum semiovale. *$P < .05$; $P < .01$.

Several significant relationships between subcortical FA measures and clinical status markers were also noted in the HIV patients. Anisotropy measures in centrum semiovale were significantly associated with measures of immune status (CD4 count: rho = −.61, $P = .047$); a similar trend was observed for viral load in plasma (rho = .56, $P = .073$). Anisotropy measurements in putamen were significantly associated with the measured hemoglobin (rho = .70, $P = .017$) and hematocrit (rho = .74, $P = .010$) levels of the HIV patients. A similar trend for hemoglobin was noted in caudate (rho = .53, $P = .091$). Examination of MD measures indicated a nearly significant inverse association between measures in caudate and hematocrit level (rho = −.57, $P = .066$). DTI measures acquired in basal ganglia did not correlate with CD4 or plasma viral load.

Discussion

Findings from this investigation indicate that DTI tissue status measurements (MD and FA) in subcortical regions are associated with cognitive impairment in HIV patients, likely involving networks that subserve memory functions. DTI measurements for

Table 2 Cognitive correlates of anisotropy measurements

Cognitive function	*Deep WM*	*Caudate*	*Putamen*
Working memory	.17	.24	.56**
Verbal memory	−.02	−.25	.19
Visual memory	−.11	.41*	.42*
Constructional	−.52**	.20	−.11
Psychomotor	.10	.20	.19
Motor speed	−.20	−.06	.21
Frontal executive	.33	.02	.31
Overall average	−.12	.16	.43*

CSEM: centrum semiovale. *$P < .05$; **$P < .01$.

putamen were significantly correlated with overall degree of cognitive decline (FA) and with impaired verbal memory (MD), working memory (FA), and visual memory (FA). Significant correlations were also identified between measures for caudate and deficits in visual memory (FA). Measures determined for centrum semiovale were significantly correlated with visual memory (MD) and visuo-construction (FA). A study examining isotropic diffusion measurements in HIV patients found a similar pattern of cognitive correlates for putamen and subcortical white matter (Cloak *et al*, 2003).

The principal advantage of DTI is quantitative sensitivity to changes that may not be detected with conventional T1-, T2-weighted magnetic resonance imaging (MRI). Postmortem studies have found that conventional MR imaging is insensitive to microscopic brain injury in HIV patients (e.g., Everall *et al*, 1997). DTI exploits the random translational movements of water molecules as a mechanism for probing and measuring tissue. In the usual time scale of the acquisition, water molecules in the brain move distances that approximate the sizes of cells and subcellular structures ($\approx$1 to 15 microns in 50 to 100 ms) (Le Bihan, 2003). Summary measures of these microscopic displacement distributions of water molecules can be derived within a given image volume (Horsfield and Jones, 2002). Diffusion alterations have been identified in cognitively asymptomatic HIV patients (Pomara *et al*, 2001) and in subjects in more advanced stages of infection (Filippi *et al*, 2001; Cloak *et al*, 2003; Ragin *et al*, 2004b; An *et al*, 2004). Experiments in nonhuman primates have detected significant changes in DTI measurements in brain tissue 11 days following inoculation with virus (He *et al*, 2003).

Measures acquired with DTI confer information concerning the status of tissue in the imaged region. Increased diffusivity (MD) reflects changes in the relative intracellular/extracellular volumes or net loss of structural barriers to diffusion (e.g., tissue destruction and irreversible change) (Gass *et al*, 2001). The directionally dependent diffusion (FA) is influenced by the presence of oriented structures (e.g., fiber tracts). Because diffusion in gray matter is generally isotropic, or similar in all directions, anisotropy measures (FA) may be more specific to changes in white matter (Basser and Pierpaoli, 1996). The measured anisotropy may reflect factors such as injury or loss of highly aligned cellular structures (e.g., axons) or replacement of axonal fibers with less ordered cells (e.g., glial cells) (Horsfield and Jones, 2002). Histopathological evidence from MS tissue indicates that anisotropy measures are highly associated with axonal density (Mottershead *et al*, 2003).

In this investigation, anisotropy measures appeared to be sensitive to tissue alterations in the studied gray matter regions (in basal ganglia), as well as those in the deep white matter (centrum semiovale). This may be due to the presence of significant numbers of myelinated axons in the basal ganglia. Widespread axonal damage has been detected in the basal ganglia and subcortical white matter of patients with HIV encephalitis, the pathologic correlate of dementia (Raja *et al*, 1997). High-resolution morphometric imaging at 4 T reveals loss of white matter occurring in the basal ganglia of HIV patients (Carasig *et al*, 2003). Many studies of HIV patients have found volumetric reductions in basal ganglia (see Bencherif and Rottenberg, 1998, for a review) and structural losses involving this region bear a relation to cognitive status (e.g., Aylward *et al*, 1995).

Significant correlations were obtained between DTI measures in basal ganglia and verbal memory, visual memory and working memory. Functional anatomical studies indicate extensive connections between striatum and prefrontal cortical structures that subserve working memory, attention, and other executive functions (Middleton and Strick, 2000). The observed relationships may reflect processes common to tasks based on transiently stored information and striatal involvement in specific subcomponents (e.g., operationalizing cues, direction of attention, implementation of search strategies, and retrieval). Demonstrable basal ganglia pathology has been associated with disturbances in working memory, retrieval, set shifting, and maintenance (Zgaljardic *et al*, 2003; Ring and Serra-Mestres, 2002).

The significance of diffusion abnormalities in basal ganglia is further supported by evidence of a relationship between reduced anisotropy for this region (particularly for putamen) and markers of anemia (hemoglobin and hematocrit). Anemia has been established as a significant risk factor (independent of CD4 count and viral load) for progression and death in HIV patients in both pre- and post-HAART (highly active antiretroviral therapy) treatment eras (see Moyle, 2002, for a review). Anemia has also been identified as a significant predictor of dementia in HIV infection (McArthur *et al*, 1993) and lower hematocrit has been associated with incident HIV-D in the post-HAART era (Sevigny *et al*, 2004). The findings of this study add to an accumulating body of evidence relating hematological status to neurological progression in HIV-infected patients (see Gartner and Liu, 2002). Formulations of HIV-D assign critical significance to increased monocyte trafficking into the brain from the bone marrow in late stages of infection and the deleterious consequences of unrelenting states of immune activation (Gartner, 2000).

Increased anisotropy in centrum semiovale was associated with more advanced immune suppression and disease progression (lower CD4 and higher plasma viral load). Other DTI findings have also identified an association between plasma viral load and diffusion abnormalities in centrum semiovale (Filippi *et al*, 2001). Pathological changes in white matter are generally presumed to reduce the directional diffusion. Increased anisotropy values have been reported, however, in white matter regions of HIV patients (Pomara *et al*, 2001) and in other brain injuries (e.g., early poststroke; Yang *et al*, 1999).

Given the ratio-metric nature of this measure (the fractional anisotropy is determined relative to the overall diffusion), localized FA increases in centrum semiovale may owe to pathological variations that augment the relative directional diffusion (e.g., more densely packed fiber tracts) or that alter the measured transverse diffusivities (Green *et al.*, 2002). The lack of relationship between anisotropy measures in deep gray matter regions and CD4 or plasma viral load is of interest and suggests that HIV-related changes in basal ganglia may reflect processes that are to some degree independent of the dynamics of systemic infection.

Formulations of HIV neuropathogenesis posit multiple pathways to injury (Avison *et al*, 2002). Postmortem findings in HIV patients include inflammatory (e.g., multinucleated giant cells, microglia and macrophages) and degenerative injury (e.g., axonal damage and neuronal apoptosis) (Bell, 1998). The number of activated macrophages in white matter is a prominent pathological correlate of HIV-D (Tyor *et al*, 1995). In this sample of HIV patients, anisotropy measures for centrum semiovale and basal ganglia demonstrated distinct patterns of relationship to markers of progression. Anisotropy measures in the studied subcortical regions may reflect different pathological processes or meaningful morphologic variation in white matter injury in HIV patients (e.g., Nebuloni *et al*, 2001). Activated microglia, for example, demonstrate morphological variants, that may depend on the local environment (Nelson *et al*, 2002).

Findings from this investigation provide further support for the validity of DTI for *in vivo* measurement of brain tissue status in HIV-infected patients. DTI may represent a promising noninvasive strategy for correlating neuroanatomic changes with deterioration in specific cognitive functions across the course of HIV infection. Additional studies are needed to replicate and clarify the relationships observed between subcortical DTI measurements and cognitive and clinical status measures. Further investigation of the pathological significance of DTI measurements in HIV patients may yield insights concerning the vulnerability of subcortical regions to injury and factors associated with neurologic progression.

Materials and methods

Participants

This prospective, controlled imaging study was conducted in collaboration with the North-East AIDS Dementia (NEAD) consortium, a large National Institutes of Health (NIH)-sponsored investigation of the natural history of neurocognitive impairment in HIV-infected patients (e.g., Sevigny *et al*, 2004). Seropositive subjects included 11 well-characterized, medically stable patients (mean age: 49.4 $\pm$ 7.3; 9 males and 2 females). Control subjects included 11 healthy volunteers, without history of neurological illness (mean age: 42.4 $\pm$ 11.2, 9 males and 2 females). There were no significant differences between the groups in age or education. Seropositivity was confirmed in the HIV patients by enzyme-linked immunosorbent assay (ELISA) and Western blot. CD4 counts for the HIV subjects ranged from 24 to 427; plasma viral load ranged from undetectable to 154,938 copies/ml. All HIV subjects were on antiretroviral regimens; however, one patient's therapy was temporarily suspended at the time of the scan. Study exclusion criteria included non–HIV-related chronic neurological disorders, current or past opportunistic central nervous system (CNS) infection, psychosis at study entry or MR contraindications. The study was conducted with Institutional Review Board approval.

Clinical assessments of the HIV subjects included the Macro-Neurological Examination created by the Aids Clinical Trials Group (Sidtis *et al*, 1993) and the motor portion of the Unified Parkinson's Disease Rating Scale to assess extrapyramidal signs (Fahn *et al*, 1987). A comprehensive neuropsychological

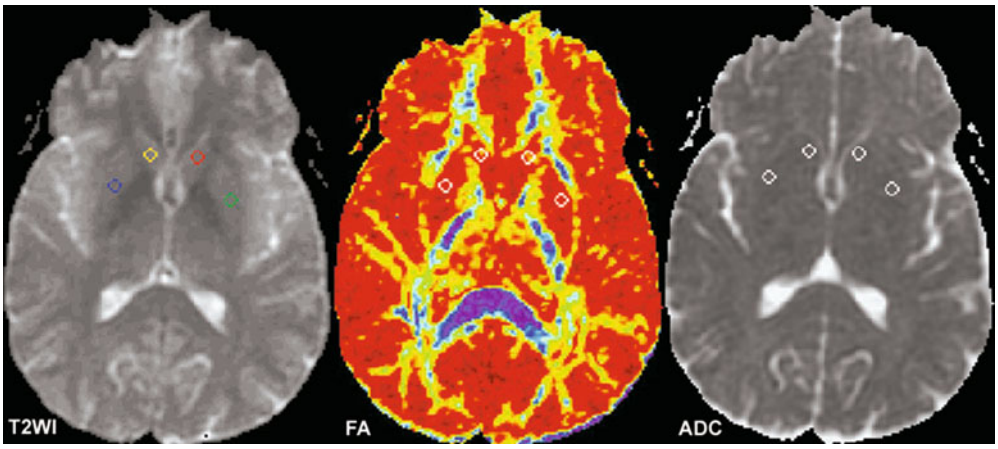

Figure 1 This axial slice through interventricular foramen shows the largest area of putamen and caudate nuclei. Uniform sized ROIs were placed on the anatomical T2-weighted image and projected on FA and MD maps to obtain DTI values.

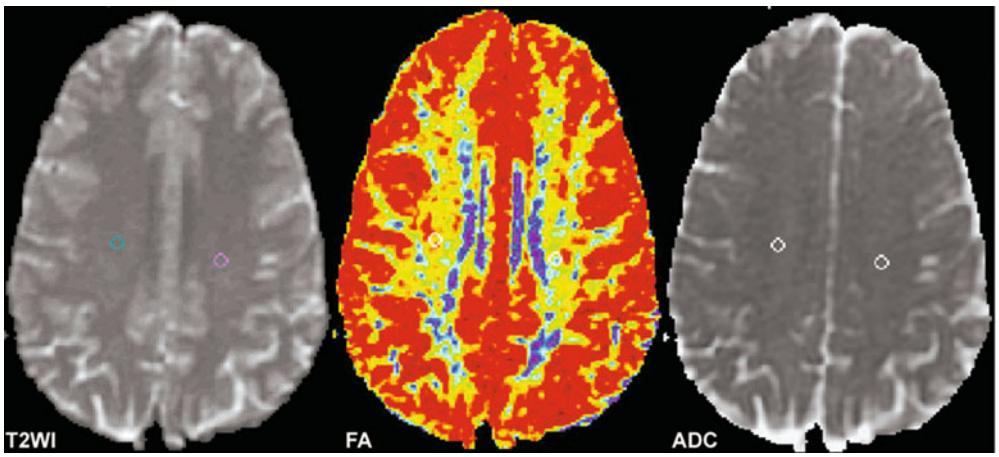

Figure 2 ROIs for centrum semiovale were placed on an axial slice above the bilateral ventricles.

battery was used to evaluate cognitive status. Standardized scores of specific individual subtests from the instruments comprising the neuropsychological battery were averaged to generate the cognitive function measures (Concha *et al*, 1995; Selnes *et al*, 1991). These included working memory (Miller *et al*, 1991), verbal memory (Rey, 1941), visual memory (Rey, 1941), constructional ability (Rey, 1941), psychomotor speed (Wechsler, 1981), motor speed (Klove, 1963), and frontal/executive systems (Benton, 1955; Flowers and Robertson, 1985). The cognitive function measures were also averaged to generate an overall measure of impairment for each subject. The derivation of the cognitive function measures have been described in extensive detail in prior reports (see Marder *et al*, 1996, 2003).

MR imaging and image processing

Imaging studies were performed on a 1.5-T twinspeed MR unit (GE, Milwaukee, USA) equipped with the zoom gradient. A quadrature birdcage headcoil was used for radiofrequency (RF) transmission and signal reception. The diffusion tensor imaging was performed with an echo planar sequence and a bandwidth of ±125 kHz using dual spin echo diffusion gradients to minimize distortion. Diffusion encoding was applied along six directions of each slice with a b-value of 1000 s/mm^2. A $b = 0$ reference image was also acquired. The entire brain was imaged inferior to superior from the base of the cerebellum to the top of the skull, using 22 contiguous 7-mm axial sections with the following parameters: field of view, 24 cm; matrix, 128 × 128, 7000/4 (TR/number of excitations).

Quantitative image analysis was performed offline using a custom software package to compute the pixel-by-pixel FA and MD (DPTools; Paris, France). After the FA and MD maps were generated, uniform sized (43 mm^2) ROIs were placed in the specified brain areas. In order to achieve better anatomical visibility and to reduce measurement bias, the $b = 0$ reference image was used for ROI placement, rather than the diffusion images or calculated diffusion maps. The following strategy was used for ROI placement. The basal ganglia ROIs were placed using a medial level axial slice across the interventricular foramen, which commonly shows the largest areas of putamen and caudate nuclei (Figure 1). For centrum semiovale placement, ROIs were aligned with the central sulcus and placed bilaterally one slice above the roof of the lateral ventricles in the approximate center of the defined white matter area (Figure 2). For each region, DTI measures were determined for both left and right hemisphere. The lateralized measures were then averaged for further analysis.

Statistical analyses

Primary dependent measures included the DTI measures (MD and FA) acquired in lateralized regions of basal ganglia (caudate and putamen) and in lateralized centrum semiovale. DTI measurements were compared in HIV and control subjects. Dementia severity and neuropsychological measures of specific cognitive functions were also correlated with the quantitative MR measurements. All statistical tests were two-tailed using a significance level of .05 and were executed in SPSS (release 10.0; Chicago, IL).

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