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A comparative evaluation of quantitative neuroimaging measurements of brain status in HIV infection

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ABSTRACT

Diffusion tensor imaging (DTI), magnetization transfer imaging (MT) and automated brain volumetry were used to summarize brain involvement in human immunodeficiency virus (HIV) infection. A multiparametric neuroimaging protocol was implemented at 1.5 T in 10 HIV+ and 24 controls. Various summary parameters were calculated based on DTI, MT, and automated brain volumetry. The magnitude of the difference, as well as the between-group discrimination, was determined for each measure. Bivariate correlations were computed and redundancy among imaging parameters was examined by principal factor analysis. Significant or nearly significant differences were found for most measures. Large Cohen's d effect sizes were indicated for mean diffusivity (MD), fractional anisotropy (FA), magnetization transfer ratio (MTR) and gray matter volume fraction (GM). Between-group discrimination was excellent for FA and MTR and acceptable for MD. Correlations among all imaging parameters could be explained by three factors, possibly reflecting general atrophy, neuronal loss, and alterations. This investigation supports the utility of summary measurements of brain involvement in HIV infection. The findings also support assumptions concerning the enhanced sensitivity of DTI and MT to atrophic as well as alterations in the brain. These findings are broadly generalizable to brain imaging studies of physiological and pathological processes.

1. Introduction

Individuals infected with the human immunodeficiency virus (HIV) are at considerable risk of brain injury and cognitive deterioration, and these neurological complications have a significant impact on survival (Sevigny et al., 2007). Ongoing injury to the brain, however, may be clinically silent for indefinite periods, and damage may be irreversible by the time symptoms present. Quantitative imaging strategies such as diffusion tensor imaging (DTI), magnetization transfer imaging (MT) and brain segmentation have been used in efforts to clarify the nature of the injury to the brain and to determine factors associated with increased risk. For example, aggregate microstructural brain alterations can be derived with DTI, which exploits the random translational movements of water molecules to probe tissue at a level approximating cellular dimensions (Basser and Pierpaoli, 1996). DTI measurements differ in human immunodeficiency virus positive (HIV+) and control subjects (Filippi et al., 2001; Pomara et al., 2001; Ragin et al., 2004, 2005; Thurnher et al., 2005; Wu et al., 2006; Pfefferbaum et al., 2007, 2009; Stebbins et al., 2007; Chen et al., 2009; Gongvatana et al., 2009), and these measures correlate with cognitive deficits (Ragin et al., 2004, 2005; Wu et al., 2006; Gongvatana et al., 2009). MT imaging has been used to quantify pathologic changes in macromolecules due to tissue injury and destruction (van Buchem et al., 1999). MT measures differ in HIV+ from control subjects and correlate with cognitive impairment (Ge et al., 2003; Ragin et al., 2004; Wu et al., 2008). Automated brain segmentation algorithms can be used to derive volume fractions of gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) within the individual cranial cavity, as well as parenchymal and ventricular volumes relative to normative population brain size (Zhang et al., 2001; Smith et al., 2002; Smith, 2004). The volumetric measurements derived with these strategies have been determined to be robust and accurate in simulation studies against known tissue volumes (Zhang et al., 2001; Smith et al., 2002; Smith, 2004). Volumetric strategies have been used to investigate brain injury in HIV infection (e.g., Thompson et al., 2005, 2006).

The summary measurements that can be derived with quantitative imaging strategies represent promising tools for identifying factors

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associated with HIV neurological outcome and for evaluating interventions aimed at preservation of the brain and cognitive function. It is not clear, however, which summary measure is the most sensitive to HIV-induced neuropathological changes, and the relationship between the different parameters is not well understood. This is problematic for reconciling findings based on different quantitative magnetic resonance (MR) parameters and for designing clinical studies. This investigation specifically focuses on which of several available quantitative MR sequences is most sensitive in discriminating HIV and control subjects for informing studies of neurological outcome. This information can also be used to inform larger studies aimed at constructing a composite measurement based on quantitative MR parameters.

The emphasis of this investigation concerned summary measurements of overall brain status. Whereas regional analyses may be more informative concerning subtle changes in localized regions, these strategies are labor intensive, subject to greater inter-operator variation associated with region-of-interest determination and difficult to implement in large, multicenter neurological studies. The objective, summary measurements of brain status that can be derived with quantitative imaging may be particularly valuable as outcome measurements for large, multicenter neurological studies. These measures may be more sensitive than behavioral measures, particularly in asymptomatic periods of infection.

Fractional anisotropy (FA), in theory, is sensitive to myelinated axons throughout the brain, including in the gray matter. Likewise, both mean diffusivity (MD) and the magnetization transfer ratio (MTR) can be used to detect microstructural (MD) and macromolecular (MTR) alterations in both tissue types. While the physiologic significance and clinical relevance of FA and MTR in gray matter is not as well understood, abnormalities have been identified with these indices in both white and gray matter (Ge et al., 2002a, 2002b; Agosta et al., 2006; Tortorella et al., 2006). The whole brain approach therefore incorporates all non-CSF voxels in the brain in the calculation. This simplifies image processing for large studies. In addition, to segment the DTI measures (e.g. FA just in white matter) would have required implemented the segmentation strategies into the FA measurements that were being compared with the segmentation measurements. Objective, quantitative summary measurements of brain status may be particularly valuable as outcome measurements for large, multicenter neurological studies.

A multiparametric imaging protocol was implemented that included DTI (Basser and Pierpaoli, 1996), MT (Wolff and Balaban, 1994), as well as anatomic imaging. The DTI data were used to calculate whole brain FA and MD. The MT data were used to derive the MTR. Segmentation strategies were used to determine volume fractions of white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF), as well as normalized brain parenchyma volume (NBPV) and normalized ventricular volume (NVV) based on the anatomic images (Fig. 1). These measurements were compared in HIV+ and control subjects. Patterns of relationships between the summary measurements and with important clinical status markers were also examined.

2. Materials and methods

2.1. Subjects

This study included 10 well-characterized subjects who were seropositive as confirmed by enzyme-linked immunosorbent assay (ELISA) and Western blot (age: 52.7±6.6; 8 males, 2 females; education: 15.5±2.6 years) and 24 healthy control subjects (age: 48.5±9.8; 16 males, 8 females; education: 16.4±2.9 years). Groups were not significantly different in age or education. All HIV+ subjects were at an advanced stage of infection (meeting criteria for acquired immunodeficiency syndrome (AIDS)) and were on antiretroviral regimens. Absolute CD4+ cell counts ranged from 50 to 777/mm^3. Plasma HIV RNA ranged from undetectable to 55,300 copies/mL. Control subjects were healthy volunteers, without history of neurologic illness. While CD4+ cell counts can be obtained for normal control subjects, plasma HIV RNA is a measure of viral replication in blood, and not detected in HIV-negative subjects. Study exclusion criteria for both HIV and control participants included history of neurological disorder, stroke, head trauma, opportunistic central nervous system (CNS) infection, psychosis or MR contraindication. Medical history questionnaires were also administered. The study was approved by the institutional review board, and all subjects provided written informed consent.

2.2. Magnetic Resonance Imaging (MRI) and image processing

MR examinations were performed on a 1.5 T twinspeed unit (GE, Milwaukee, USA) with high performance gradients using a quadrature birdcage headcoil for radiofrequency (RF) transmission and signal reception. T_2- and proton-density-weighted images were acquired using dual spin echo sequences, with repetition time (TR) = 3300 ms, and echo times (TE) = 20 ms and 90 ms. Other parameters were as follows: FA: 90°, matrix size: 256×256, field of view (FOV): 24×18 cm, number of excitations (NEX) = 2, slice thickness/gap: 3.5/0, 42 contiguous slices covering whole brain. DTI was performed with an

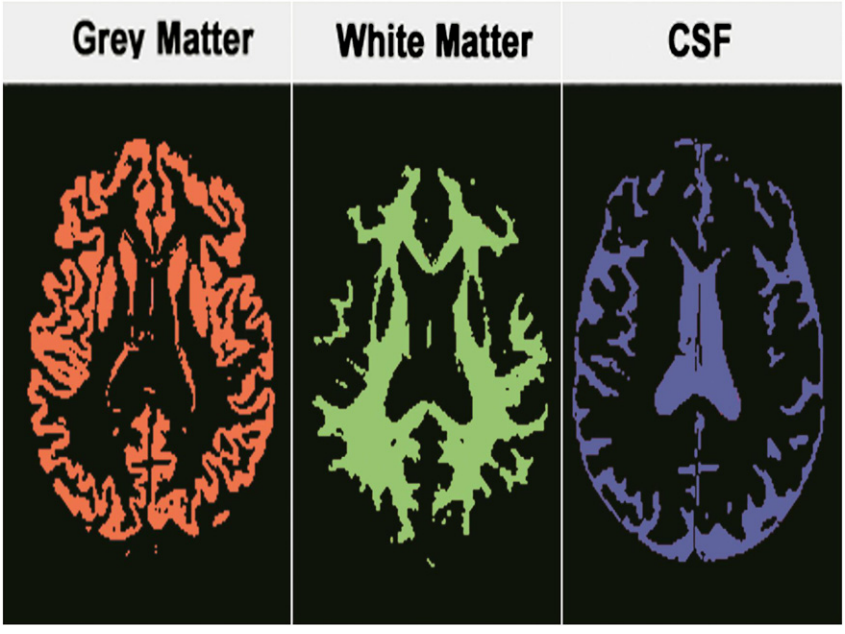

Fig. 1. Brain segmentation results for gray matter, white matter and CSF, for deriving the volume fractions.