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A diffusion tensor imaging and neurocognitive study of HIV-positive children who are HAART-naïve "slow progressors"

Jacqueline Hoare · Jean-Paul Fouche · Bruce Spottiswoode · Kirsty Donald · Nicole Philipps · Heidre Bezuidenhout · Christine Mulligan · Victoria Webster · Charity Oduro · Leigh Schrieff · Robert Paul · Heather Zar · Kevin Thomas · Dan Stein

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Abstract There are few neuropsychological or neuroimaging studies of HIV-positive children with "slow progression". "Slow progressors" are typically defined as children or adolescents who were vertically infected with HIV, but who received no or minimal antiretroviral therapy. We compared 12 asymptomatic HIV-positive children (8 to 12 years) with matched controls on a neuropsychological battery as well as diffusion tensor imaging in a masked region of interest analysis focusing on the corpus callosum, internal capsule and superior longitudinal fasciculus. The "slow progressor" group performed significantly worse than controls on the Wechsler Abbreviated Scale of Intelligence Verbal and Performance IQ scales, and on standardised tests of visuospatial processing, visual memory and executive functioning. "Slow progressors" had lower fractional anisotropy (FA), higher mean diffusivity (MD) and radial diffusivity (RD) in the corpus callosum (p=<0.05), and increased MD in the superior longitudinal fasciculus, compared to controls. A correlation was found between poor performance on a test of executive function and a test of attention with corpus callosum FA, and a test of executive function with lowered FA in the superior longitudinal fasiculus. These data suggest that demyelination as reflected by the increase in RD may be a prominent disease process in paediatric HIV infection.

Keywords Imaging · Diffusion tensor · HIV/AIDS · Paediatric · Cognitive impairment

J. Hoare · J.-P. Fouche · N. Philipps · D. Stein
Department of Psychiatry and Mental Health,
University of Cape Town,
Cape Town, South Africa

B. Spottiswoode
MRC/UCT Medical Imaging Research Unit,
Department of Human Biology, University of Cape Town,
Cape Town, South Africa

B. Spottiswoode
Department of Radiological Sciences and Oncology,
Stellenbosch University,
Stellenbosch, South Africa

K. Donald · H. Bezuidenhout · C. Mulligan · H. Zar
Department of Paediatrics, School of Child and Adolescent Health,
UCT,
Cape Town, South Africa

V. Webster · C. Oduro · L. Schrieff · K. Thomas
Department of Psychology, University of Cape Town,
Cape Town, South Africa

R. Paul
Department of Psychology and Behavioural Neuroscience,
University of Missouri,
St. Louis, MO, USA

J. Hoare (✉)
Division of Liaison Psychiatry, Department of Psychiatry and Mental Health, University of Cape Town,
Anzio Road Observatory,
7925, Cape Town, South Africa
e-mail: hoare.jax@googlemail.com

Introduction

In the HIV literature, "slow progressors" are typically defined as children or adolescents who were (a) vertically infected with HIV, but who (b) received no or minimal therapy (defined as single or dual nucleoside therapy) before the age of 10 years and who (c) remained clinically and immunologically stable for the first decade of life (e.g. had maintained CD4 counts above 25 % over that period) (Bagenda et al. 2006). In South Africa, as many as 35 % of all infected children are believed to meet these criteria for slow progression (Archary et al. 2010), yet little is known about the neurocognitive characteristics of these children.

Regarding neuropsychological aspects, few studies have, in fact, described the cognitive profile of older (>6 years) vertically infected HIV-positive children. Previous studies have focused mainly on younger children and described specific cognitive impairments associated with HIV infection. They highlighted deficits in the domains of visual perceptual and visual motor skills, attention, executive functions, memory and language (Nozyce et al 2006; Fundaro et al. 1998; Boivin et al. 1995). A recent article reviewing studies in sub-Saharan Africa that used development, cognition and behaviour in HIV-positive children as their primary outcomes highlighted the paucity of data in this field as well as the fact that all except one study had focused on the pre-school age group (Abubakar et al. 2008).

Even fewer studies in the field of HIV neuropsychology have focused specifically on HAART-naïve slow progressors. The findings have been inconsistent, with some reporting no cognitive deficits, whilst others did report significantly poorer performance in the children with slow progression. Bagenda et al. (2006) investigated Ugandan children, aged 6–12 years, who were asymptomatic, vertically HIV-infected and who were HAART-naive. They compared those children to a control group of HIV-negative children. Although scoring slightly lower on academic achievement measures and showing more signs of acute illness and malnutrition, the patient group did not differ from the control group on tests of sequential processing, simultaneous processing and memory. Another study of asymptomatic HIV-infected children reported relatively normal performances on tests of general intellectual functioning and language, in the presence of executive function impairments (Bisuacchi et al. 2000; Brown and Lourie 2000).

These data suggest that even though a child might be described as asymptomatic, HIV infection may still have an impact on particular aspects of CNS function, leading to discrete and subtle deficits in specific cognitive domains (De Baets et al. 2007). The deficits could have far-reaching impacts on the child's academic performance and hence schooling outcome. These findings underscore the importance of investigating specific cognitive domains in addition to general intellectual functioning.

Structural brain imaging studies of HIV in children have shown a range of abnormalities including cortical atrophy with ventriculomegaly and basal ganglia calcifications on CT, and MRIs show white matter lesions (DeCarli et al 1993; George et al 2009). Atrophy is more frequently seen in younger children, and the amount of atrophy correlates with plasma HIV RNA levels (Angelini et al. 2000). Atrophy has also been noted in asymptomatic children, although to a lesser degree (Gavin and Yogev 1999). Should neuropsychological impairments exist in slow progressors, these should be underpinned by loss of white matter integrity.

Whereas traditional MRI only describes the location and extent of white matter damage, diffusion tensor imaging (DTI) is capable of examining the microstructural integrity and directionality of the white matter. We regarded it as particularly suitable for use with this sample of children because it is a non-invasive technique that allows for rapid data collection, and because it has demonstrated utility in studies of HIV-positive adults (Filippi et al. 2001; Pomara et al. 2001). Traditional scalar metrics derived from DTI data include fractional anisotropy (FA), which represents axon integrity and/or packing density, and mean diffusivity (MD), which represents the mean water mobility within the white matter. High FA and low MD values are typically associated with healthier neural microstructure and better cognitive performance, whereas low FA and high MD values are indicative of white matter damage. Axial diffusivity (AD) and radial diffusivity (RD) are additional DTI-derived metrics corresponding to diffusion parallel and perpendicular to the direction of the white matter tract, respectively. Myelin loss (measured in DTI by an index of RD) and axonal damage (measured in DTI by an index of AD) are both observed in white matter injuries, such as might occur in HIV. Because AD and RD have potential for use in differentiating between axonal injury and myelin loss (Song et al. 2002), separate analyses of the changes in these two indices may provide insight into the underlying mechanisms of white matter damage associated with HIV infection in children. Hence, in the current study, one of our specific aims was to determine whether, in this group of slow progressors, clade C HIV affects the DTI indices of FA, MD, RD and AD in specific regions of interest, selected based on a previous DTI study of HIV-positive adults from the same community (Hoare et al. 2011) (viz., the corpus callosum, internal capsule and superior longitudinal fasciculus).

This study aimed to examine neuropsychological and DTI in slow progressors compared to matched controls. The neuropsychological battery assessed general intellectual functioning as well as specific domains of cognition diffusion tensor imaging was used to assess myelin loss.

Methods

Subjects and sampling

We recruited 12 HIV-positive slow progressor children from the Infectious Diseases clinic at Red Cross War Memorial Children's Hospital in the Western Cape Province of South Africa. A study coordinator identified potentially eligible candidates, and then invited those children and their parents/guardians to participate. Eligible children were those who had attended the Infectious Disease clinic at least once, who were HAART-naïve and who met the inclusion criteria listed below.

We also recruited a control group of 12 HIV-negative children, matched to the patient group on age, gender and race. These children were resident in the same community as the HIV-positive children in order to control for socio-economic status and quality of education.

After enrolment, parents/guardians provided full informed consent for the child to participate in the study, and the child provided assent. Parents/guardians were compensated for transport costs and loss of time. Ethical approval was obtained from the University of Cape Town's Faculty of Health Sciences research ethics committee.

HIV-infected children had to satisfy the following criteria in order to be included in the study: age between 8 and 12 years; positive diagnosis of HIV infection (including initial and confirmatory tests); HAART-naïve and asymptomatic (i.e. no AIDS-defining stage 4 illness and a CD4 count of >25 %). Individuals with any of the following were excluded from participation: an uncontrolled medical condition, such as poorly controlled diabetes mellitus, epilepsy or active tuberculosis requiring admission; an identified CNS condition (other than HIV), such as TB meningitis and bacterial meningitis, documented cerebrovascular accident and lymphoma; a positive history of drug or alcohol exposure in pregnancy; a history of head injury with of loss of consciousness greater than 5 min or any radiological evidence of skull fracture; a history of perinatal complications such as hypoxic ischemic encephalopathy or neonatal jaundice requiring exchange transfusion or neurodevelopment disorder not attributed to HIV and contra-indications to MRI (such as metal in the body and claustrophobia).

Instruments and measures

Neuropsychological assessment

Each participant was assessed using a standardised battery of neuropsychological tests commonly used in paediatric neuropsychology clinical assessment and research internationally and in South Africa. Test instructions were translated and back-translated into Xhosa, and we took steps to ensure test administration maintained compliance with International Test Commission guidelines (Bartram 2001).

The test battery comprised the following instruments: the *Wechsler Abbreviated Scale of Intelligence* (WASI; Wechsler 1999) measured general intellectual functioning; the *Grooved Pegboard Test* (GPT; Lafayette Instrument Company 2003) measured eye–hand coordination and motor speed; the Symbol Search, Digit Symbol—Coding and Digit Span subtests from the *Wechsler Intelligence Scale for Children—Fourth Edition* (WISC-IV; Wechsler, 1999) measured information processing speed, attention and concentration and working memory; the *Color Trails Test* (CTT; Williams et al. 1995) measured visual attention and cognitive flexibility; the *Rey Complex Figure Test* (RCFT; Meyers and Meyers 1995) measured visuospatial processing and visual memory and a category fluency test and the NEPSY-II Inhibition subtest (Korkman et al. 2007) measured elements of executive functioning (generativity and inhibition of automatic responses, respectively).

Brain imaging protocol

Diffusion-weighted images were acquired at the Cape Universities Brain Imaging Centre on a 3 T MRI scanner (Siemens Magnetom Allegra, Erlangen, Germany). The diffusion-weighted images were acquired in an axial orientation with the following parameters: $1.8\times1.8\times2.0$ mm^3 spatial resolution, 220 mm FOV, TR=8,800 ms, TE=88 ms, 65 slices, 0 % distances factor and twofold GRAPPA acceleration. Gradients were applied in 30 directions with b=1,000 mm/s^2 and three volumes were acquired without any diffusion-weighting. This sequence was repeated three times.

For analyses of these data, images were imported into the FSL (FMRIB Software Library) 4.1.8 toolbox (Smith 2002) and corrected for eddy current distortions. The images were then imported into MATLAB (Mathworks, Natick, MA) for further pre-processing. The three acquisitions were linearly co-registered with the b=0 mm/s^2 image of the first average used as a reference. For each of the three co registered acquisitions, outliers were determined relative to the tensor estimate by calculating the Z-value at the 25th and 75th percentiles, and ignoring values three standard deviations away from the mean. The three acquisitions were then averaged and exported to the tract-based spatial statistics toolbox (TBSS; Smith 2002) of FSL for voxel-wise analysis. Fractional anisotropy, mean diffusivity, radial and axial diffusivity images were created by fitting a tensor model to the averaged data. Brain extraction was performed with FSL BET (Smith 2002). A study-specific paediatric FA template was created for the purpose of registering data to MNI space.

After images were pre-processed with the TBSS pipeline, a region-of-interest mask (ROI) was created. For mask creation the JHU-White matter atlas (Mori et al. 2005) included with FSL was used. Age, gender and total white matter volume were included as covariates in the analysis.

Statistical analyses

All analyses were completed using SPSS version 19. All data upheld assumptions underlying parametric statistical tests, and did not need to be transformed in any way. Alpha was set at .05.

The first analytic step involved a series of independent samples *t* tests comparing neuropsychological test performance in the HAART-naïve and control groups. Although our research design, and this particular analysis, focused on hypothesis testing, the public health context of this research, together with the small sample sizes, meant that we were more concerned about missing real effects rather than controlling alpha values strictly. In statistical terms, our concerns were more about avoiding the possibility of type II errors than about controlling the possibility of type I errors (see Jacobson and Jacobson 2005 for a complete discussion of decision-making in this regard).

Three ROI were defined for statistical analysis: The corpus callosum, superior longitudinal fasciculus and the internal capsule. Statistical analysis was performed at 5,000 permutations with threshold-free cluster enhancement in FSL's randomise. An unpaired two-sample *t* test was performed to compare DTI matrices between the two groups ($p<0.05$ corrected for multiple comparisons).

The third analytic step involved a series of correlations describing the relationship between white matter integrity FA, as measured by diffusion tensor imaging, and neuropsychological test performance. The correlation coefficient used here was Pearson's *r*.

Results

Sample characteristics

The HIV-positive HAART-naïve group and HIV-negative healthy control group were homogeneous and well-matched. Regarding age at testing, all children were between 8 and 12 years, and there were no significant between-group differences (patients: $M=10.40$, SD=1.45; controls: $M=9.83$, SD=1.16), $t(1, 11)=0.85$, $p=.411$. Regarding level of education at the time of testing, all children had completed between 1 and 5 years of formal schooling successfully, and there were no significant between-group differences (patients: $M=3.00$, SD=1.00; controls: $M=2.43$, SD=1.27), $t(1, 11)=1.01$, $p=.311$.

All participants were right-handed and of low socio-economic status. All participants except one (a female in the HAART-naïve group, who had a home language of English) had a home language of isiXhosa. Regarding race, all participants except one (the same female in the HAART-naïve group, who was coloured) were Xhosa. The difference in sex distribution across groups was not statistically significant, χ^2 (1)=1.57, p (two-tailed)=.210. The mean CD4 count in the HIV-positive group was 585. Only one of the HIV-positive children had a detectable viral load at the time of testing (vL= 24,032).

Neuropsychological test performance

Table 1 presents the results of statistical analyses comparing the HIV-positive HAART-naïve group to the HIV-negative healthy control group. Patients performed significantly more poorly ($p<.05$ in all cases) than controls on tests of general intellectual functioning, visuo-spatial processing, visual memory and semantic fluency. There were also trends ($p<.10$ in all cases) toward significantly poorer performance by patients than controls on tests of motor functioning, processing speed, executive function and cognitive flexibility. As the table shows, each of these comparisons was associated with an effect size estimate in the range conventionally described as large (Cohen 1988).

Diffusion tensor imaging

Table 2 presents summary data for significant changes in FA, MD and RD (there were no significant changes in AD) for the three ROI (corpus callosum, internal capsule and superior longitudinal fasciculus). In the patient group, we observed decreased FA (Fig. 1) and increased RD (Fig. 2) in the corpus callosum. We also observed increased MD (Fig. 3) and increased RD in the superior longitudinal fasciculus. There were, however, no significant changes in all four DTI parameters in the internal capsule.

Associations between neuropsychological and neuroimaging data

Table 3 presents the statistically significant correlations between DTI measures of white matter integrity and neuropsychological test performance. Correlations between lower FA values in the corpus callosum and superior longitudinal fasciculus, and poorer neuropsychological test performances were found for Colour trails 1 and semantic fluency.

Table 1 Neuropsychological test performance: between-group differences

Domain/test/subtest	HAART-naïve (n=12)	Healthy control (n=12)	t	p	ESE
General intellectual functioning					
WASI					
Verbal IQ	87.78 (15.24)	101.20 (14.26)	1.98	.032*	0.91
Performance IQ	73.67 (8.85)	85.70 (9.89)	2.78	.007**	1.28
Motor functioning					
Grooved Pegboard Test					
Dominant hand z-score	3.32 (4.65)	−0.31 (2.19)	−1.76	.051***	−1.0
Non-dominant hand z-score	2.86 (3.68)	0.17 (2.58)	−1.52	.077***	−0.85
Processing speed					
WISC-IV Processing Speed Index	75.00 (14.04)	83.50 (7.62)	1.66	.057***	0.75
Attention and concentration					
WISC-IV Digit Span Forward SS	6.78 (2.17)	8.10 (3.07)	1.07	.149	0.50
Color Trails Test Trail 1 raw score	118.88 (99.90)	79.50 (24.19)	−1.21	.122	−0.54
Working memory					
WISC-IV Digit Span Backward SS	6.00 (2.50)	5.20 (1.23)	−0.90	.191	−0.41
Visuospatial processing					
WASI Block Design T-score	36.00 (5.55)	57.10 (18.25)	3.32	.002**	1.56
Rey Complex Figure Test copy z-score	−4.51 (1.64)	−2.37 (2.28)	2.05	.032*	1.08
Memory – visual					
Rey Complex Figure Test					
Immediate recall T-score	36.75 (6.74)	38.30 (5.27)	0.55	.296	0.26
Delayed recall T-score	29.88 (8.49)	36.40 (6.85)	1.81	.045*	0.85
Executive function					
Semantic fluency: Animals total	6.38 (3.25)	9.00 (2.26)	2.02	.030*	0.94
Color Trails Test Trail 2 raw score	203.38 (46.61)	168.10 (40.04)	−1.73	.051***	−0.81
NEPSY-II Inhibition: Inhibition SS	5.75 (1.98)	7.10 (3.35)	1.01	.165	0.49
WASI Matrix Reasoning T-score	6.12 (2.04)	35.30 (17.53)	0.11	.045*	2.34

Means are presented with standard deviations in parentheses. The p values presented are for one-tailed hypothesis tests. ESE = effect size estimate (in this case, Cohen's d). A larger effect size indicates a greater advantage for the control group, except in the case of dependent variables measured in time (viz., all GPT measures and all CTT measures); in those cases, better performance is indicated by a smaller score (i.e. shorter time to complete the task), and hence negative effect sizes in those cases indicate better performance by the control group

WASI Wechsler Abbreviated Scale of Intelligence, *WISC-IV* Wechsler Intelligence Scale for Children, Fourth Edition, *SS* age-adjusted scaled score

*p<.05; **p<.01; ***p<.10

Table 2 Summary of significant findings in the ROI analysis

Anatomy	MNI coordinates	Cluster size (mm^3)	Mean FA controls (SD)	Mean FA HIV + HAART-naive (SD)	p value
Decreased FA in HAART-naive children compared to controls					
Corpus callosum body	−13; 12; 28	87	0.589543 (0.054)	0.541084 (0.052)	0.046
	14; 4; 32	32	0.613396 (0.032)	0.55771 (0.056)	0.048
Anatomy	MNI coordinates	Cluster size	Mean RD controls (SD)	Mean RD HIV + HAART-naive (SD)	p value
Increased RD in HAART-naive children compared to controls					
Right superior longitudinal fasciculus	37; −7; 26	137	5.22702×10^{-4} (3.84×10^{-5})	5.99947×10^{-4} (3.37×10^{-5})	0.028
Corpus callosum body	−13; 12; 28	239	4.70343×10^{-4} (5.70×10^{-5})	5.27587×10^{-4} (4.99×10^{-5})	0.033
	14; 5; 32	58	4.55828×10^{-4} (3.90×10^{-5})	5.24485×10^{-4} (4.78×10^{-5})	0.045
	-14; -6; 33	43	4.53333×10^{-4} (4.92×10^{-5})	5.29677×10^{-4} (5.11×10^{-5})	0.049
Anatomy	MNI coordinates	Cluster size	Mean MD controls (SD)	Mean MD HIV+ HAART-naive (SD)	p value
Increased MD in HAART-naive children compared to controls					
Right superior longitudinal fasciculus	33; 1; 20	166	7.16474×10^{-4} (5.32×10^{-5})	7.65064×10^{-4} (6.42×10^{-5})	0.034

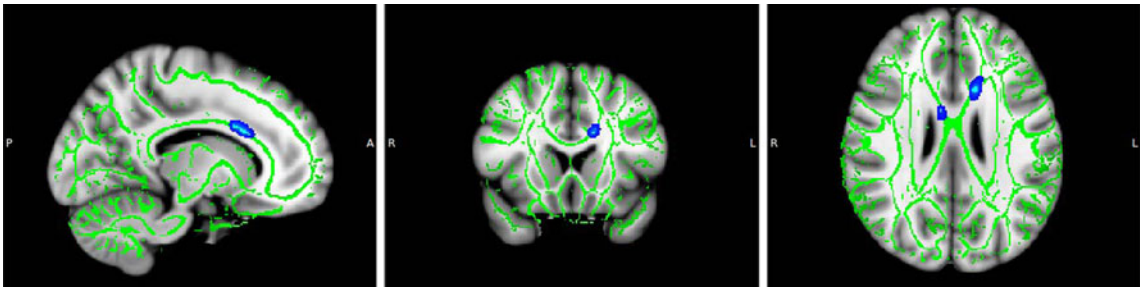

Fig. 1 Significant decreases in the corpus callosum FA of HIV+ HAART-naive children when compared to HIV− controls

Discussion

The purpose of this study was to examine, relative to a group of demographically matched HIV-negative controls, the neuropsychological and DTI characteristics of 12 HIV-positive, slow-progressing, HAART-naïve children. Our data showed that, compared to HIV-negative matched controls, both cognitive function and white matter integrity were altered in asymptomatic children infected with HIV.

Our results suggest that the patient group performed significantly more poorly than the control group on the WASI Verbal and Performance IQ scales (i.e. on measures of general intellectual functioning). Additionally, patients performed significantly more poorly than controls on standardised tests of visuospatial processing, visual memory, executive function and semantic fluency. Effect size estimates for these between-group comparisons suggest that the differences are clinically significant in the population.

The pattern of neuropsychological findings reported here is quite different to previously published studies conducted in Europe and Africa. For instance, Bisuacchi et al. (2000) reported, in a study of a neurologically asymptomatic HIV-positive Italian sample, that all infected children presented with executive function impairments, whereas only those with full-blown AIDS presented with additional memory and visuospatial deficits. Scores on tests of language abilities and general intellectual functioning (IQ) were unimpaired. In contrast, Bagenda et al. (2006) reported that a sample of long-surviving and ART-naïve Ugandan children did not differ significantly, on both neurologic and cognitive assessments, from age- and sex-matched HIV-negative children.

Clearly, the differences across neuropsychological studies of slow progressors are stark. Whether these differences can be attributed to particular characteristics of the study populations (e.g. the clade of the virus with which they are infected) is a matter for future studies to resolve. Taken together with Bisuacchi et al. (2000), however, the current study does suggest that, in neurologically asymptomatic HIV-positive children, neuropsychological evaluation can identify impairment of specific cognitive functions.

This is the first study of which we are aware that has utilised DTI to examine the effects of HIV on white matter in HIV-positive children who are slow progressors. A number of DTI studies of HIV-positive adults have reported white matter damage to the corpus callosum (Wu et al. 2006; Chang et al. 2008; Thurnher et al. 2005). In a study of clade C HIV-positive adults from the same community, decreased FA was found in the corpus callosum, superior longitudinal fasciculus and cingulum and sagittal stratum (Hoare et al. 2011). Research with animal models has demonstrated that the myelin structure impedes perpendicular diffusivity. Increased perpendicular diffusivity could thus be an indicator of myelin damage (Song et al. 2002). The region of interest analyses revealed that RD was affected to a much greater

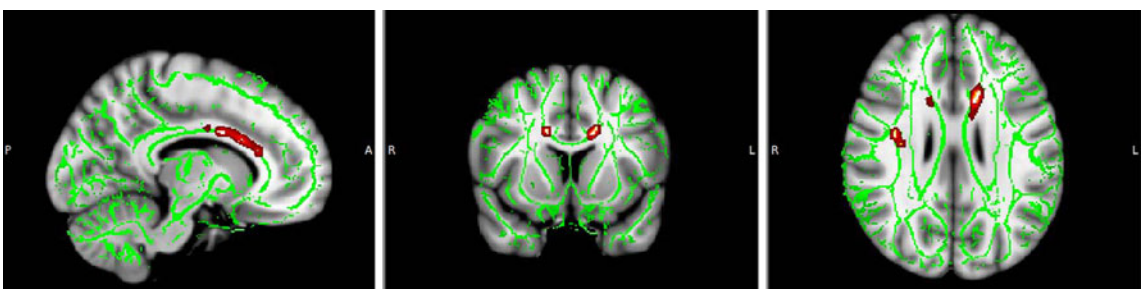

Fig. 2 Significant RD increases in the corpus callosum and right superior longitudinal fasciculus of HIV+ HAART-naive children when compared to HIV− controls

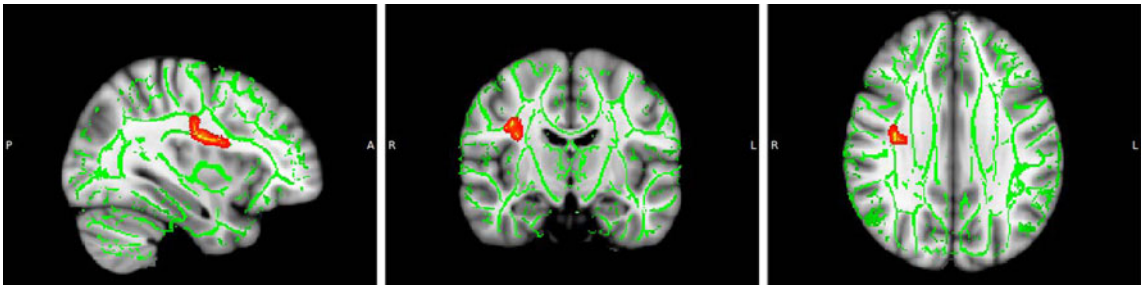

Fig. 3 Significant MD increases in the right superior longitudinal fasciculus of HIV+ HAART-naive children when compared to controls

extent than AD by HIV infection, which may suggest that demyelination is the prominent disease process in white matter in paediatric HIV. A previous DTI study of HIV-positive adults reported increases in RD that were more significant than the increases in AD. The results suggested that the alteration in these two diffusivities is different, that demyelination as reflected by the increase in RD may be the prominent disease process associated with HIV infection in HIV, and axonal injury may occur at a weaker level (Chen et al. 2009).

RD was increased in the corpus callosum while FA was increased. Taken together these DTI parameters indicate poor directional diffusion in the corpus callosum. The reported white matter abnormalities identified with RD in this study agrees with previous literature. Autopsy studies have demonstrated diffuse white matter damage in HIV-positive adults which appeared as pallor in sections stained for myelin damage (Price et al. 1998). Myelin pallor and subsequent gliosis has even been observed at the asymptomatic stage of infection (Gray et al. 1996). Increased myelin basic protein (MBP) measured in cerebrospinal fluid of adult HIV-positive patients has been found in all patients with severe dementia, while no elevation in MBP was observed in those without neurological disorders. Thus myelin injury may predict the extent of neurocognitive problems in HIV (Liuzzia et al. 1992).

A correlation between poor performance on a test of executive function and a test of attention with corpus callosum FA, and a test of executive function with lowered FA in the superior longitudinal fasiculus was found. This is consistent with a previous DTI study in adults showing a correlation with executive function and DTI parameters in frontal white matter and in the superior longitudinal fasciculus (Sasson et al. 2011). Decline in the white matter integrity of the corpus callosum was associated with poor performance in tests of memory and executive function (Voineskos et al. 2010). Taken together, the findings here are consistent with a view that decline in the microstructural integrity of white matter fibres accounts for cognitive decline in slow progressors.

Limitations of our study are the sample size is small and our data are cross-sectional and as such are not able to address the question of whether changes in DTI parameters represent an early marker of subsequent cognitive decline.

Despite these limitations, the findings here suggest demyelination in the corpus callosum giving an indication that this medial brain region is differentially affected by in HIV disease in children. Future work could usefully focus on DTI measurements of the corpus callosum as a quantitative imaging biomarker in larger longitudinal studies. Studies examining response to HAART treatment in children infected with HIV will be important to determine whether DTI abnormalities observed reflect reversible or more advanced irreversible injury. Correlates of white matter damage and neurocognitive decline need to be sought, including whether measures of central viral load, illness duration, age, treatment exposure and treatment adherence. These factors may well be critical in determining the overall impact of paediatric HIV on brain function, and in particular on white matter integrity.

Table 3 Significant correlations between white matter integrity and neuropsychological test performance

	Brain region			
	Corpus callosum		Superior longitudinal fasciculus	
Neuropsychological test	Genu	Splenium	Left hemisphere	Right hemisphere
Color Trails Test Trail 1	–	.479 (.044)	–	–
Semantic fluency	.471 (.048)	.474 (.047)	.579 (.010)	–

Pearson's *r* values are presented, with *p* values in parentheses

Conflicts of interest No conflicts of interest.

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