A DIFFUSION TENSOR IMAGING AND NEUROCOGNITIVE STUDY OF CLADE C HIV POSITIVE CHILDREN WHO ARE HAART-NAÏVE 'SLOW PROGRESSORS'

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Introduction

Our preliminary data examine the neuroimaging and neuropsychological signatures of clade C HIV among 10 'slow progressors' between the ages of 8 and 12 years.

Compared to 10 children matched for age from the same community

Slow progressors

- Children vertically infected with HIV
- remain clinically and immunologically stable for a long period
- receiving no or minimal therapy (defined as single or dual nucleoside therapy) before the age of 10 years
- maintained CD_4 counts above 25%

- In South Africa, as many as 35% of all infected children are believed to meet criteria of slow progressors (1)
- little information is known about this group of individuals in terms of neurodevelopment.

- (1) Archary D, Gordon ML, Green TN, Coovadia HM, Goulder PJ, Ndung'u T. HIV-1 subtype C envelope characteristics associated with divergent rates of chronic disease progression. Retrovirology 2010;7:92.

Ugandan study of asypmtomatic HIV+ children

- Bagenda et al. (2006)
- aged 6-12 years
- asymptomatic, perinatally HIV-infected
- never received any antiretroviral treatment.
- scored slightly lower than controls
- still scored well within the average range on tests of neuropsychological function.
- tests primarily included measurement of sequential-processing, simultaneous-processing and memory.

- despite a child being described as asymptomatic
- HIV infection still has an impact on the CNS
- Causing deficits in certain cognitive domains
- importance of investigating specific cognitive domains
- Asymptomatic children may have been classified as such due to their scores on global measures

Aim

- to determine the neurocognitive and behavioural outcomes of 10 HIV positive children
- defined as slow progressors
- who are HAART naïve
- compared to 10 HIV negative children.
- FA and MD of CC, SLF and IC as measured by DTI

Methods

10 HIV positive children who met the criteria for 'a slow progressor' and who were HAART naive, were recruited from Red Cross Children's Hospital in Cape Town. 10 controls who were HIV negative were drawn from the same low SES community as the HIV positive children.

Measures

1) Neurocognitive assessment
2) Behavioural questionnaire
3) Diffusion tensor imaging

Neurocognitve assessment

- neuropsychological tests that are standardized, with sound psychometric properties
- and are commonly used in pediatric neuropsychology research
- and clinical assessment in South Africa.
- Tests been translated and back-translated into Xhosa

General intellectual functioning

- WASI
  - Verbal IQ
  - Performance IQ

Motor functioning

- Grooved Pegboard Test
  - Dominant hand
  - Non-dominant hand

Processing Speed

- WISC-IV Processing Speed Index

Attention and Concentration

- WISC-IV Digit Span Forward SS
- Color Trails Test Trail

Working Memory

- WISC-IV Digit Span Backward SS

Visuospatial Processing

- WASI Block Design
- Rey Complex Figure Test copy

Memory – Visual

- Rey Complex Figure Test
  - Immediate recall T-
  - Delayed recall T-

Executive Function

- Semantic fluency: Animals
- Color Trails Test Trail 2
- NEPSY-II Inhibition: Inhibition SS
- WASI Matrix Reasoning

Psychosocial/Behavioral.

- The *Child Behaviour Checklist (CBCL*; Achenbach & Resclora, 2001)
- requires a parent/guardian to rate the child's problem behaviours and competencies.
- This instrument is suitable for use in children aged 6-18 years.

Diffusion Tensor Imaging

- Diffusion-weighted images were acquired at the Cape Universities Brain Imaging Centre
- on a Siemens Magnetom 3T Allegra scanner
- 30 diffusion directions
- sequence was repeated a total of three times to acquire averages.
- The images were analysed using TBSS which is a part of the FMRIB Software Library (FSL) (Smith, Jenkinson et al. 2006) and MATLAB R2007b (Mathworks Inc, Natick, MA)
- The FA image was "thinned" to create a mean FA skeleton which represents the centre regions of WM tracts for each subject
- Each subject's co-registered FA and MD data were projected onto the mean FA skeleton for subsequent statistical analysis with FSL randomise.
- Controls and HAART-naive HIV^+ subjects were compared by applying a two-tailed Student t-test ($p < 0.05$) across the groups
- For correction of multiple comparisons, threshold free cluster enhancement was utilised and 5000 permutations were acquired for each contrast.
- Age and gender effects were introduced as confounder variables in the analysis.

Results

Demographic data

- the groups were homogeneous and well-matched.
- *Handedness:* All participants were right-handed.
- *Language:* All participants had a home language of isiXhosa.
- *Sex:* The difference in sex distribution across groups was not statistically significant, $\chi^2(1) = 1.57$, p (two-tailed) = .210.
- *Socioeconomic status:* All participants were of low socioeconomic status.
- Mean CD_4 count was 585

Age and Level of Education in the Current Sample

*Note.*The first two columns show means, with standard deviations in parentheses. The *p*-value is two-tailed. ESE = effect size estimate; in this case, Cohen's *d*.

	Group				
	HAART-naïve	Control			
Variable			*t*	*p*	ESE
Age (years)	10.40 (1.45)	9.83 (1.16)	0.85	.411	0.40
Education (years)	3.00 (1.00)	2.43 (1.27)	1.01	.331	0.48

Between-Group Differences on Neuropsychological Test Battery

Domain / Test / Subtest	HAART-naïve *n* = 10	Healthy control *n* = 10	*t*	*p*
General intellectual functioning				
WASI				
Motor functioning				
Grooved Pegboard Test[a]				
Processing Speed				
Attention and Concentration				
WISC-IV Digit Span Forward SS	**6.78 (2.17)**	**8.10 (3.07)**	**1.07**	**.149**
Color Trails Test Trail 1 raw score[b]	**118.88 (99.90)**	**79.50 (24.19)**	**-1.21**	**.122**
Working Memory				
WISC-IV Digit Span Backward SS	**6.00 (2.50)**	**5.20 (1.23)**	**-0.90**	**.191**
Visuospatial Processing				
Rey Complex Figure Test copy *z*-score[a]	**-4.51 (1.64)**	**-2.37 (2.28)**	**2.05**	**.032***
Memory – Visual				
Rey Complex Figure Test				
Immediate recall *T*-score[b]	**36.75 (6.74)**	**38.30 (5.27)**	**0.55**	**.296**
Delayed recall *T*-score[b]	**29.88 (8.49)**	**36.40 (6.85)**	**1.81**	**.045***
Executive Function				
Semantic fluency: Animals total[a]	**6.38 (3.25)**	**9.00 (2.26)**	**2.02**	**.030***
Color Trails Test Trail 2 raw score[a]	**203.38 (46.61)**	**168.10 (40.04)**	**-1.73**	**.051†**
NEPSY-II Inhibition: Inhibition SS[a]	**5.75 (1.98)**	**7.10 (3.35)**	**1.01**	**.165**
WASI Matrix Reasoning *T*-score	**6.12 (2.04)**	**35.30 (17.53)**	**0.11**	**.456**

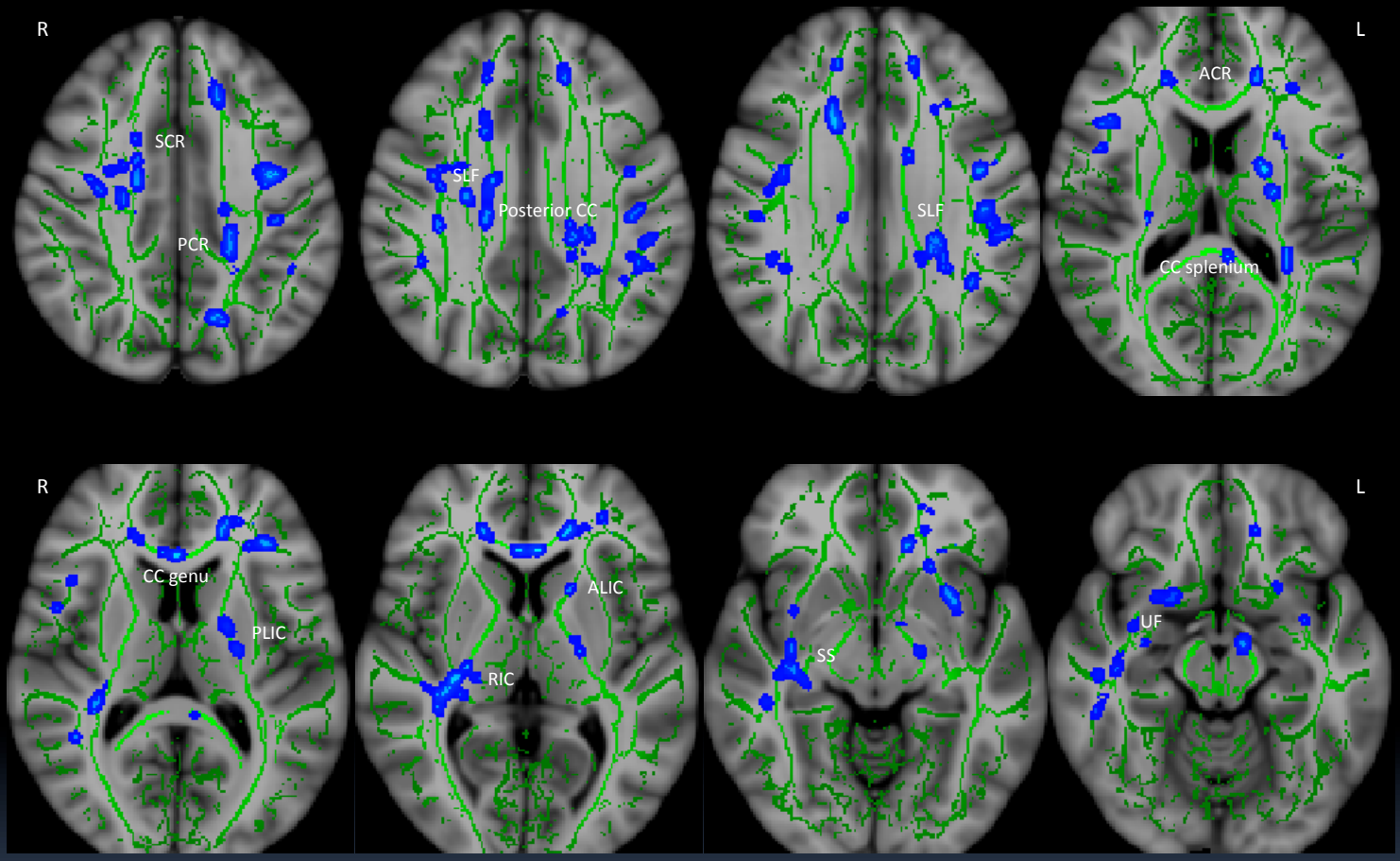
Behavioural Disturbances among HIV infected children

- asymptomatic participants experienced difficulty at school
- such as repeating grades, attending special classes and having problems with schoolwork
- parents or caregivers reported Internalizing behaviours in the clinical range
- behaviours included somatic complaints, withdrawal and depression
- experiencing more Internalizing behaviours as compared to Externalizing behaviours.

Summary of FA results for HIV$^+$ subjects compared to controls ($p < 0.05$ corrected)

Anatomy	Hemisphere	MNI coordinates of local maxima	Control FA	HAART-naive HIV$^+$ FA
posterior body of the corpus callosum	left	X108; Y98; Z106	0.474511	0.443324
	right	X73; Y112; Z106	0.509568	0.463262
superior longitudinal fasciculus	left	X132; Y107; Z102	0.480299	0.410473
	right	X55; Y100; Z106	0.469838	0.460934
corpus callosum genu	left + right	X89; Y153; Z83	0.756269	0.736229
corpus callosum splenium	left	X96; Y86; Z87	0.857265	0.842264
posterior limb of internal capsule	left	X109; Y123; Z83	0.65426	0.628784
anterior limb of internal capsule	left	X108; Y138; Z77	0.488441	0.436205
retrolenticular part of internal capsule	right	X59; Y100; Z77	0.602785	0.566248

Visualization of the decreased FA in HAART-naive HIV^{+} subjects when compared to controls.



Abbreviations: **SCR** – superior corona radiata; **PCR** – posterior corona radiata; **SLF** – superior longitudinal fasciculus; **CC** – corpus callosum; **ACR** – anterior corona radiata; **PLIC** – posterior limb of internal capsule; **ALIC** – anterior limb of internal capsule; **RIC** – retrolenticular part of internal capsule; **SS** – sagittal stratum;**UF** – uncinate fasciculus.

Correlations Between White Matter Integrity and Neuropsychological Test Performance

Note. Pearson's *r* values are presented, with *p* values in parentheses. RCF = Rey Complex Figure Test.

	Brain region					
	Corpus callosum		Internal capsule (left hemisphere)		Superior longitudinal fasciculus	
Neuropsychological test	Genu	Splenium	Anterior limb	Posterior limb	Left hemisphere	Right hemisphere
Color Trails Test Trail 1	----	----		-.729 (.001)	----	----
RCF Copy	----	----	.579 (.030)	----	----	----
Semantic Fluency	.471 (.048)	.474 (.047)	----	----	.579 (.010)	

Conclusion

- The results indicate that cognitive function and white matter integrity as defined by DTI is altered among asymptomatic HIV positive children
- Specifically, FA but not MD is altered among asymptomatic individuals in the superior longitudinal fasiculus, the corpus callosum and the internal capsule ($p=<0.05$)
- The asymptomatic patients performed poorly on Performance and Verbal tasks of the WAIS-R and on tests of visuospacial processing, visual memory and executive function($p= <0 .05$).
- Furthermore, parents or caregivers reported Internalizing behaviours in the clinical range.