COBRA

Co-morbidity in relation to AIDS

Brain MRI changes associated with poorer cognitive function despite suppressive antiretroviral therapy

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Financial disclosures

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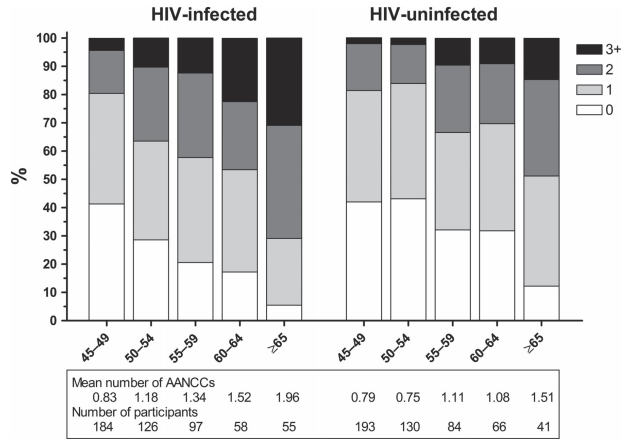
Background

Reported prevalence of HIV-associated cognitive impairment remains high

European cohort studies with **appropriate** HIV-control populations now established

Distribution of the number of age-associated non-communicable comorbidities stratified by age



Judith Schouten et al. Clin Infect Dis. 2014;59:1787-1797

POPPY
Pharmacokinetic and clinical observations in people over 50

Neurological sub-study

COBRA
CO-MORBIDITY IN RELATION TO AIDS

agehiv cohort study

Hypotheses tested

Despite suppressive cART, compared to an appropriate control population, HIV+ individuals will have evidence of:

- Poorer cognitive performance
- Grey and white matter atrophy
- White matter microstructural abnormalities

Structural brain and cognitive abnormalities would occur together and be more common in HIV+ individuals

Participants

Inclusion criteria

HIV+ group (n=134)

- documented HIV infection
- age ≥ 45 years at study entry
- documented plasma HIV RNA <50 copies/mL > 12 months on cART

HIV- group (n=79)

- documented negative HIV test in past 6 months or at screening
- age ≥ 45 years at study entry

Exclusion criteria

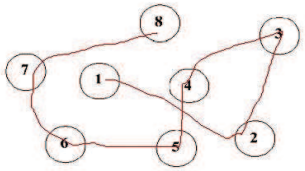
- current major depression (PHQ-9 ≥ 15)
- chronic neurological diseases
- history of severe head injury
- history of cerebral infections (including AIDS defining illnesses)
- severe psychiatric disease

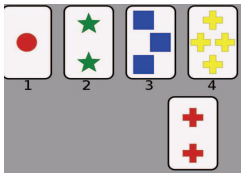
All underwent: **cognitive testing, MRI scanning** (several modalities) and CSF examination (not presented today)

Methods

Cognitive battery

(testing attention, executive function, language, memory, motor function and processing speed)





Methods

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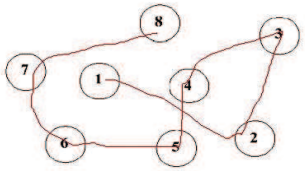
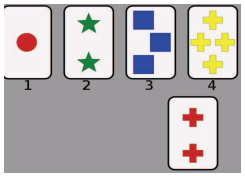
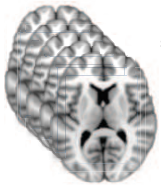




Neuroimaging (3T)

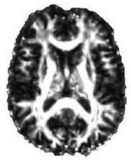
Volumetric

Diffusion

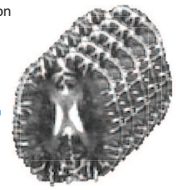


Bias correction and segmentation (SPM12)

Data acquisition and pre-processing



Eddy current correction and diffusion tensor fitted (FSL)

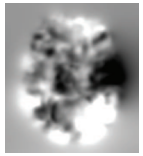


T1 data (n=212)

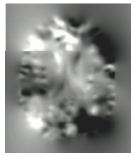
SPM12 (DARTEL)

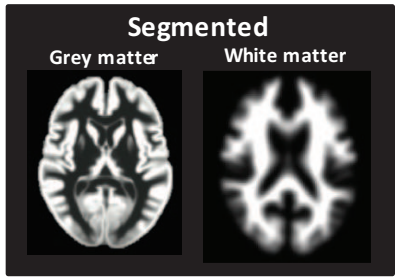
DTITK

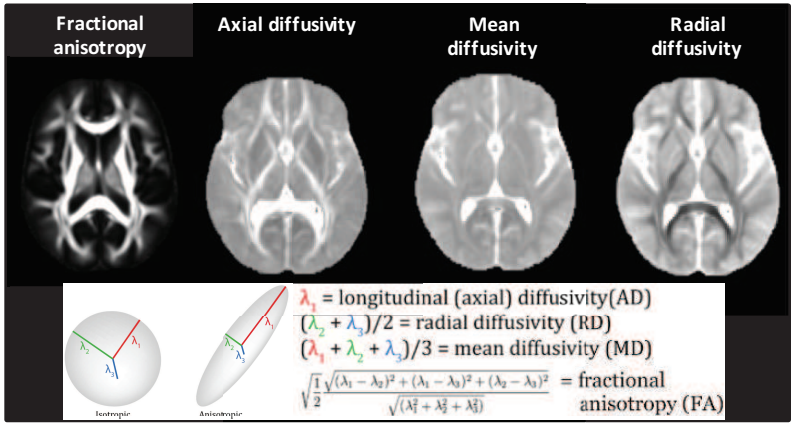
64 direction diffusion weighted data (n=208)



Spatial normalisation



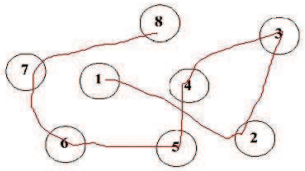


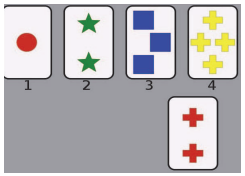


Statistics

Cognitive battery

(testing attention, executive function, language, memory, motor function and processing speed)





Raw scores converted to demographically adjusted cognitive domain T-scores

Cognitive impairment defined using Frascati[1], GDS[2] and MNC[3] criteria

Group comparison
(with chi-squared and Wilcoxon rank-sum as appropriate)

[1]Antinori A et al, *Neurology* (2007); [2]Carey CL et al. *J Clin Exp Neuropsyc* (2004); [3]Huizenga HM et al, *Neurospychologia* (2007)

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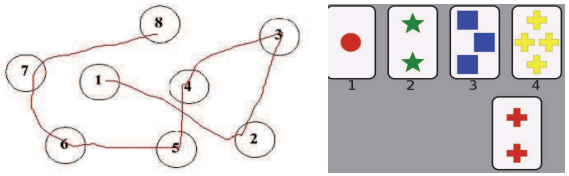
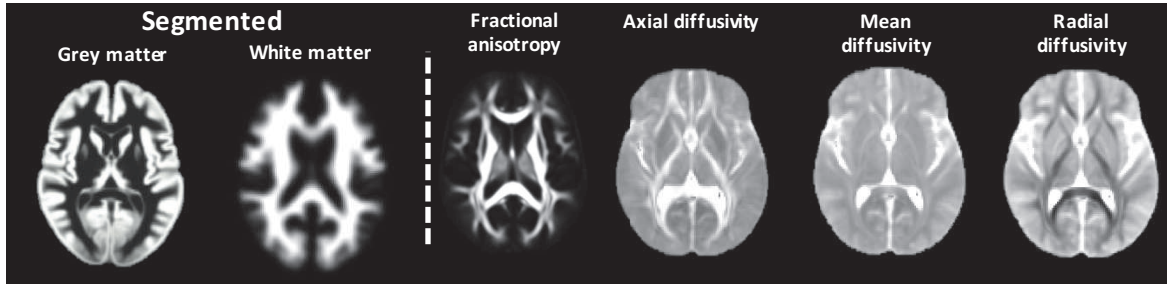


Neuroimaging (3T)

Volumetric | Diffusion



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Group comparison (with chi-squared and Wilcoxon rank-sum as appropriate)

Group comparison with non-parametric permutation testing (using FSL's *randomise* 10,000 permutations, adjusted for age, ICV and scanner)

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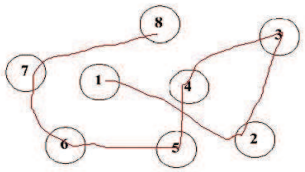

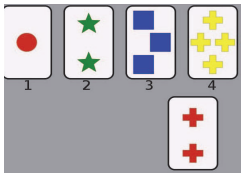

Neuroimaging (3T)

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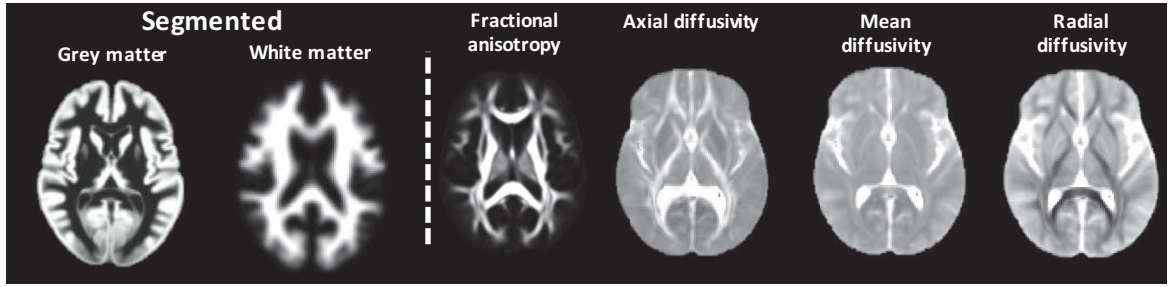


Raw scores converted to demographically adjusted cognitive domain T-scores

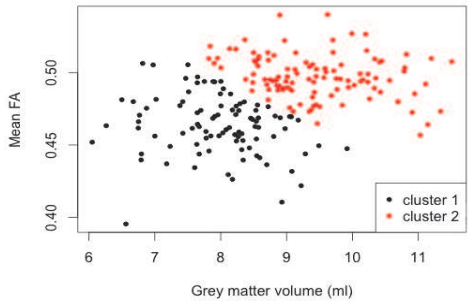
Extraction of summary statistics using atlases (FSL)

Group comparison with non-parametric permutation testing (using FSL's *randomise* 10,000 permutations, adjusted for age, ICV and scanner)

Cognitive impairment defined using Frascati[1], GDS[2] and MNC[3] criteria

Group comparison (with chi-squared and Wilcoxon rank-sum as appropriate)

k-means clustering *(R)*



[1]Antinori A et al, *Neurology* (2007); [2]Carey CL et al. *J Clin Exp Neuropsyc* (2004); [3]Huizenga HM et al, *Neurospychologia* (2007)

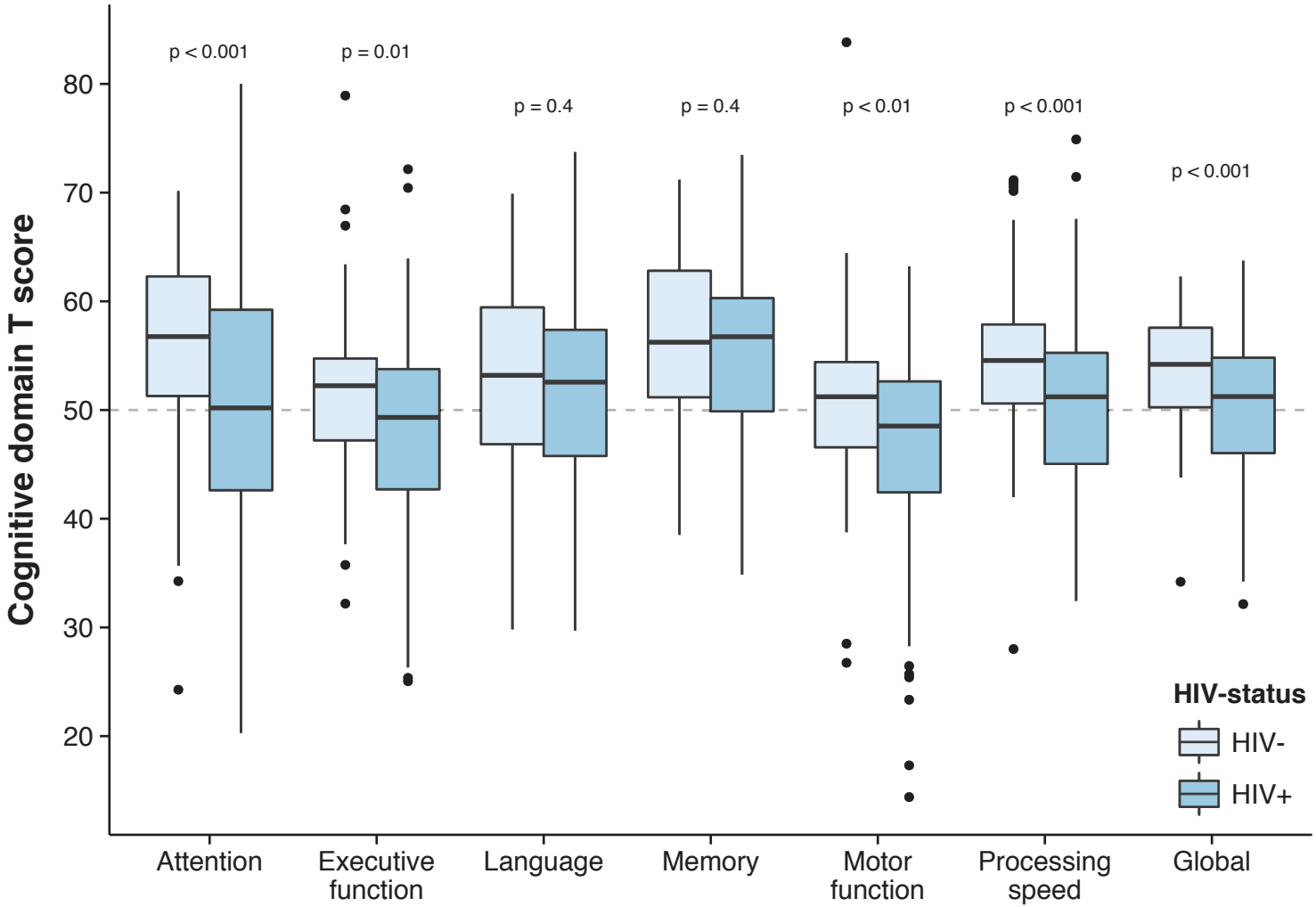
Baseline characteristics

	HIV+ (n=134)	HIV- (n=79)	p-value
Age (years), median (IQR)	55 (51-62)	57 (52-64)	0.24
Gender, n (%)			0.79
Female	9 (7%)	6 (7%)	
Male	125 (93%)	73 (92%)	
Ethnicity, n (%)			0.03
Black-African	16 (12%)	2 (3%)	
White	117 (88%)	76 (97%)	
Sexuality, n (%)			0.45
MSM	104 (77%)	59 (75%)	
Bisexual	10 (8%)	4 (5%)	
Heterosexual	18 (13%)	16 (20%)	
Years of education, median (IQR)	14 (13-16)	16 (14-17)	0.23
Smoking status, n (%)			0.24
Current smoker	40 (30%)	20 (25%)	
Ex-smoker	58 (43%)	29 (37%)	
Never smoked	36 (27%)	30 (38%)	
Alcohol consumption, n (%)			0.04
Current drinker	104 (78%)	71 (90%)	
Previous drinker	18 (13%)	3 (5%)	
Never drunk	12 (9%)	4 (5%)	
Use of recreational drugs in past 6 months, n (%)	44 (33%)	18 (23%)	0.16

Baseline characteristics – HIV+ group

	n=134
Likely route of HIV transmission, n (%)	
MSM	115 (86%)
Heterosexual sex	15 (11%)
IVDU/Blood product	1 (1%)
Unknown	3 (2%)
Years since HIV diagnosis, median (IQR)	15.0 (9.1-20.0)
Duration of cART (years), median (IQR)	12.5 (7.4-16.9)
HIV RNA viral load < 200 copies/mL, n (%)	134 (100%)
CD4 count (cells/µL), median (IQR)	629 (472-806)
Nadir CD4 count (cells/µL), median (IQR)	180 (90-250)
CD4+:CD8+ cell count ratio, median (IQR)	0.84 (0.60-1.12)

HIV-positive group has poorer cognitive function



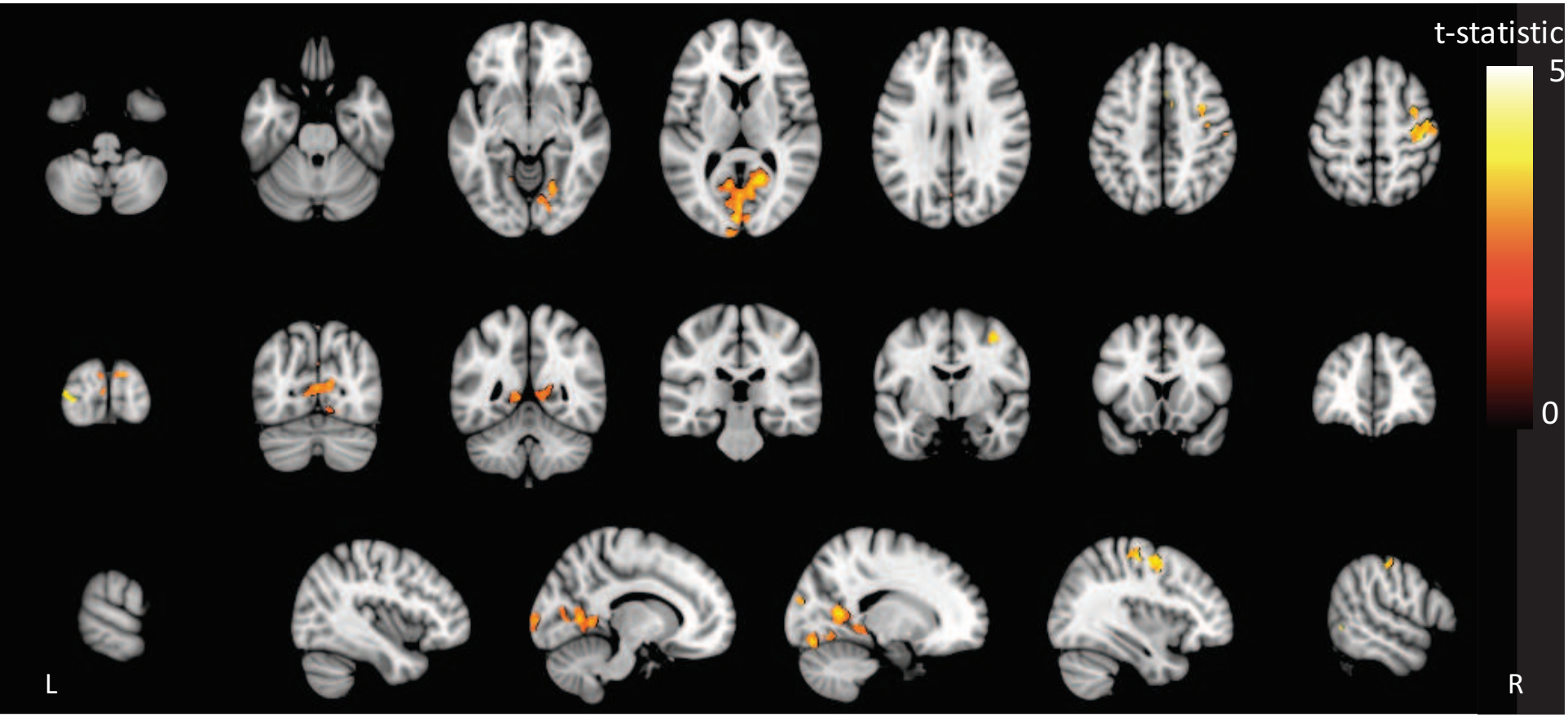
Global deficit score:
- 18% vs. 4%
- OR 5.6 (1.9-24.1)

Frascati criteria:
- 18% vs. 4%
- OR 5.6 (1.7-24.1)

Multivariate normative comparison:
- 20% vs. 3%
- OR 9.4 (2.7-59.2)

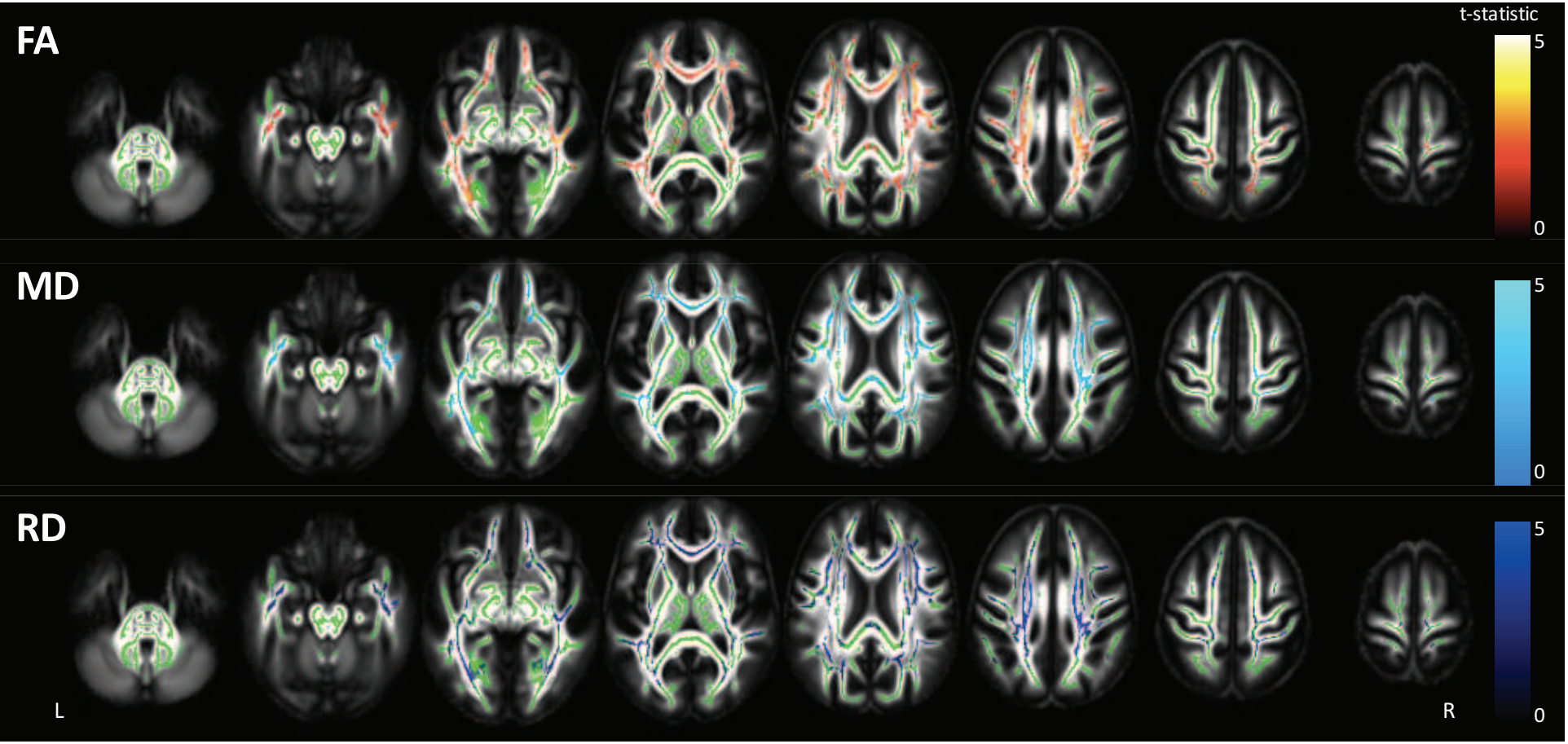
Boxplots of demographically adjusted cognitive domain T-scores by HIV-serostatus. P values calculated using Wilcoxon rank sum test.

HIV-associated grey matter atrophy



Grey matter voxel based morphometry group comparison. Areas with significantly ($p < 0.05$) lower grey matter volume coloured by the t-statistic - corrected for multiple comparisons (TFCE) and adjusted for age, intracranial volume and scanner. Statistical image overlaid on MNI 152 T1

HIV-associated white matter injury

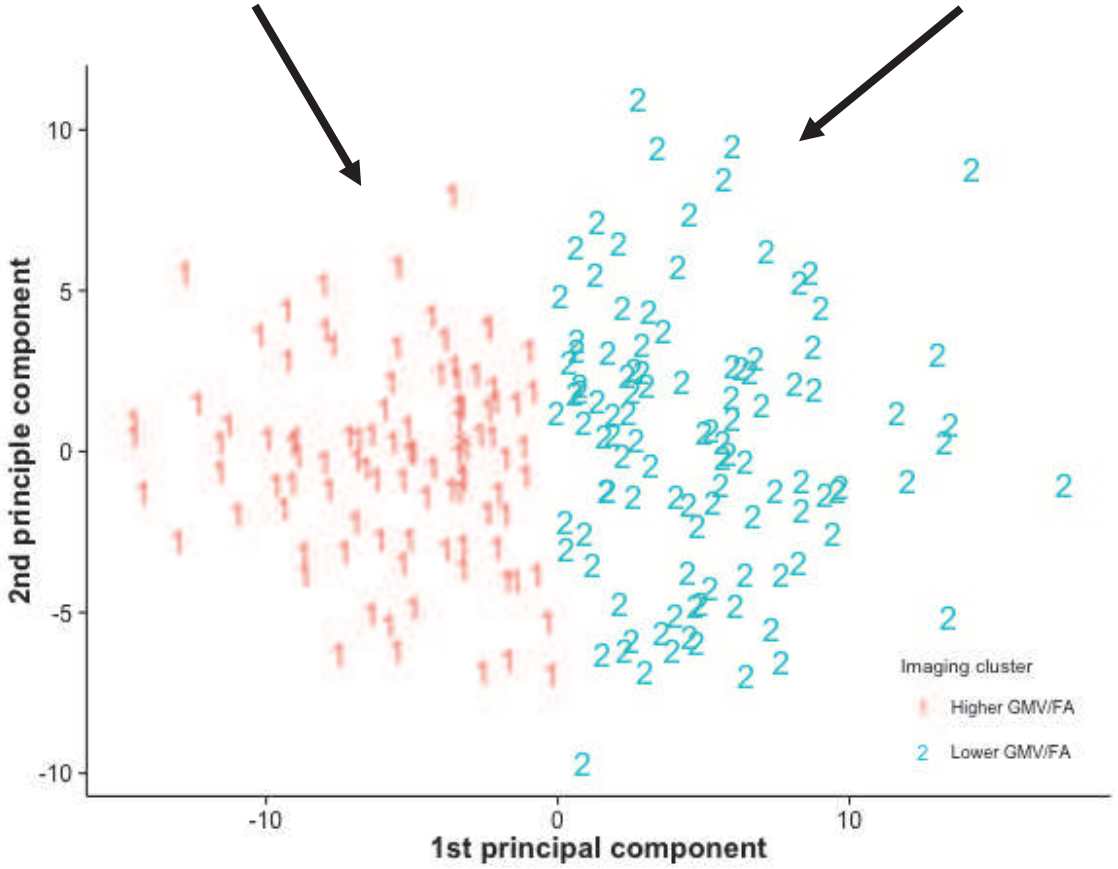


White matter tract based spatial statistics group comparison. Areas of significantly ($p < 0.05$) lower fractional anisotropy (FA), higher mean diffusivity (MD) and higher radial diffusivity (RD) are coloured by t-statistic red-yellow, light blue and dark blue respectively - corrected for multiple comparisons (TFCE) and adjusted for age, intracranial volume and scanner. Overlaid on the white matter skeleton (green) and the mean FA image (greyscale).

K-means cluster analysis: both groups

Higher GM volume/FA (n=99)

Lower GM volume/FA (n=109)



Discriminant coordinate plot showing the separation of the clusters based on the k-means cluster analysis of parcellated grey matter and mean fractional anisotropy data. Each individual number represents a participant with the number representing their cluster assignment

2 cluster solution optimally partitioned data

- Duda-Hart test: $p<0.0001$

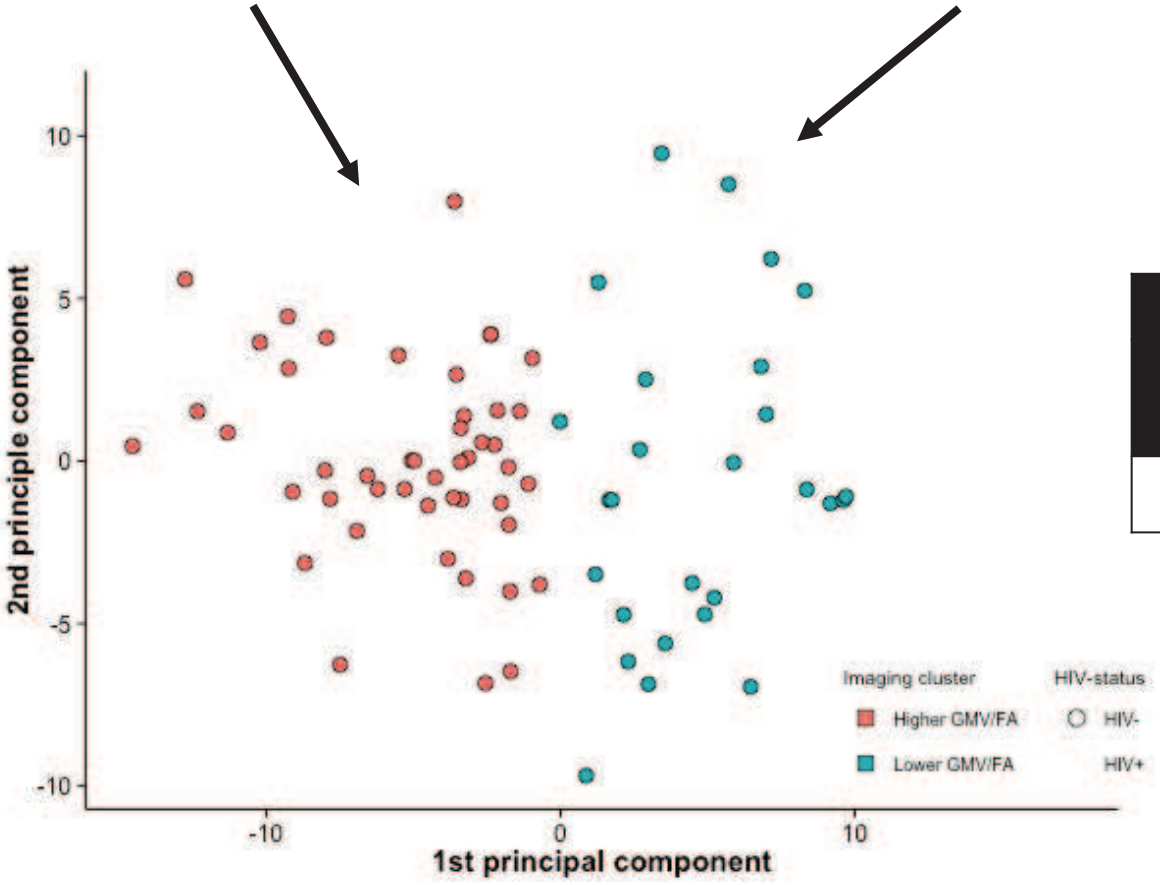
High degree of stability to resampling

- Jaccard bootstrap mean 0.99 for both clusters

K-means cluster analysis: HIV-

Higher GM volume/FA (n=47)

Lower GM volume/FA (n=27)



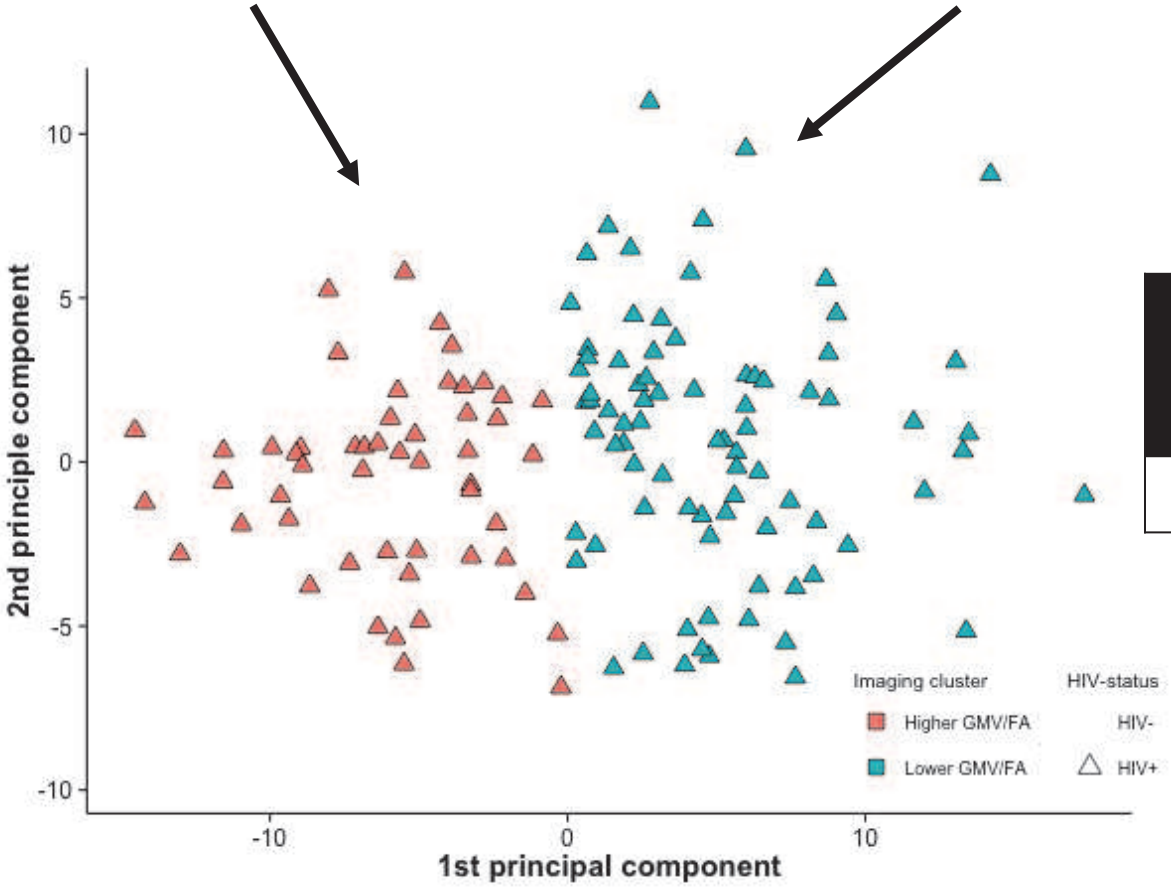
Cluster		Lower GMV/FA
Higher GMV/FA	Lower GMV/FA	Odds ratio (95% CI)
64%	36%	0.36 (0.20-0.66)

Discriminant coordinate plot showing the separation of the clusters based on the k-means cluster analysis of parcellated grey matter and mean fractional anisotropy data. Each individual number represents a participant with the number representing their cluster assignment

K-means cluster analysis: HIV+

Higher GM volume/FA
(n=52)

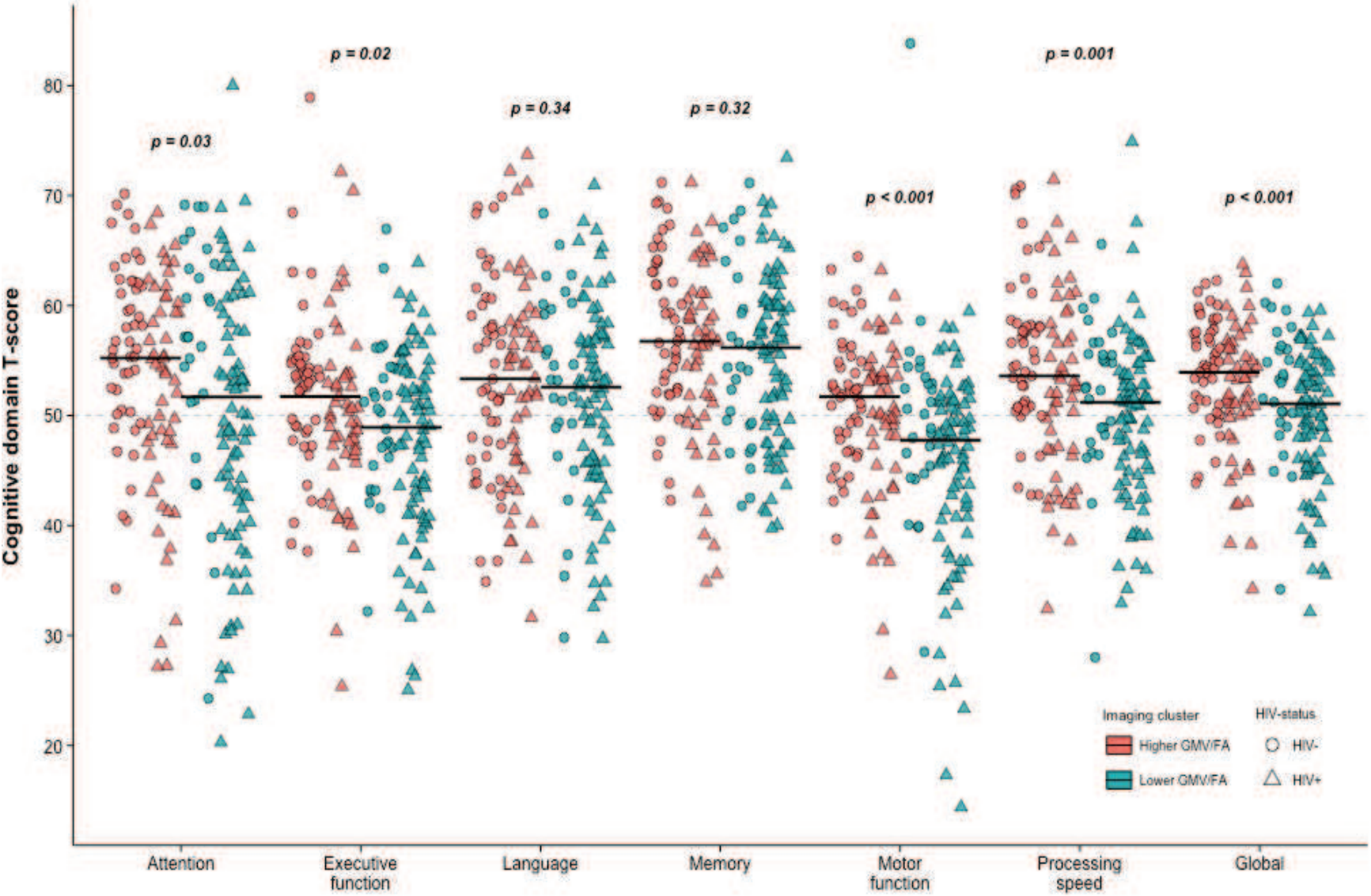
Lower GM volume/FA
(n=82)



Cluster		Lower GMV/FA
Higher GMV/FA	Lower GMV/FA	Odds ratio (95% CI)
36%	61%	2.7 (1.5-5.0)

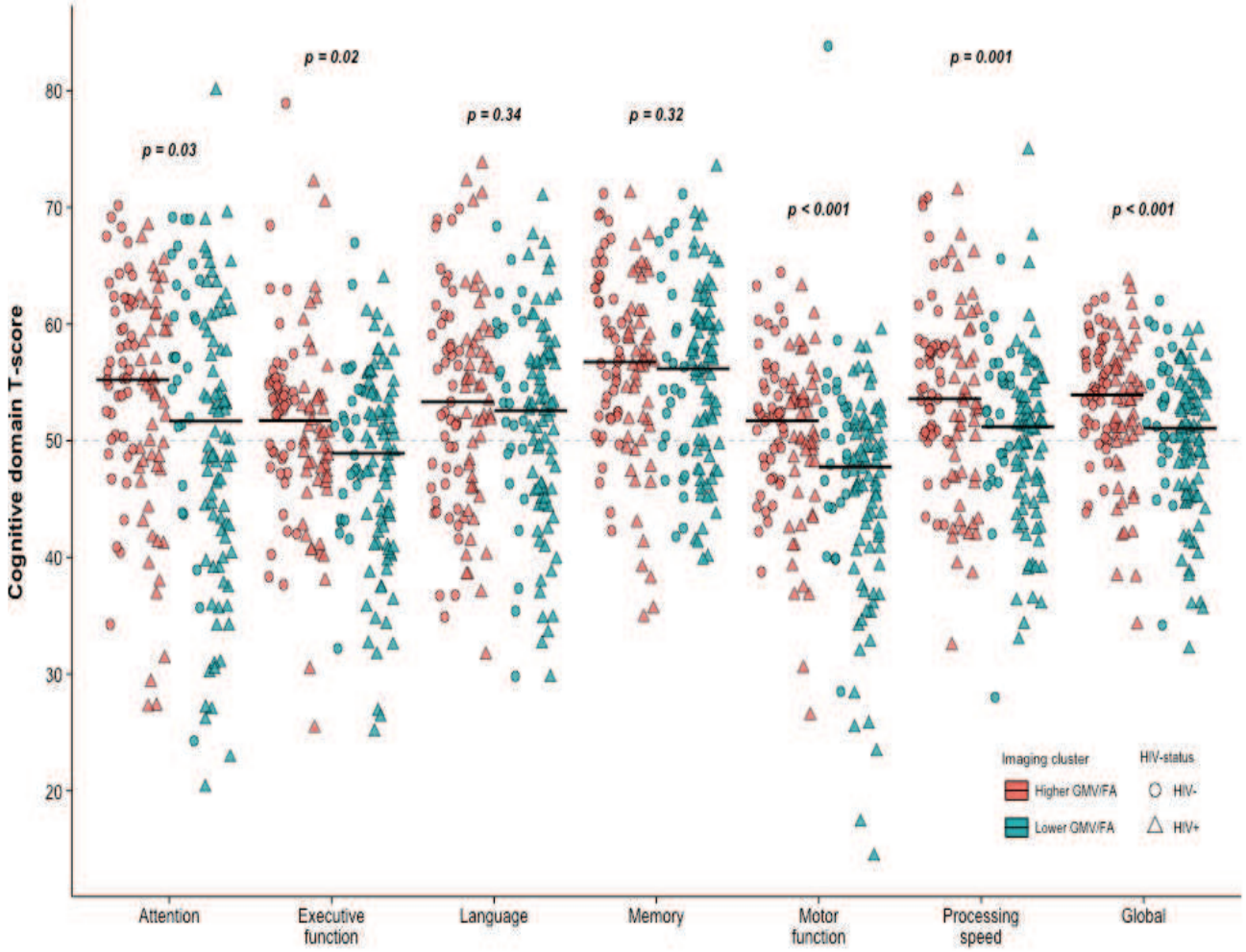
Discriminant coordinate plot showing the separation of the clusters based on the k-means cluster analysis of parcellated grey matter and mean fractional anisotropy data. Each individual number represents a participant with the number representing their cluster assignment

Imaging phenotype associated with poorer cognitive function



Jitterplot of cognitive domain T-scores grouped by k-means cluster analysis. Black lines represent medians for each cluster with p-values calculated using the Wilcoxon rank sum test.

Imaging phenotype associated immune activation and older age



Jitterplot of cognitive domain T-scores grouped by k-means cluster analysis. Black lines represent medians for each cluster with p-values calculated using the Wilcoxon rank sum test.

HIV+ individuals:

Parameter	Cluster		
	Higher GMV/FA	Lower GMV/FA	p-value
Age	53.2	58.6	<0.001
CD4:CD8 ratio	1.06	0.82	0.01

NB: Cognitive domain T-scores account for age and level of education and groups are matched for age

Conclusions

HIV+ individuals have evidence of cognitive impairment, grey matter atrophy and white matter microstructural injury

- despite fully suppressive cART
- compared to an appropriate control population

Structural brain abnormalities tend to occur together

- found more commonly in HIV+ individuals
- associated with poorer cognitive function
- associated with markers of immune dysregulation

Limitations – cohort study

- unmeasured differences could confound group comparisons
- *but* mitigated against this with an appropriate HIV- control group

The Co-morBidity in Relation to Aids (COBRA) Collaboration

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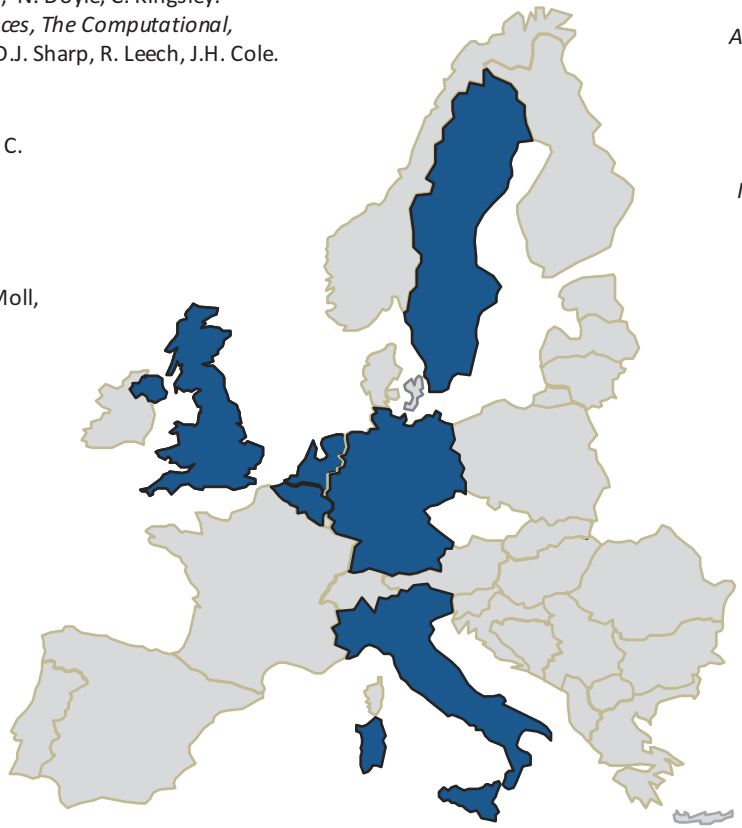

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Thank you for listening. Any questions?