MULTIVARIATE PATTERN ANALYSIS OF VOLUMETRIC NEUROIMAGING DATA IN TREATED HIV-DISEASE

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BACKGROUND

Accurate prediction of longitudinal changes in cognitive function in treated HIV-disease would potentially allow targeted intervention in those at greatest risk of cognitive decline.

High resolution neuroimaging and machine learning techniques have shown promise in other disease areas but there are little data in treated HIV-disease. We sought to build a multivariate model using T1-weighted neuroimaging data only to accurately predict cognitive function.

AIMS

- To assess the ability of T1-weighted neuroimaging data to predict cognitive impairment using multivariate methods.
- To assess the ability of T1-weighted neuroimaging data to predict longitudinal changes in cognitive function using multivariate methods.

METHODS

Participants

Virally suppressed HIV-positive participants from the CHARTER cohort were included if they had plasma HIV RNA <50 copies/ml at the time of baseline neuroimaging data (n=139).

Comorbid conditions were classified as per Antinori *et al* (2007) into '**incidental**' (e.g. none or mild traumatic brain injury [TBI] with no functional sequelae), '**contributing**' (e.g. mild TBI with evidence of mild functional sequelae) and '**confounding**' comorbidities (e.g. TBI without return to work/school).

Neuropsychological assessment

Cognitive function was assessed across seven cognitive domains using a comprehensive test battery. Neuropsychological testing was repeated approximately every six months and was available for the majority of patients (n=111 with 391 separate assessments of cognitive function, mean 3.5 visits).

Demographically adjusted T-scores, where higher scores represent better cognitive function, were converted to deficit scores and cognitive impairment was defined by a global deficit score (GDS) ≥0.5. Longitudinal changes in cognitive function were defined using regression based change scores using an independent normative sample (n=296) for reference as previously described (Heaton *et al* 2015).

Neuroimaging (figure 1)

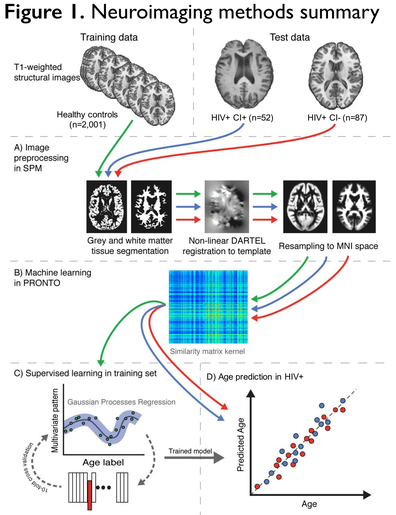
T1-weighted MRI data were collected with General Electric 1.5T scanners at

- Johns Hopkins University (n=30)
- Mt. Sinai School of Medicine (n=25)
- University of California at San Diego (n=47)
- University of Texas Medical Branch (n=29)
- University of Washington (n=8).

The multivariate brain age prediction model accurately predicted chronological age in the normative training set (n=2,001, age range 18-90, r= 0.94, R^2=0.88, MAE=5.01 years, p=0.001). – see Cole *et al* 2017..

Brain-predicted age difference (brain-PAD), a measure of deviance from the normal ageing trajectory = brain-predicted age – chronological age. Positive scores therefore represented brains that appear 'older' than expected.

Figure 1. Neuroimaging methods summary



Statistical analysis

Supervised classification and regression was performed with the Pattern Recognition for Neuroimaging Toolbox (PRoNTo)12 software package v.2.0 (Machine Learning and Neuroimaging Lab, University College London).

For classification, models were computed with **support vector machines** (SVM) and **Gaussian processes classification** (GPC) and were assessed using leave-one-out cross-validation (LOOCV). P-values were calculated using permutation testing with 1,000 repetitions. To predict cognitive function in a continuous nature the global T-score was used as an outcome with **Gaussian processes regression** (GPR) and **kernel ridge regression** (KRR) models. For longitudinal prediction, separate models using SVM and GPC were tested using longitudinal change status and sRCS as outcome variables.

Relationships between cognitive measures and brain-PAD were determined with multiple linear regression covarying for age, comorbidity status, scanner and TICV. **Binary logistic regression and multiple linear regression** were used to assess the relationship between longitudinal change status and sRCS with brain-PAD accounting for the same covariates.

RESULTS

Table 1. Baseline demographics

Demographic	n=139
Age (years), median (IQR)	44 (44-50)
Male, n (%)	110 (79.1%)
Ethnicity, n (%)	
White	64 (46.0%)
Black	61 (43.9%)
Hispanic	13 (9.4%)
Other	1 (0.7%)
Comorbidity, n (%)	
Incidental	88 (63.3%)
Contributing	35 (25.2%)
Confounding	16 (11.5%)
Years of education, median (IQR)	13.0 (12.0-15.0)
Weight (kg), median (IQR)	77.7 (70.5-87.8)
Duration of HIV-infection (years), median (IQR)	12.2 (6.3-15.8)
Current CD4+ (cells/μL), median (IQR)	540 (353-698)
CD4+:CD8+ cell count ratio, median (IQR)	0.60 (0.42-0.91)
Nadir CD4+ (cells/μL), median (IQR)	121 (20-237)
Duration of antiretroviral therapy (years), median (IQR)	6.3 (2.6-9.4)
Plasma HIV RNA <50 copies/mL, n (%)	139 (100%)
Prior clinical AIDS, n (%)	55 (39.6%)

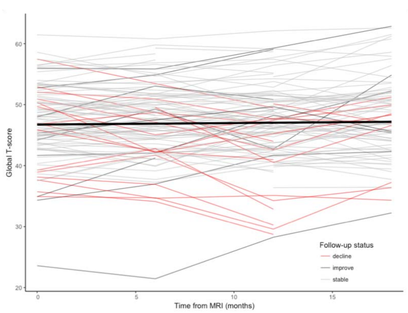
Cognitive function

Cognitive impairment was present in 52 (37.4%) participants.

It occurred more frequently in those with comorbidities (25/88 [28%] with 'incidental' comorbidities, 14/35 [40%] with 'contributing' and 13/16 [81%] with 'confounding', p<0.001).

17 (14.5%) experienced cognitive decline, 83 (75.5%) remained stable and 10 (9.1%) improved. (figure 2). There was no association between longitudinal cognitive outcome and comorbidity status (p=0.21) nor cognitive impairment at baseline (p=0.34).

Figure 2. Spaghetti plot of the global T-score



Each line represents a participant's longitudinal cognitive function. Red lines represent those with clinically significant cognitive decline. Thick black line represents the linear fit line across the entire group.

Multivariate prediction of cognitive function

Multivariate classification performance was not better than chance for both predicting baseline cognitive impairment nor those who would experience longitudinal cognitive decline (Table 2). However, multivariate prediction of cognitive function was more accurate than a comparable linear model (Table 3) using total grey and white matter volumes which did not predict global T-scores (model adjusted R^2=0.01, $F_{2,136}$=1.99, p=0.14).

Table 2. Prediction performance for cognitive impairment by model.

Model	Accuracy (%)	p-value	PPV (%)	Accuracy (%)	p-value	PPV (%)	Accuracy (%)	AUC	p-value
	Not impaired (n=87)			Impaired (n=52)			Overall		
SVM	72.4	0.33	65.0	34.6	0.25	42.9	53.5	0.56	0.22
GPC	77.0	0.56	65.7	32.7	0.10	46.0	60.4	0.59	0.14
	Non-decliners (n=93)			Decliners (n=17)			Overall		
SVM	97.9	0.48	84.3	0.0	1.00	0.00	48.9	0.42	0.63
GPC	98.9	0.86	84.4	0.0	1.00	0.00	49.5	0.42	0.87

Abbreviations: AUC: area under the receiver operator curve; GPC: Gaussian process classification; PPV: positive predictive value; SVM: support vector machine.

Table 3. Multivariate prediction performance of the global T-score using structural imaging data by model.

Model	Correlation	p-value	R^2	p-value	MSE	p-value	Norm MSE	p-value
GPR	0.27	0.001	0.07	0.28	37.7	0.001	1.00	0.001
KRR	0.28	<0.01	0.08	0.02	41.5	0.02	1.10	0.02

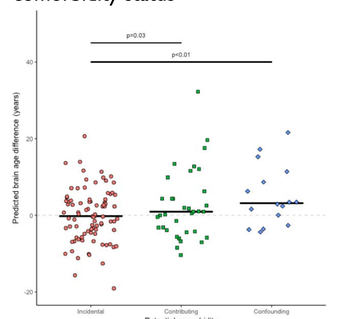
Abbreviations: GPC: Gaussian process classification; KRR: kernel ridge regression; MSE: mean squared error.

Multivariate prediction of brain age

Brain-predicted age exceeded chronological age by 1.17 (-0.14-2.53) years, but was greatest in those with confounding comorbidities (5.87 [1.74-9.99] years, figure 3) and prior AIDS (3.03 [0.00-6.06] years, p=0.05).

Increased brain-PAD was independently associated with greater global deficit scores (regression estimate [95% CIs] 0.011 [0.001-0.022] years per unit increase in GDS, p=0.03). However, there was no association between brain-PAD and individual cognitive, longitudinal changes in cognitive function (p=0.52), nor with longitudinal change status (p's>0.4).

Figure 3. Jitterplot of brain-PAD by comorbidity status



Black lines represent the median for each group. P-values for comparisons between groups calculated using multiple regression models adjusted for age, intracranial volume and site/scanner.

CONCLUSIONS

Although cognitive impairment was present in about a third of virally suppressed patients it was confounded by comorbid conditions. Accurate prediction of cognitive function using multivariate models from T1-weighted MRI data was not achievable, which may reflect the small sample size, heterogeneity of the data or that impairment was usually mild and stable.

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