Multimodal neuroimaging biosignatures of perinatally acquired HIV/early ART in 7-year-old children

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INTRODUCTION

- HIV is a far-reaching public concern in southern Africa [1]
- HIV may affect neurodevelopment in children even with antiretroviral therapy (ART) [2].
- Neuroimaging techniques such as structural magnetic resonance imaging (MRI), diffusion tensor imaging (DTI) and proton magnetic resonance spectroscopy (^{1}H-MRS) can identify HIV-related brain alterations.
- Few studies have used a multivariate approach to combine multiple MRI measures to classify HIV-infection [e.g. 3].
- The elastic net (EN) [4] performs variable selection using penalized regression to shrink variables unimportant in the classification to zero weighting.
- Here we use the embedded feature selection of EN to identify neuroimaging features characteristic of HIV infection.

HYPOTHESIS

- A multimodal, multivariate analysis of neuroimaging data produces better classifiers with higher sensitivities, accuracies, and specificities than unimodal classifiers.
- The elastic net classifier will result in a subset of features (biosignatures) characteristic of HIV infection at age 7.

PARTICIPANTS

- Study involves 7-year old HIV+ patients from the Children with HIV Early Antiretroviral therapy (CHER) trial
- HIV+ ($n_1 = 70$) and HIV- healthy controls ($n_2 = 55$), $age\ (mean \pm sd) = 7.22 \pm 0.13$ years
- HIV+ children received ART and their viral loads were suppressed from a young age (between 6 and 76 weeks of age)

AIM 1: Identify neuroimaging features that are most predictive of HIV
AIM 2: Improve classification performance by combining MRI modalities

METHODS

A. IMAGE ACQUISITION

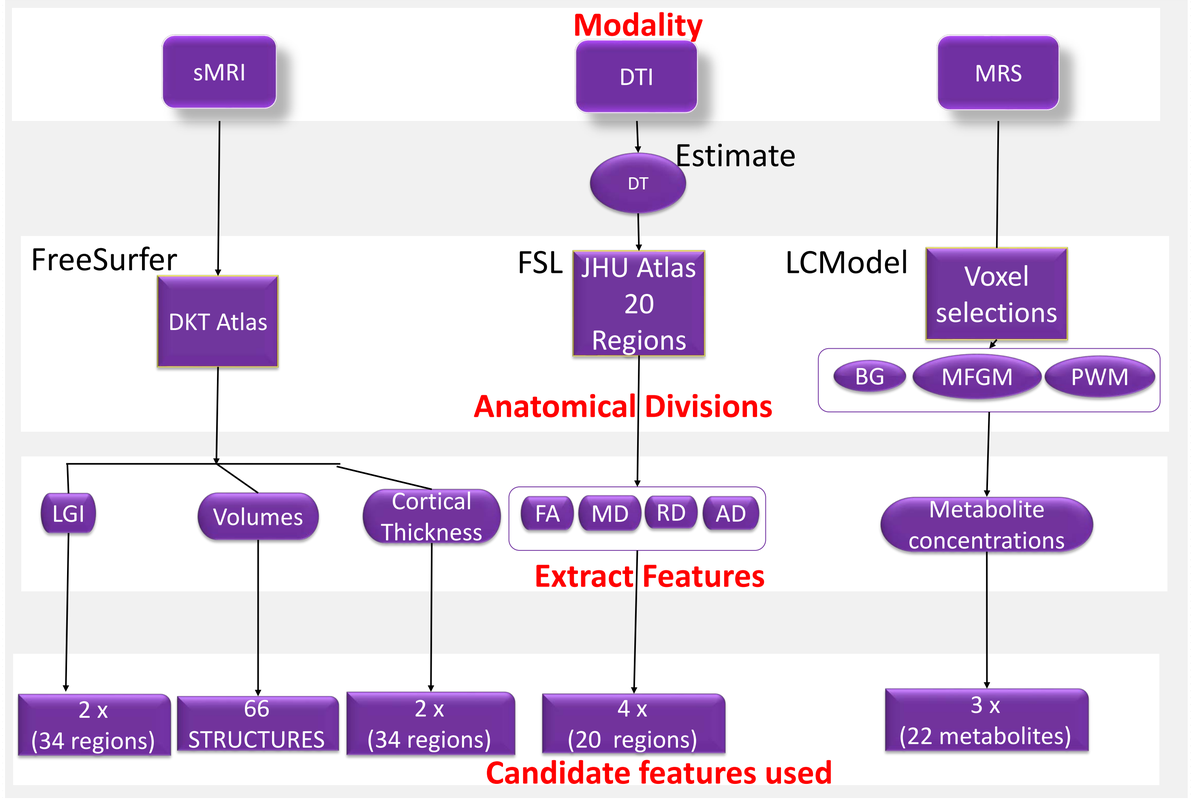
The children were scanned on a 3T Allegra MRI scanner (Siemens Erlangen, Germany). We obtained structural MRI, spectroscopy and diffusion tensor imaging data using the following parameters:

sMRI: 3D EPI and navigated MEMPRAGE [5] sequence—$TR = 2530ms, FOV\ of\ 224 \times 224 \times 114mm^3, voxel\ size\ of\ 1.3 \times 1 \times 1mm^3, bandwidth\ 650Hz/px, 144\ slices, TI = 1160ms,\ TEs\ at\ 1.53, 3.19, 4.86, and\ 6.53ms$

^{1}H-MRS: Obtained from 3 voxels of interest, basal ganglia (BG), midfrontal grey matter (MFGM), and peritrigonal white matter (PWM) with PRESS sequence—$TR = 2000ms, voxel\ size\ of\ 15 \times 15 \times 15mm^3, TE = 30ms, 7°\ flip\ angle, and\ averages = 64$

DTI: Volumetric navigated TRSE sequence—$TR/TE = 10000/86ms, FOV\ of\ 224 \times 224 \times 114mm^3, voxel\ size\ of\ 2.0 \times 2.0 \times 2.0mm^3, matrix\ size = 112 \times 112 \times 72, b_0 = 0\ s \cdot mm^{-2}, b_1 = 1000\ s \cdot mm^{-2},\ \ and\ 30\ diffusion\ directions$

B. DATA PROCESSING



C. ELASTIC NET REGULARISATION

- A logistic EN regression model with repeated 15-fold cross validation (CV) and nested CV for tuning λ was implemented in R, initially on each feature set separately.
- Ethnicity, sex, age and total intracranial volume were included as confounders with no shrinkage penalty.
- For each model, the classification performance for HIV+ vs HIV- was assessed by computing the mean area under the receiver operator characteristic curve (AUC) across 15 CV folds and 200 repeats.
- The prediction model's classification parameters: sensitivity, specificity, and accuracy were also recorded.

RESULTS

Classification Performance shown in steps of increasing AUC (ROC)

Concatenation steps	**sMRI** Volumes	**DTI**	**^{1}H-MRS** BG	**^{1}H-MRS** MFGM	**^{1}H-MRS** PWM	**sMRI** Cortical thickness
1. **Single modality measure**	**0.754**	0.656	0.523	0.561	0.561	0.549
2. +**sMRI** Volumes	—	**0.796**	0.748	0.667	0.622	0.614
3. +**sMRI** Volumes + DTI	—	—	**0.801**	0.783	0.728	0.783
4. +**sMRI** Volumes + DTI + **^{1}H-MRS** BG	—	—	—	0.735	0.745	0.660

A. CLASSIFICATION PERFORMANCE

Classification performance (AUC) of modality combination shown in steps of improving AUC (orange). The first column gives the feature set combination with which the feature set in each column is concatenated.

Best performing modality	FEATURES
sMRI Volumes Sensitivity = 81.9% Specificity = 78.3% Accuracy = 81.0%	11 features selected out of 42 •Optic chiasm •Corpus callosum posterior • Right ventral diencephalon • Right choroid vessel • Right vessel • Cerebrospinal fluid • Right and Left Amygdala • Right cerebellum white matter • Left and Right Pallidum
sMRI Volumes **+ DTI** Sensitivity = 85.1% Specificity = 84.1% Accuracy = 85.1%	18 features selected out of 122 • Left amygdala • Left ventral diencephalon • Right cerebellum white matter • Right amygdala • AD and MD in Left corticospinal tract • Right vessel • Optic chiasm • Right and left Pallidum • RD and MD in Left uncinate fasciculus • RD and MD in Right uncinate fasciculus • RD and MD in Left cingulate gyrus • MD in right cingulate gyrus
sMRI Volumes **+ DTI + ^{1}H-MRS** BG Sensitivity = 82.1% Specificity = 84.5% Accuracy = 83.8%	25 features selected out of 144 • BG total choline • BG glutamate + glutamine ratio to creatine • BG macromolecules at 20ppm • BG macromolecules at 20ppm ratio to creatine • BG macromolecules + lipids at 20ppm ratio to creatine • BG N-acetylaspartate • BG glycerophosphocholine • Left lateral ventricle • Left cerebellum white matter • Third ventricle • Brainstem • Left/Right ventral diencephalon • Right amygdala • Right pallidum • Right cerebellum white matter • Right vessel • Optic chiasm • Corpus callosum anterior • Left cingulate gyrus MD • Right cingulate gyrus MD • Left uncinate fasciculus RD • Right uncinate fasciculus MD • BG guanidinoacetate to creatine ratio

B. NEUROIMAGING BIOSIGNATURES

Selected features, sensitivity, accuracy, and specificity of the best performing elastic net models

DISCUSSION

- Volumes obtained from sMRI provide reasonable discrimination between HIV+ and HIV-.
- The addition of measures from DTI and BG ^{1}H-MRS present only marginal improvements to classification accuracy.
- While the ability to predict HIV status on neuroimaging data is not clinically advantageous, demonstration of its feasibility helps to identify common biosignatures in treated HIV infection.

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