Magnetic resonance spectroscopy (MRS) and neurodevelopment:

applications to HIV infection and exposure in children

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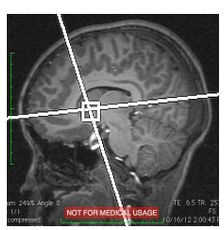
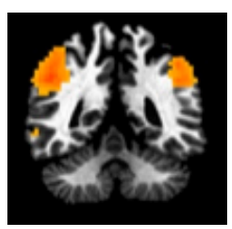
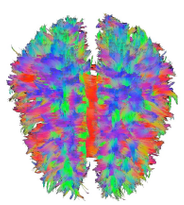
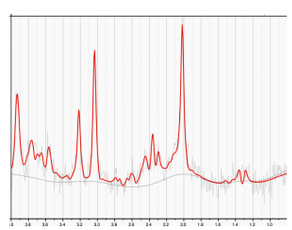
Neuroimaging and neurodevelopment

MRI (structural)	fMRI (functional)	DTI (diffusion)	^{1}H MRS (spectroscopy)
			
Structural properties change throughout childhood	Functional activations and networks change during childhood	Structural networks evolve in childhood	Localized neurochemical levels change in childhood

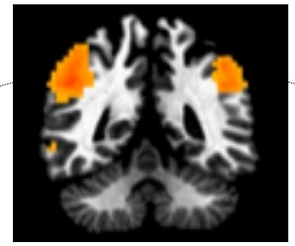
As the brain undergoes healthy maturation, significant changes in structure, function and metabolism occur.

Deviations from healthy maturation may indicate neurodevelopmental delays or disorders.

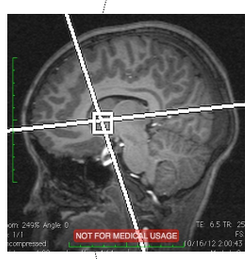
Study overview

A well-characterized cohort of children: HIV-infected, HIV-exposed, uninfected and HIV-unexposed, uninfected children were scanned longitudinally

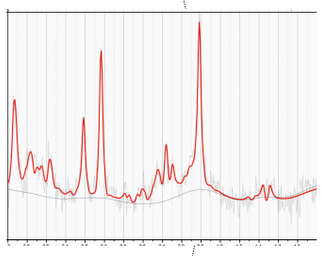
5 yrs → 7 yrs → 9 yrs



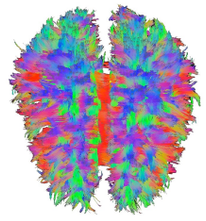
fMRI (functional)



MRI (structural)



^{1}H MRS (spectroscopy)

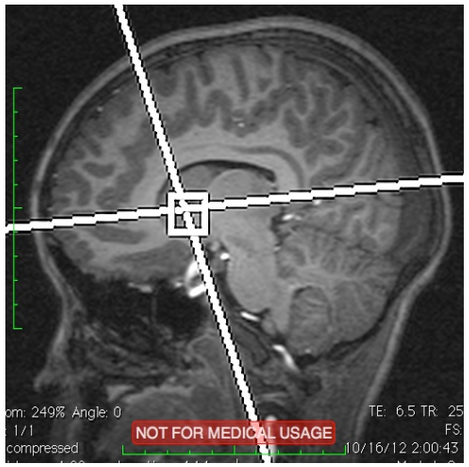


DTI (diffusion)

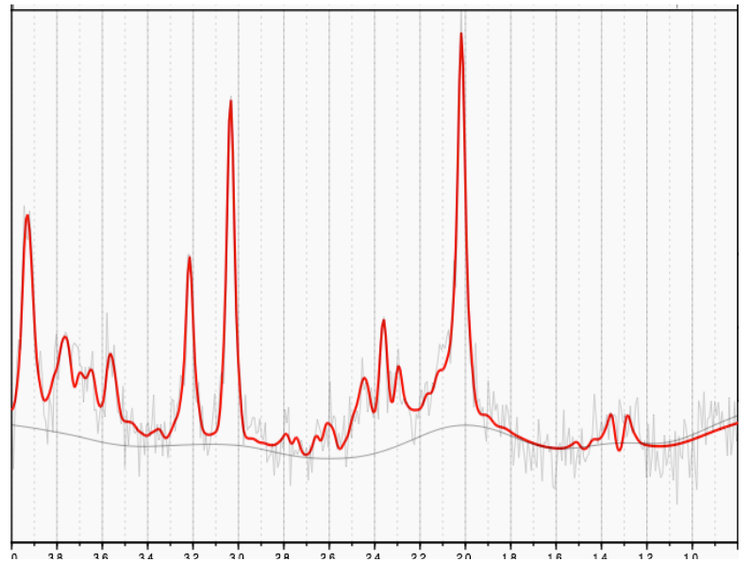
Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) identifies and quantifies biochemical information about tissues in the form of a spectrum.

1.5 x 1.5 x 1.5 cm^3 voxel in basal ganglia



^1H MRS spectrum from 1.5 x 1.5 x 1.5 cm^3 voxel in basal ganglia



The area under the curve is the metabolite concentration.

Different biochemicals, or metabolites, present unique information about brain health - such as neuronal integrity, cellular density, and neurotransmission - in localized regions.

MRS and neurodevelopment

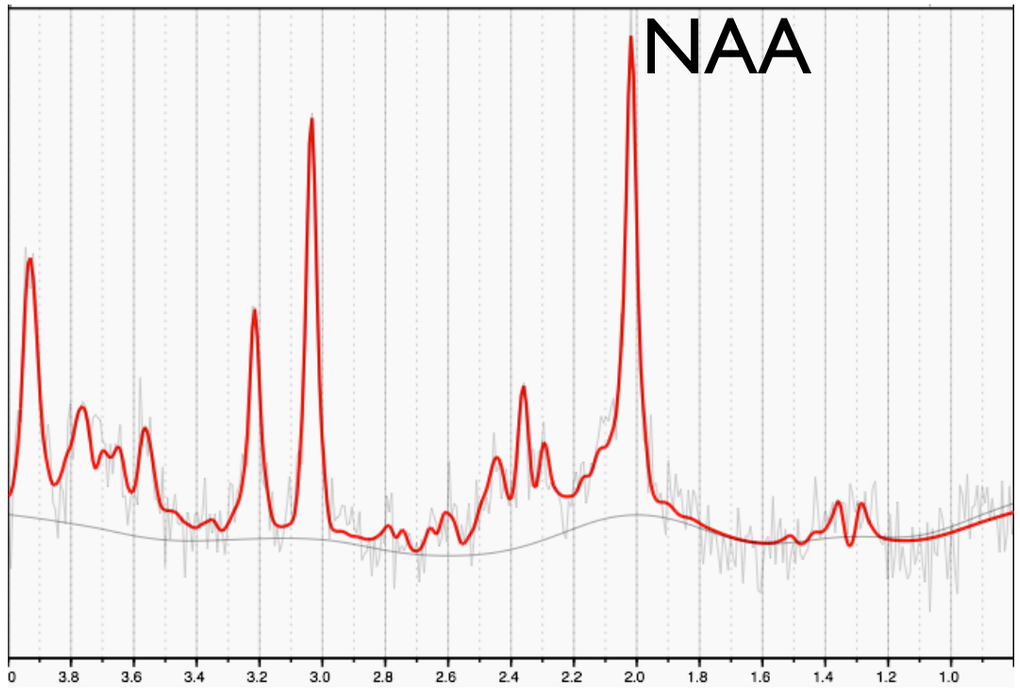
How is MRS useful in examining questions related to neurodevelopment?

- Metabolite levels have been found to correlate with neurological development and cognitive measures.

- Changes in normal ^{1}H MRS spectrum are observed in many neurological disorders - alterations in metabolite levels may precede observable changes to brain structure or cognition.

MRS and neurodevelopment

Metabolite levels as biomarkers of neurodevelopment.



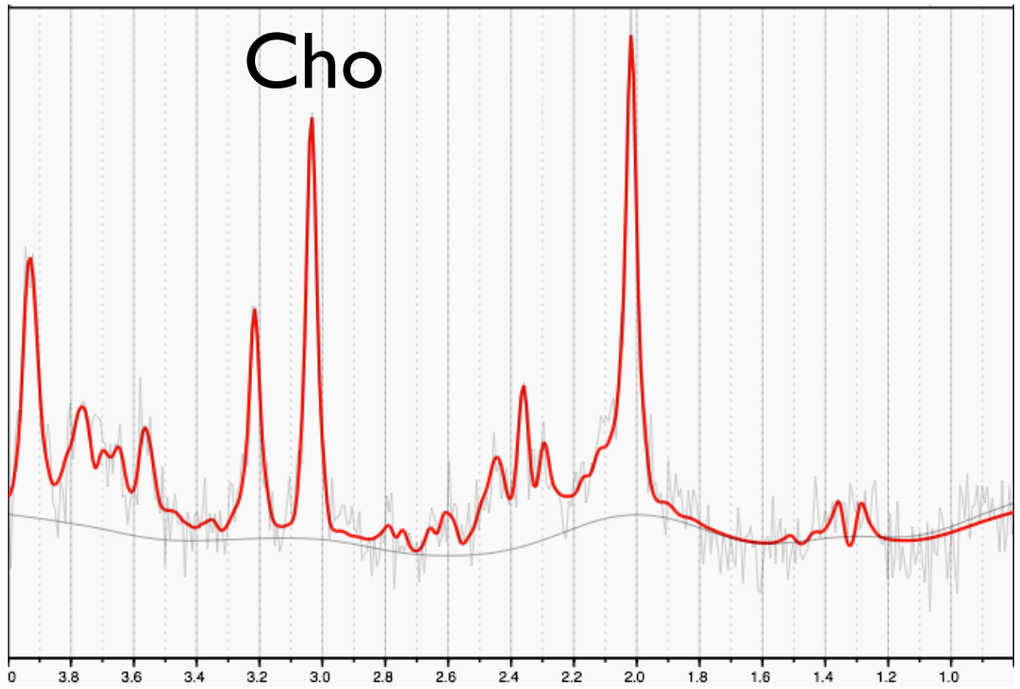
<u>N-acetylaspartate (NAA)</u>

NAA levels increase with age in children, with the steepest increases observed in infancy and early childhood.

NAA observed to decrease in disease → indicating loss or damage to neuron populations, axons, dendrites and synaptic terminals.

MRS and neurodevelopment

Metabolite levels as biomarkers of neurodevelopment.



<u>Choline/phosphocholine/glycerophosphorylcholine (Cho)</u>
Cho levels are highest in infancy, and remain relatively constant in childhood.

Cho levels increase/decrease in disease → increased Cho levels imply glial proliferation/inflammation or increased cellular membrane breakdown; decreased Cho levels suggest overall cell loss.

MRS and neurodevelopment: applications to HIV

As a result of prevention of mother-to-child transmission programs, mother-to-child transmission rates have declined globally

In South Africa, 95% of HIV-positive pregnant women and 68% of HIV-exposed infants have been receiving antiretroviral therapy (ART).

New, growing population of HIV-infected children on ART as well as HIV-exposed, uninfected (HEU) children.

MRS and neurodevelopment: applications to HIV

What kinds of clinical questions can be investigated with MRS?

1. HIV-infected children: How do different ART initiation times affect neurodevelopment?

2. HIV-exposed, uninfected children: Are children born HIV uninfected, but exposed to HIV and ART, at risk of neurodevelopmental delays?

I HIV-infected children

Children from Cape Town who are enrolled in the "children with HIV early antiretroviral" (CHER) trial

HIV-infected mothers

in utero: zidovudine antenatally from 28 to 34 weeks

at birth: single dose nevirapine (sd NVP) to the mother, and zidovudine for a week and a sd NVP to the infant

HIV-infected children (n = 38)

randomised study enrollment at 6 - 8 weeks old

Arm 1 - Deferred treatment

Arm 2 - Early treatment (for 40 weeks)

Arm 3 - Early treatment (for 96 weeks)

Examine relationship between metabolite levels (marker of neurodevelopment) and treatment/clinical measures.

I HIV-infected children

Based on previous studies and CHER findings:

We hypothesized that at age 5 years, the children who initiated ART early (12 weeks or younger) would have improved metabolite levels in the basal ganglia compared to children who received later ART (older than 12 weeks).

I HIV-infected children

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	NAA	Choline
Early ART	5.31mM	1.11mM
Late ART	5.20mM	1.03mM

Significantly lower choline levels ($p = 0.05$) in later ART group

Mean choline levels at age 5 indicate advantage of early ART treatment regimen.

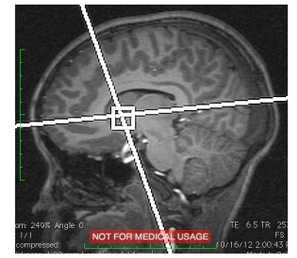
mM = millimolar

I HIV-infected children

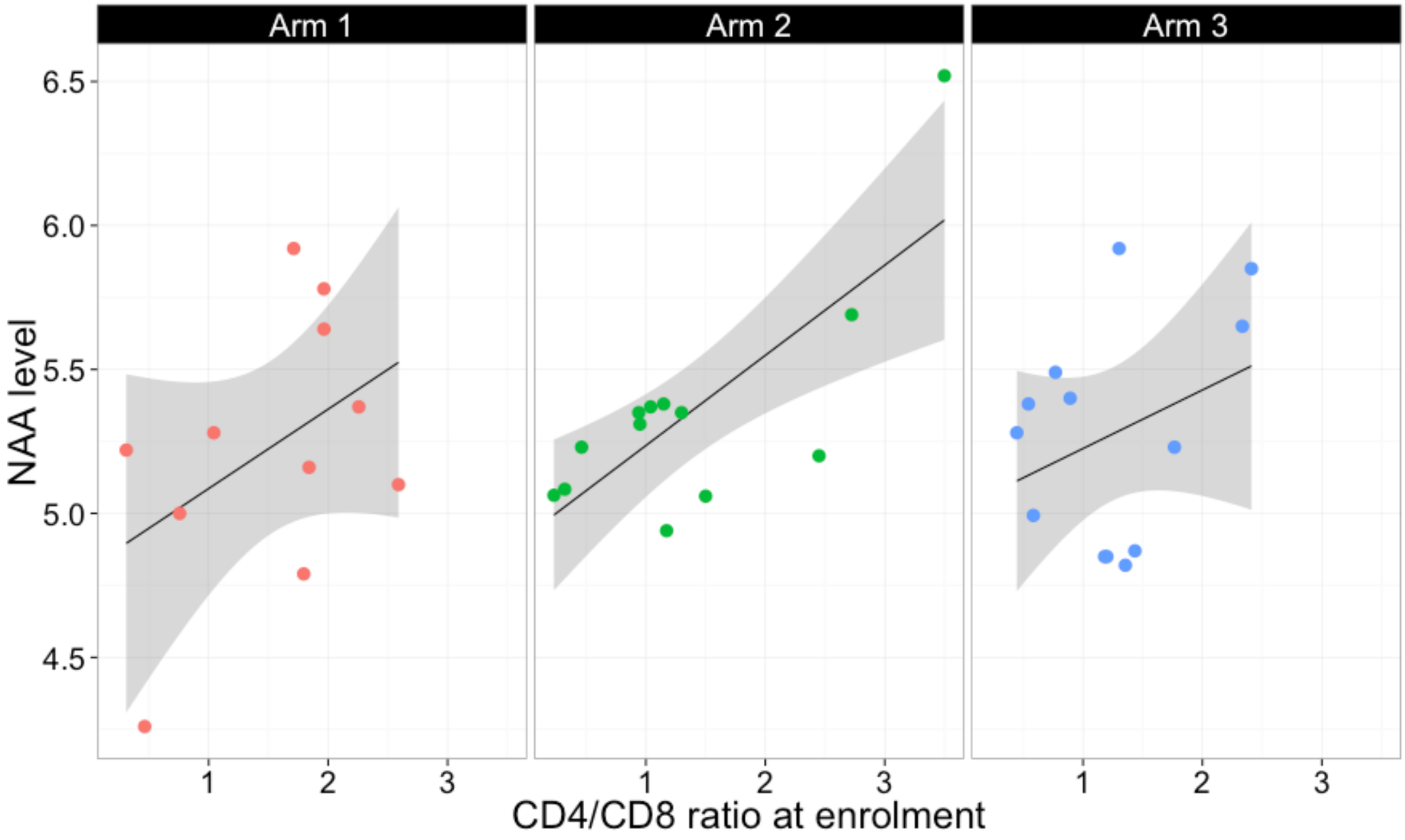
Do metabolites levels (as markers of neurodevelopment) at age 5 relate to clinical measures in infancy?

Measurement in infancy	Measurement in basal ganglia at age 5
CD4 count at enrollment CD8 count at enrollment Viral Load at enrollment	Choline levels — cellular density NAA levels — neuronal density

I HIV-infected children



basal ganglia



NAA levels at age 5 correlate significantly with CD4/CD8 ratio (a measure of immune system health) in infancy (median age ~ 7 weeks old) — across all treatment regimens.
Indicates damage (low CD4/CD8 ratio) in early infancy persists into childhood

Conclusions

Results indicate advantages - higher mean choline levels - of early ART compared to deferred treatment.

Results suggest damage from HIV infection sustained in early infancy persists into childhood in the basal ganglia - regardless of treatment regimen.

MRS and neurodevelopment: applications to HIV

1. HIV-infected children: How do different ART initiation times affect neurodevelopment?

2. HIV-exposed, uninfected children: Are children born HIV uninfected, but exposed to HIV and ART, at risk of neurodevelopmental delays?

2 HIV-exposed, uninfected children

HIV-infected mothers

in utero: zidovudine antenatally from 28 to 34 weeks

at birth: single dose nevirapine (sd NVP) to the mother, and zidovudine for a week and a sd NVP to the infant

HEU children

HIV-uninfected mothers

HUU children

Follow these children longitudinally to compare neurodevelopment

HEU = HIV exposed, uninfected

HUU = HIV unexposed, uninfected

2 HIV-exposed, uninfected children

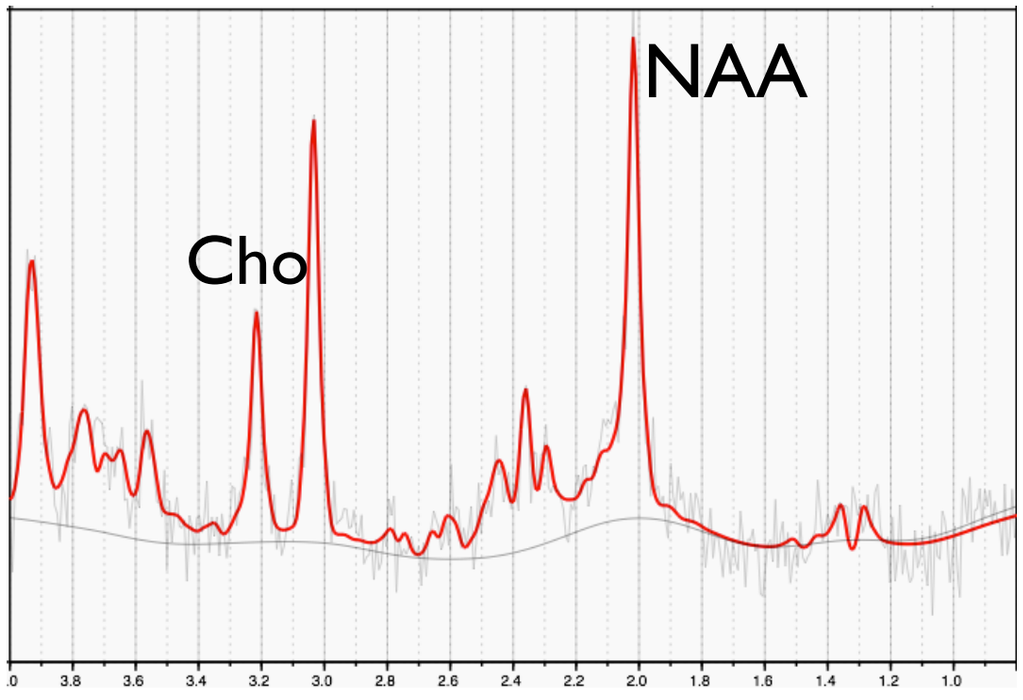
Hypothesis

We hypothesize that from 5 to 7 years of age, HEU children would exhibit different NAA and choline level trajectories in gray matter compared to HUU children.

Test hypothesis

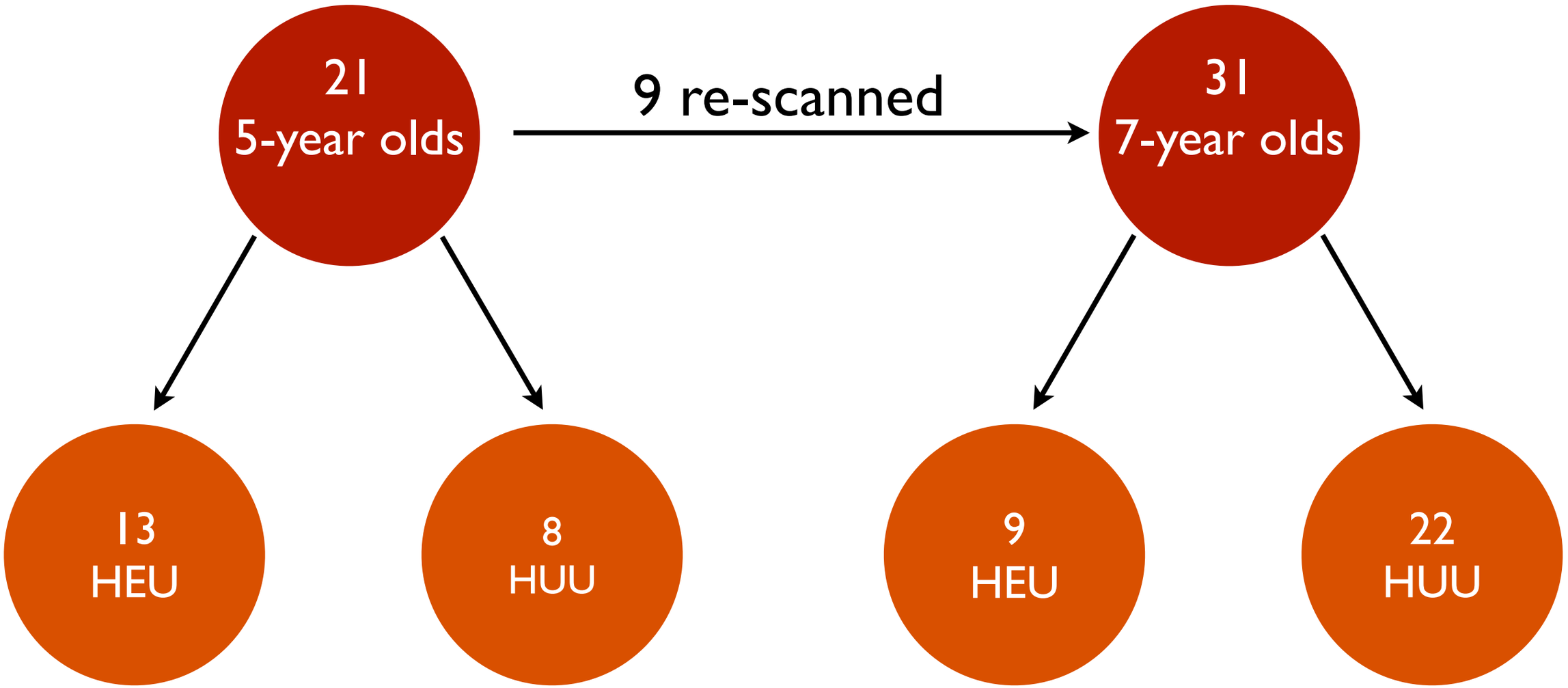
Measure metabolite levels in gray matter as a marker of typical neurodevelopment in children over time (from age 5 to 7 years).

Constant choline levels
Increased NAA levels

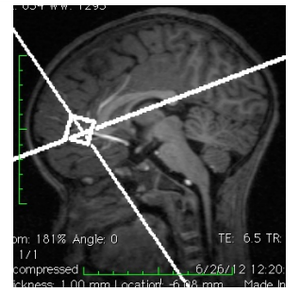


2 HIV-exposed, uninfected children

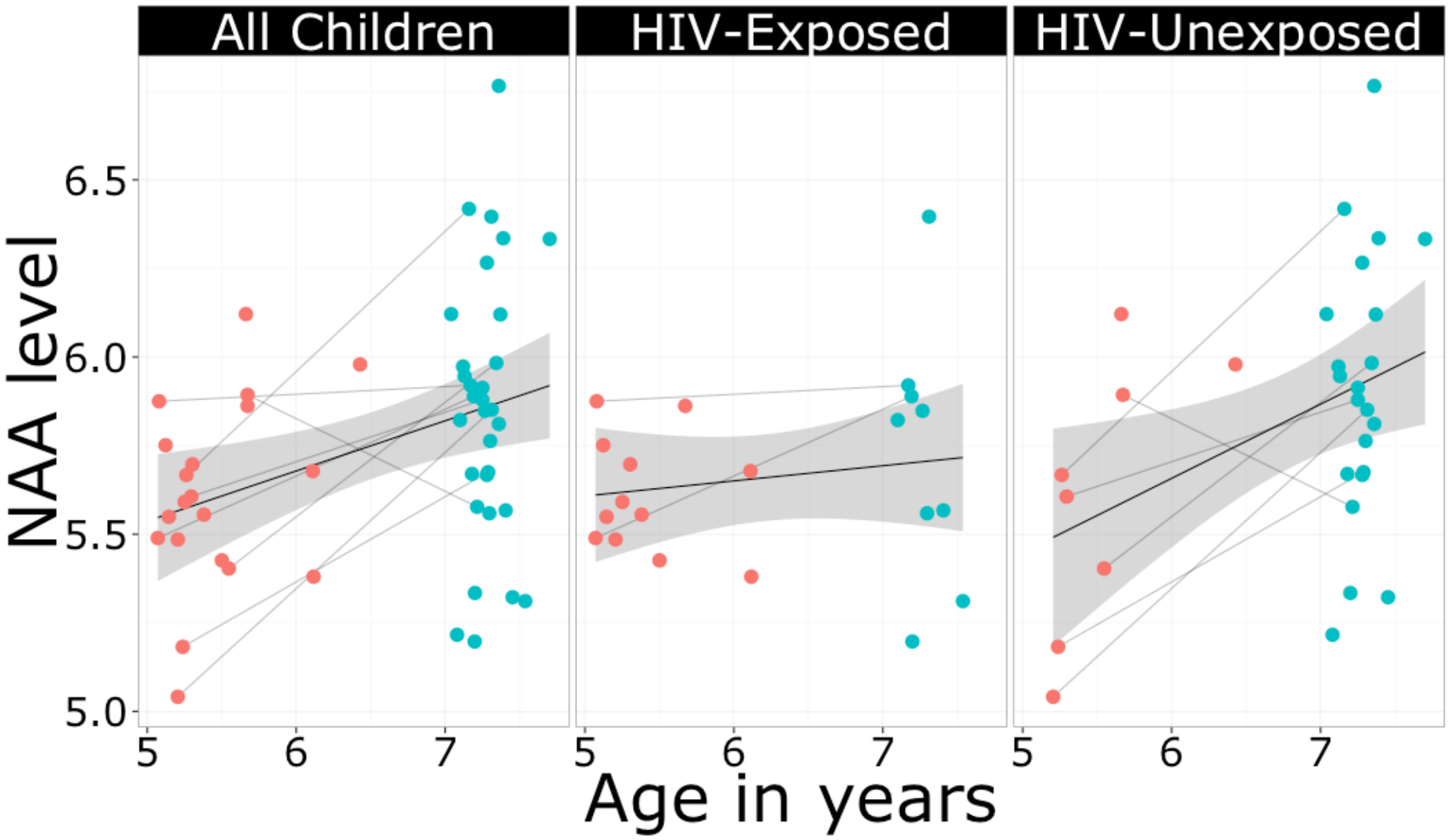
Cohort description



2 HIV-exposed, uninfected children

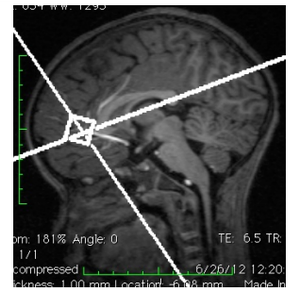


Midfrontal gray matter

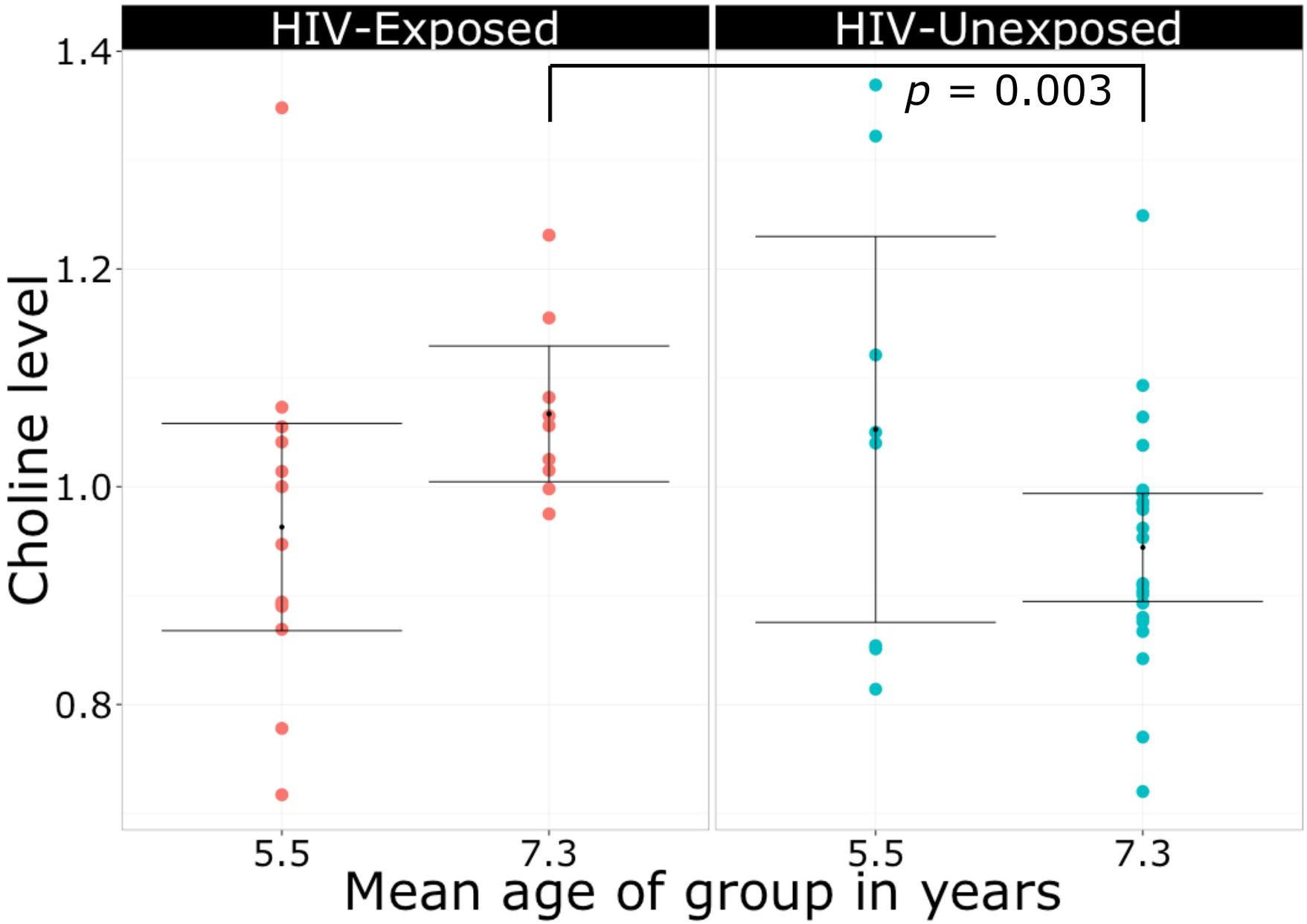


Mean NAA levels increase significantly from age 5 to age 7 in HUU children *only*

2 HIV-exposed, uninfected children



Midfrontal gray matter



HEU children have HIGHER mean choline levels at age 7

Conclusions

Results suggest HIV-exposure may affect normal neurological development in young children in gray matter.

Results indicate a disruption or delay in development between preschool age (5 years) and school age (7 years).

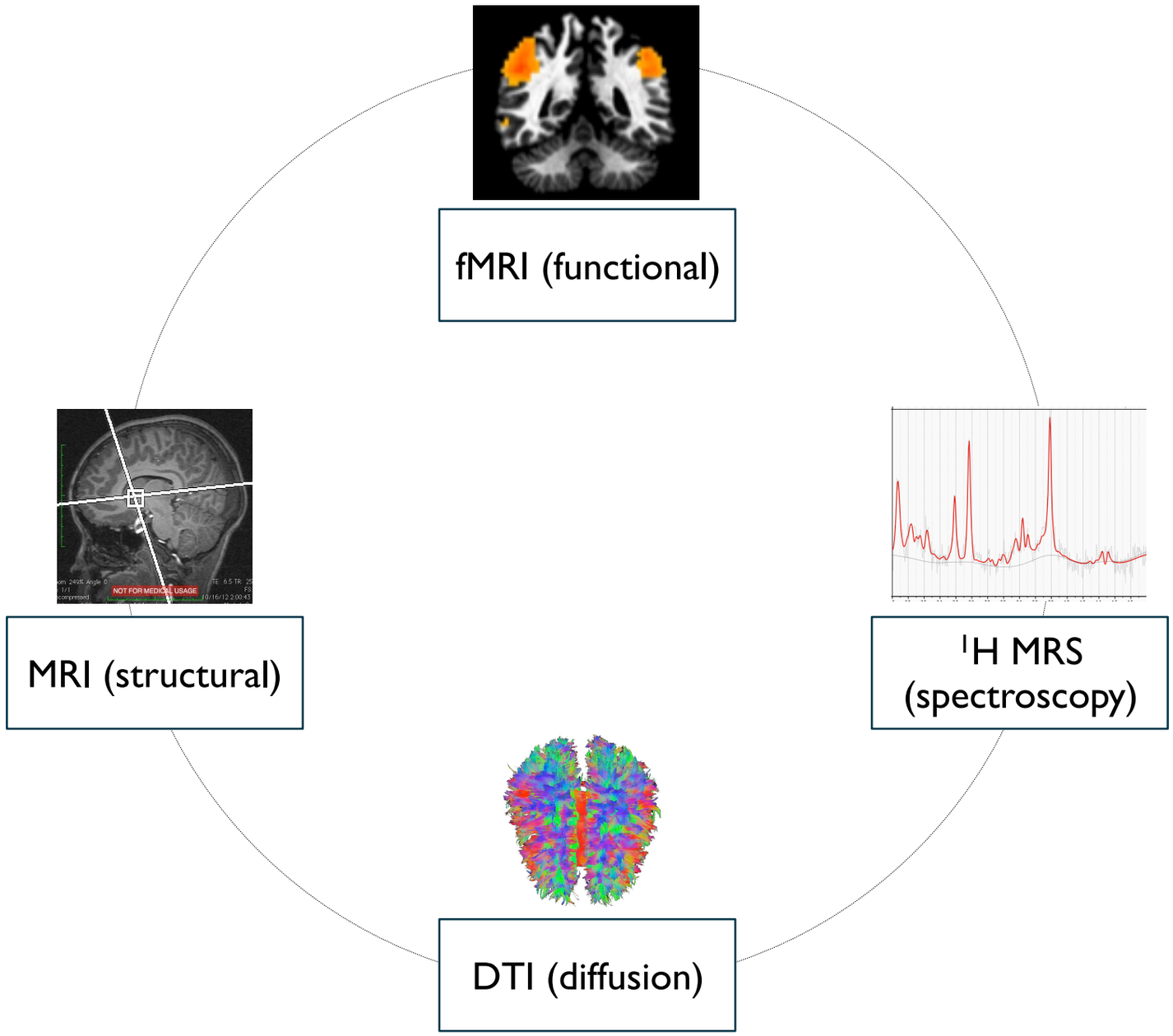
1 2 HIV-infected and HIV-exposed, uninfected children

Future work

Can NAA and choline levels recover? Do differences persist at ages 7 and 9?

- Currently examining MRS data at age 7
- At present, acquiring 9 year old data.
- Examine neuropsychological and behavioral data in combination with metabolite levels.

Conclusions



Ultimately, we would like to use all modalities in combination to create a more complete picture of neurodevelopment - in terms of brain structure, function and metabolism - within these children at ages 5, 7 and 9 years.

Acknowledgements

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