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**RARE DISEASE WORKSHOP SERIES**  
Improving the Clinical Development Process

**Advanced neuroimaging methods for assessing  
brain anatomy, biochemistry and function  
in urea cycle disorders**

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# Conference goals

- Discuss the major imaging features of two UCDs
  - Ornithine transcarbamylase deficiency
  - Arginase deficiency
- Present previous research using multiplatform advanced neuroimaging to identify brain biomarkers in UCDs



# Neurological phenotype of UCD

- Previous clinical research has demonstrated that there is a specific pattern of brain injury in UCDs
  - Affects the white matter of the brain (connections/wiring)
  - Functionally this correlates with the known neuropsychological phenotype of deficits inwith attention and fine motor skills



# Urea cycle rare disorders consortium

- Longitudinal study of patients with UCDs
  - Incidence, prevalence
  - Clinical factors
  - Treatment approaches
  - Neuropsychological outcomes
- Pilot projects
  - Assessing neural markers of injury using advanced neuroimaging



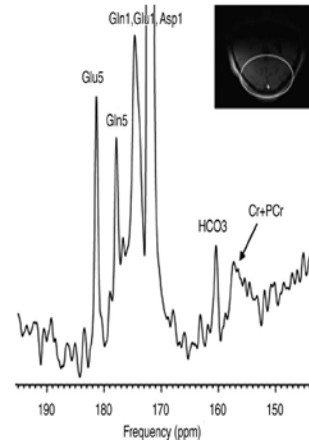
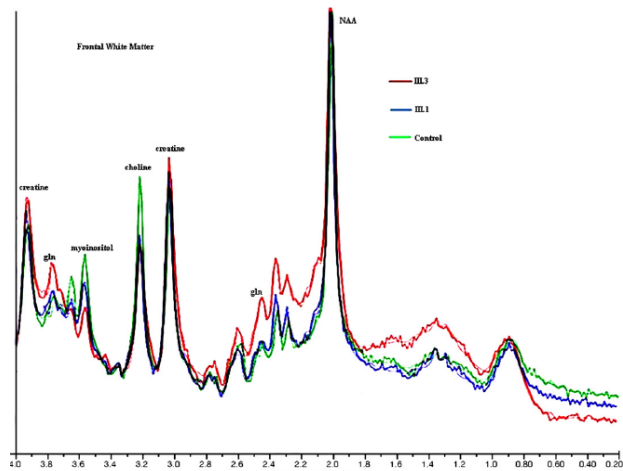
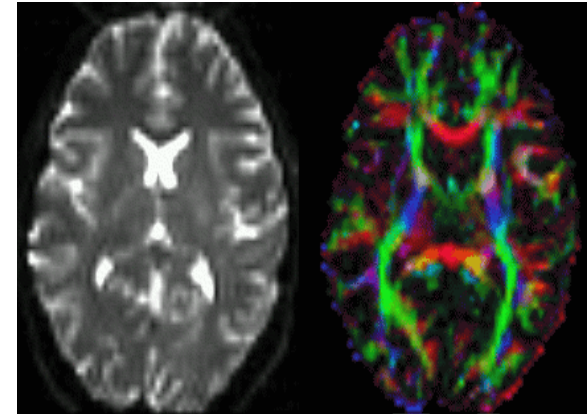
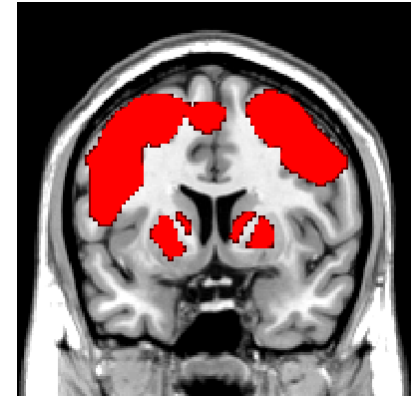
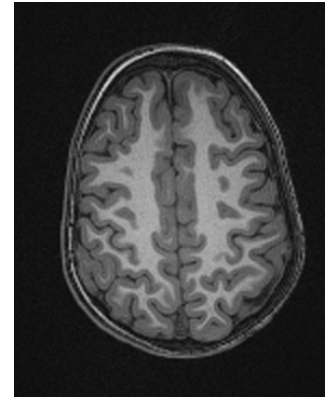
# Can neuroimaging help identify biomarkers that predict...

- Who is affected/not
  - OTCD carriers
- Who is at risk for poor outcome
  - More sensitive than ammonia
- Protective factors
- Recovery after brain injury
- Response to therapeutics
- Neurocognitive outcomes



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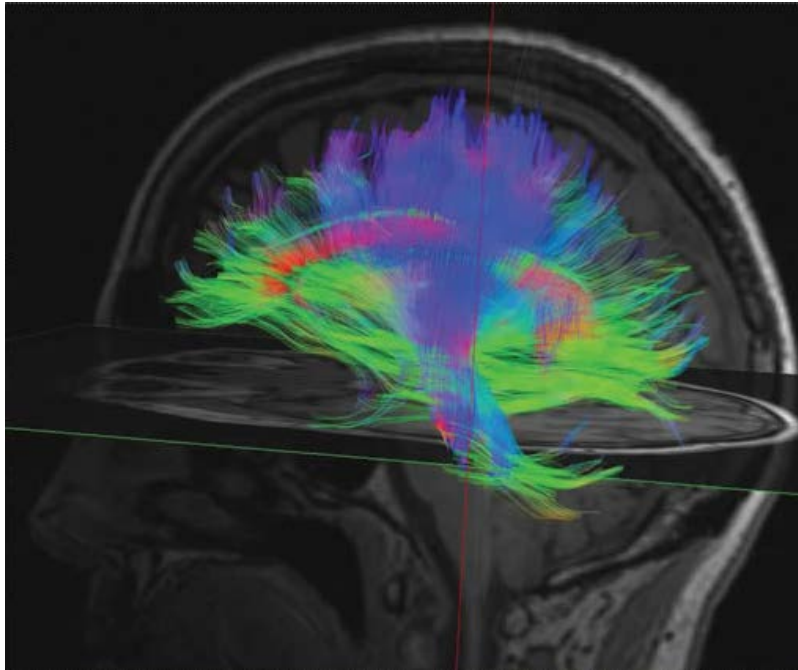


# What have we learned

- Reversible injury
  - Older age of onset/Late onset
  - Potentially milder excursions of ammonia level
  - Other protective factors??
- Irreversible brain injury
  - Related to stage of maturity of the brain
  - Related to duration of ammonia elevation, age of insult, and other factors
- Different pattern of injury depending on age and which UCD



# Diffusion tensor imaging

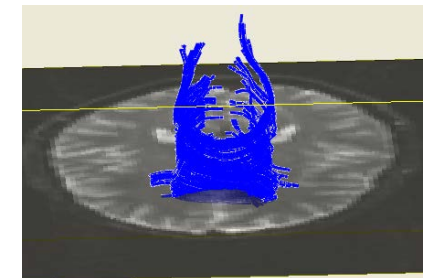
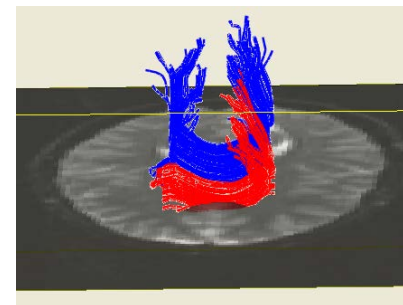
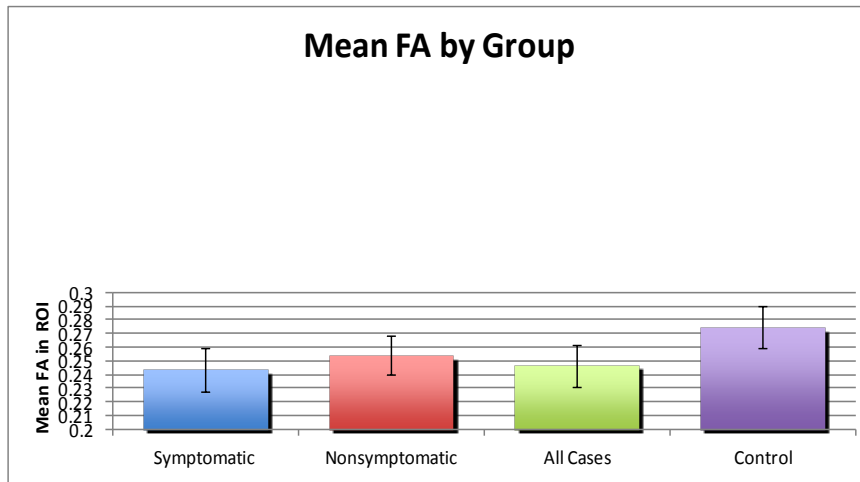
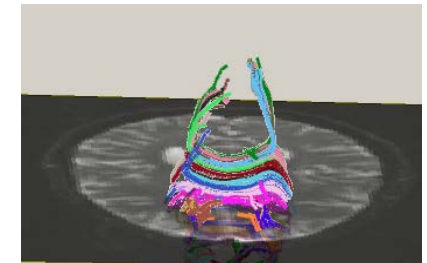
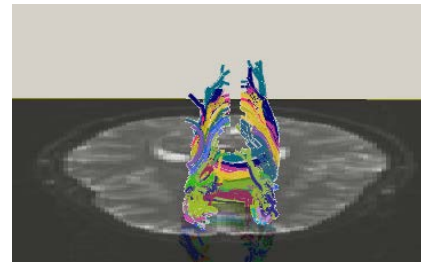
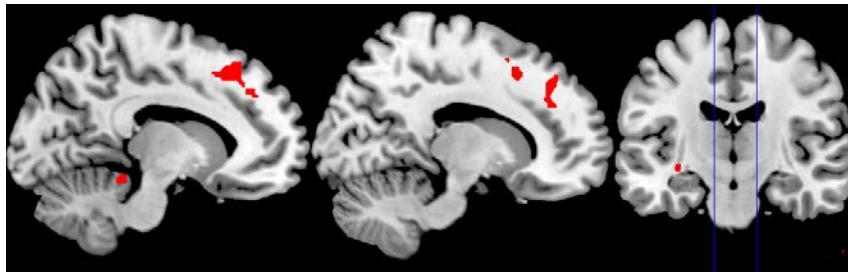


Produces images of brain tissue weighted by local characteristics of water diffusion within biological membranes.

The degree of diffusion anisotropy can yield useful information about the microstructure of brain tissue, such as the degree of myelination.

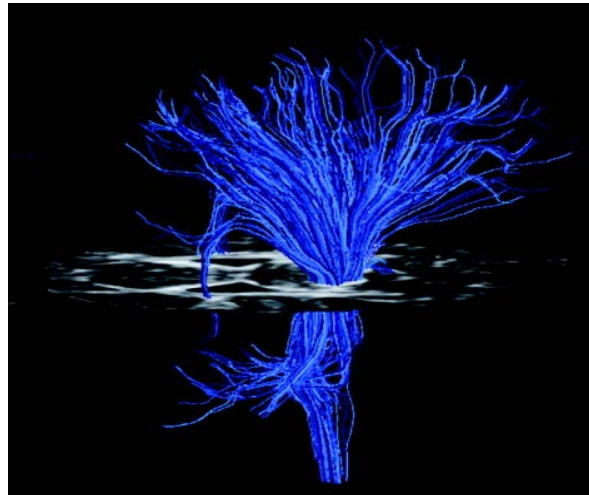
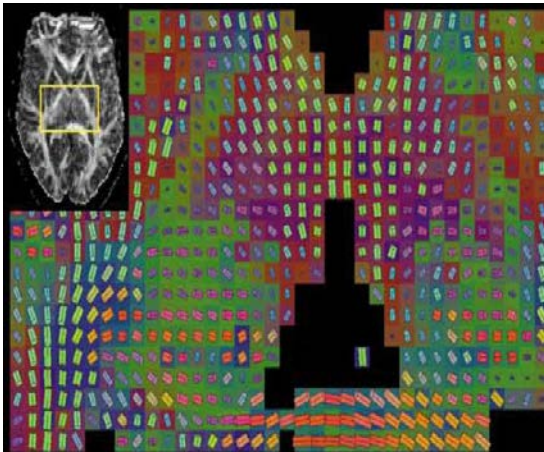
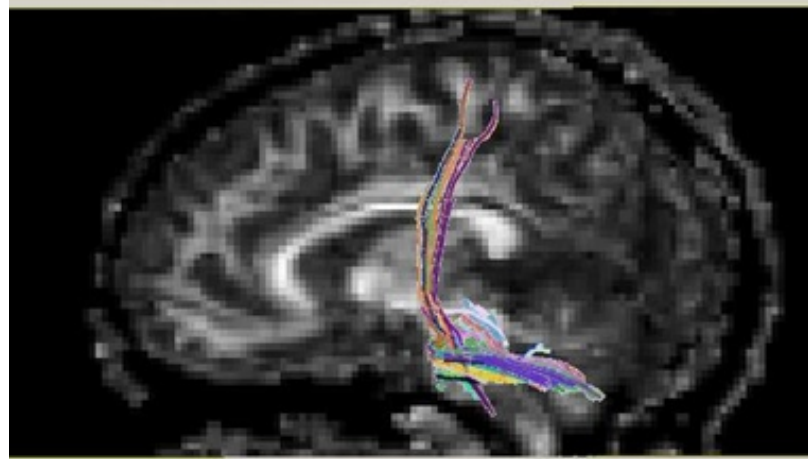
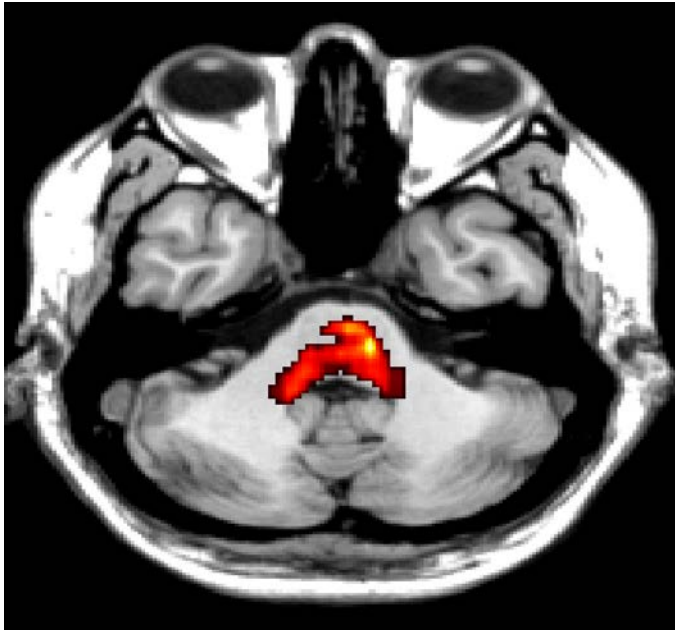


# Diffusion tensor imaging shows evidence of white matter injury in motor tracts that connect parts of the brain important in attention and memory





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## **NAA**

Marker of neuronal number and integrity, may be decreased in disorders that damage neurons

## **Lactate**

May be elevated in disorders that impair energy metabolism

## **Creatine**

Marker of energy status

## **Choline**

Marker of integrity of nerve cell membranes, elevated with membrane damage

## **Myoinositol**

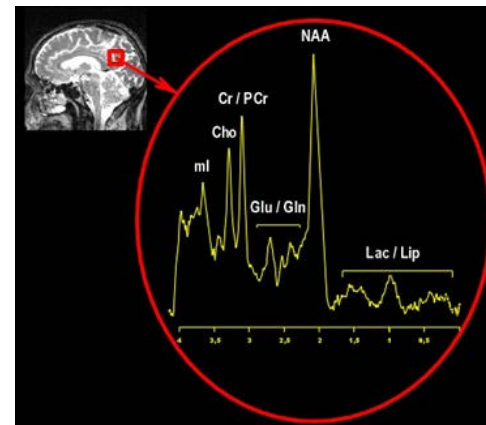
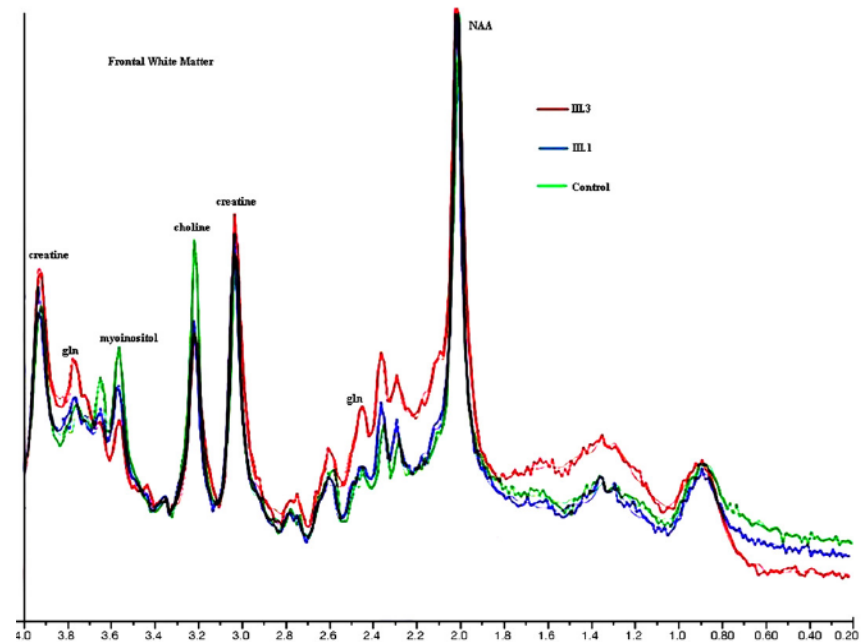
Involved in cell signaling, may indicate cell volume

## **Glutamate**

Excitatory amino acid  
neurotransmitter  
Precursor for GABA, inhibitory neurotransmitter

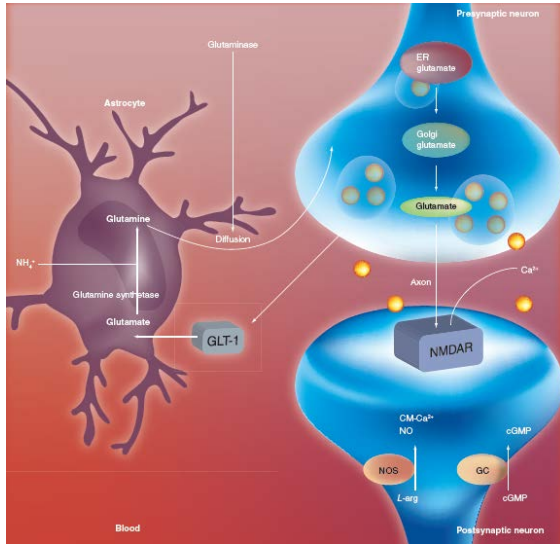
## **Glutamine**

Storage depot for ammonia

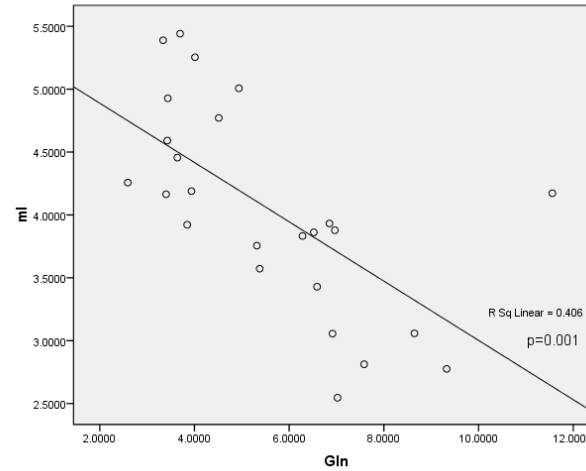




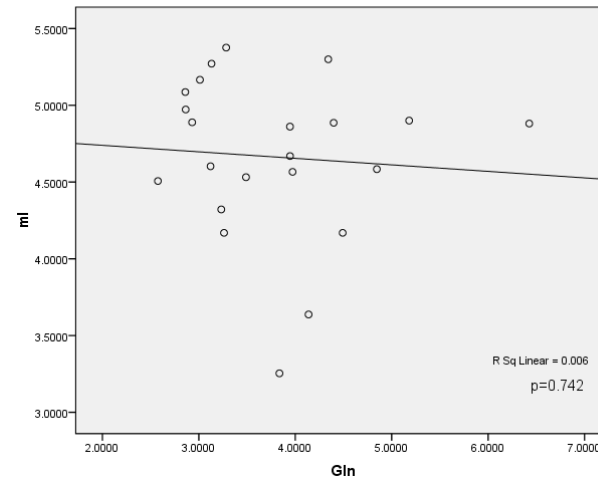
# Glutamine and myoinositol



Gln vs ml concentration in PCGM - cases



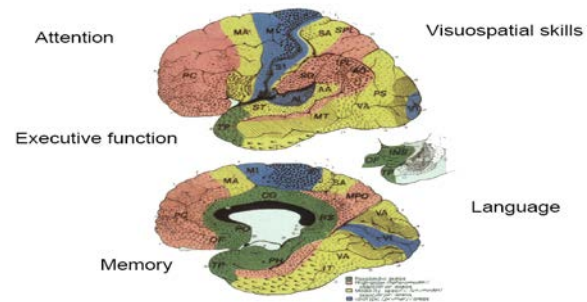
Gln vs ml concentration in PCGM for controls





# Current projects

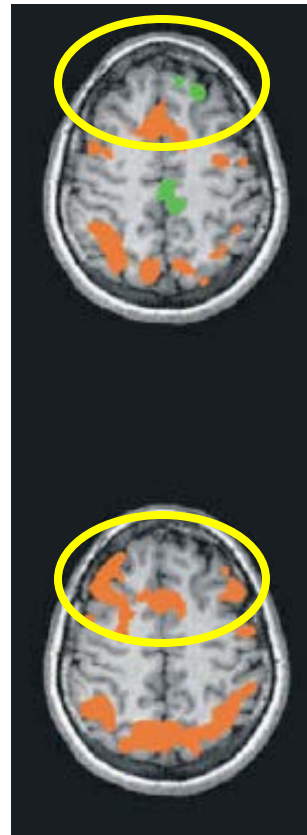
- Preclinical dose response
  - Use marker on a drug approval
  - Treatment study with our marker, drugs on the market
- Evolution of biomarkers after HA and recovery
- Nice story, generalizable brain imaging markers
- Patient screening for therapeutic considerations



## Executive Deficits in OTCD

- Working memory
- Attention
- Task shifting/cognitive flexibility
- Response inhibition/top-down cognitive control
- Functions closely related to function of brain's prefrontal cortex, which relies heavily on dopamine for intercellular neurotransmission
- Severe mental retardation in untreated/poorly managed patients
- Deficits seen these cognitive domains in well managed patients despite normal global IQ

Control Group



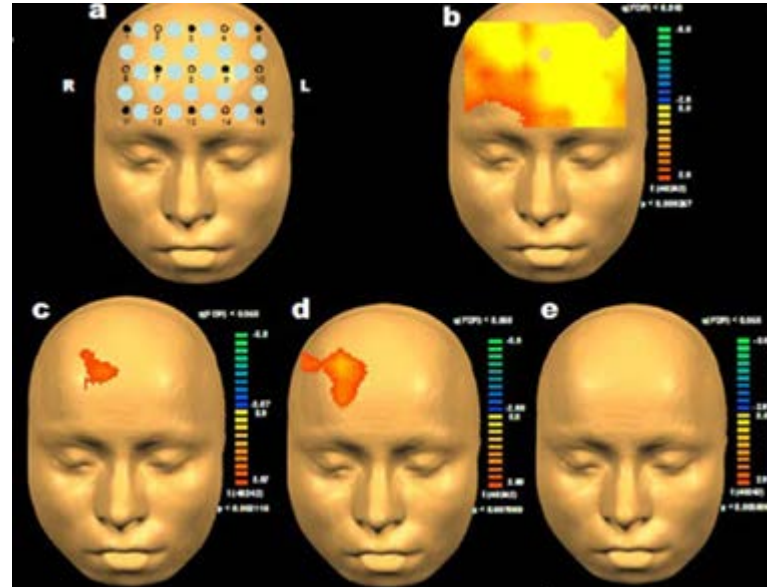
OTCD Group

When memory performance is controlled for, patients have to do more “brain work” to do the same cognitive task relative to healthy controls, indicating “inefficient” neuronal activation.



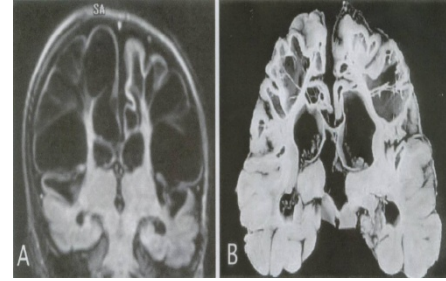
# NIRS

Recent advances in NIRS (near infrared spectroscopy) sensitive to activity dependent changes in blood flow and intracerebral light scattering raise promise that some elements of cerebral function may be imaged outside high field MRI environment





# Alterations in white matter (and gray with longstanding HA) pathology



## Hyperammonemia

Glial swelling

Alterations in neurotransmitters

Long term consequences

Cognitive sequelae

Osmolar damage

impairment of cholinergic and glutamatergic transmission

Increase in water

Activation of NMDA receptors

Brain electrophysiological changes

Executive function

Working memory

Fine motor deficits

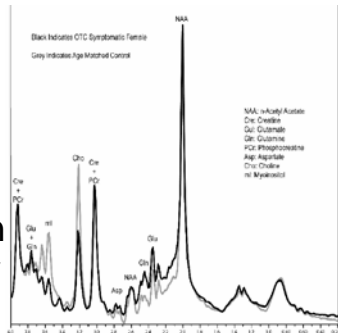
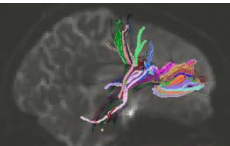
Ca<sup>++</sup> release

Calcium mediated cell damage

Trail making

N back fMRI task

Brain edema



Alterations in biochemistry on 1H MRS

Abnormal activation patterns on fMRI

