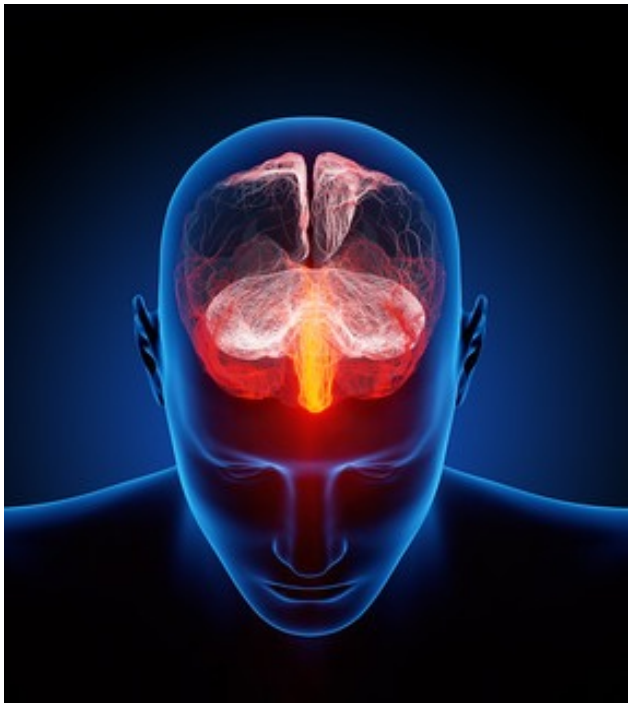
Emerging knowledge from MRI imaging studies: is ammonia control enough?



Andrea Gropman, M.D.

Kosar Khaksari, Ph.D.

Children's National Hospital, Washington, DC

NUCDF conference, April 6, 2024

The Woodlands

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Goals

- To review the neuroimaging work done as part of the Urea cycle consortium
  - All subjects
  - Carriers
  - infants
- To review lines of evidence that ammonia alone may not be the only factor to contribute to neurological outcome in UCD
- To highlight new areas of investigation

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Introduction

- UCDs represent a group of rare inborn errors of metabolism that lead to accumulation of ammonia, a toxic product of protein metabolism
- The symptoms of these disorders may present at any age
- Consequences are neurological of varying severity
  - Neonatal: severe disabilities, especially for proximal disorders
  - Childhood: ranges from very mild to severe mental and behavioral sequelae
  - Adults: may be misdiagnosed as having psychiatric disorders

Introduction

- Research has shown that ammonia is harmful to the brain if the levels remain elevated for extended periods of time
- Several decades ago, there was no testing or care to monitor the effect of hyperammonemia (HA) on neurological function in urea cycle disorders (UCD)

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Presentations of the UCDs

- Common theme of proximal UCDs is hyperammonemia (HA)
- Acute and chronic changes in behavior and level of consciousness
  - Seizures
  - Brain edema
  - Encephalopathy

High ammonia

- Clinical signs of may occur at concentrations >60 micromol/L and are very individual as some patients may tolerate higher levels before symptoms are noticed
- The short-term changes may include initially anorexia, irritability, lethargy, somnolence, disorientation, vomiting, and asterixis (flapping tremor).

MRI scanning

- Magnetic resonance imaging (MRI) was not done routinely, if at all, so it was not known what changes were occurring in the brain, during and after recovery from HA
- Decades ago, a diagnosis of a UCD meant severe disability and early death

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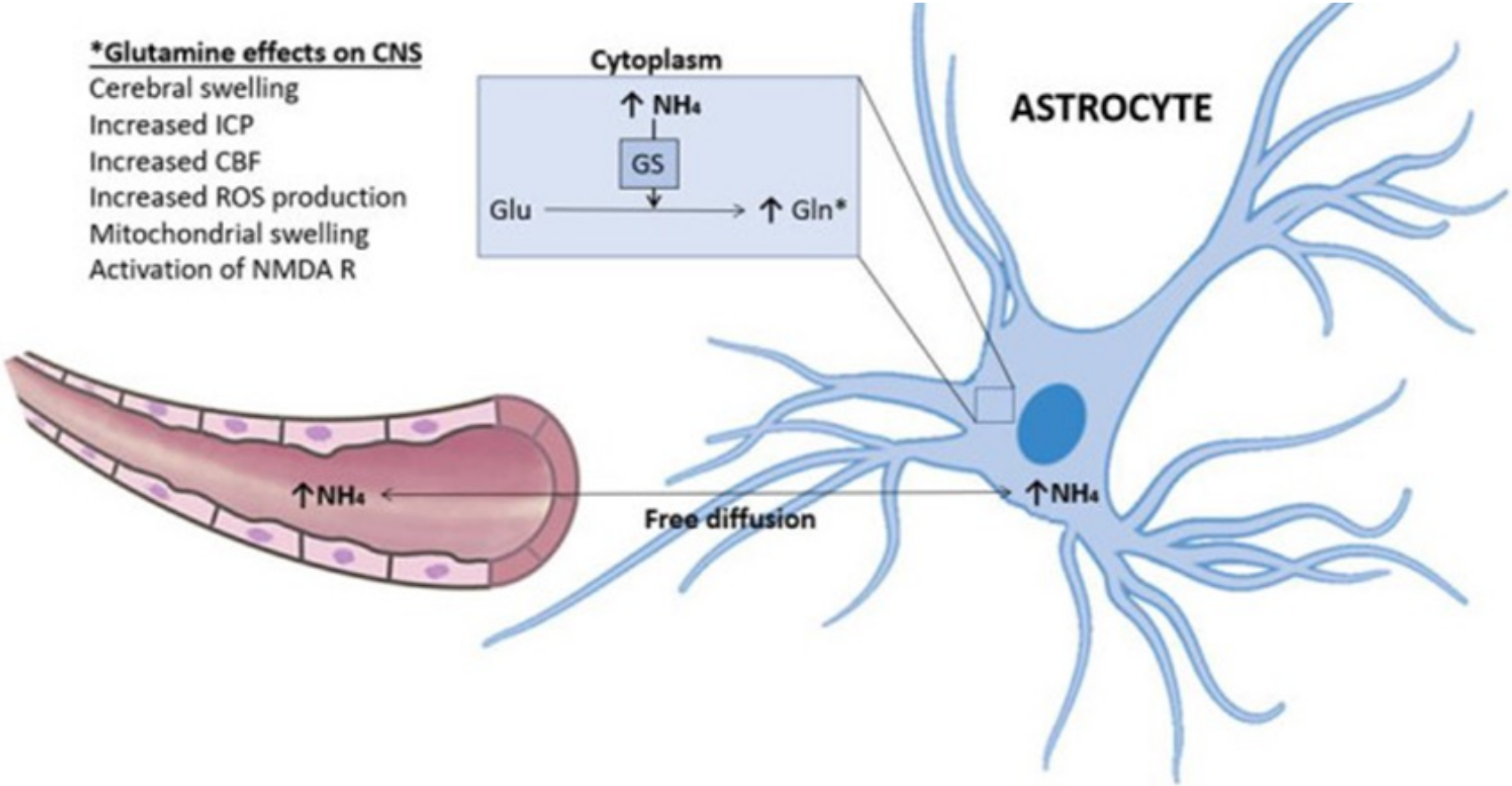
***Glutamine effects on CNS**

Cerebral swelling
Increased ICP
Increased CBF
Increased ROS production
Mitochondrial swelling
Activation of NMDA R



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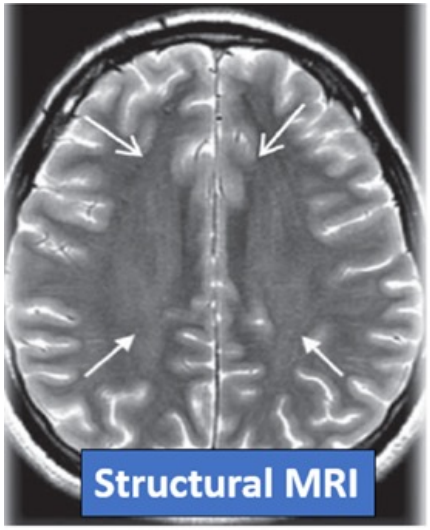
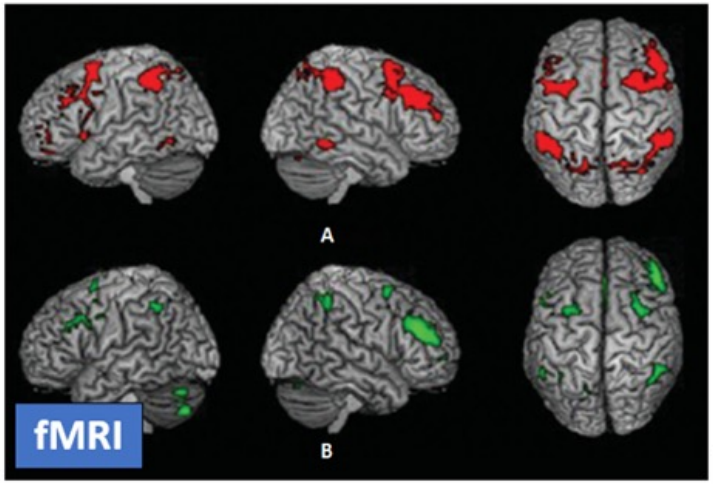
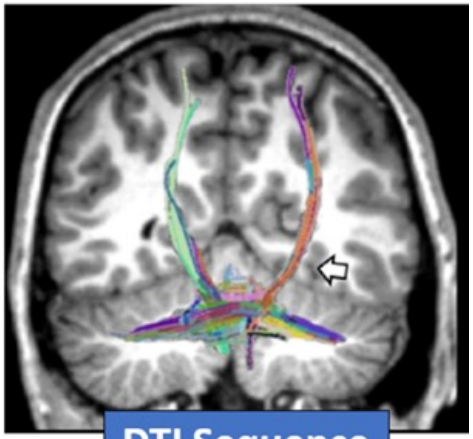
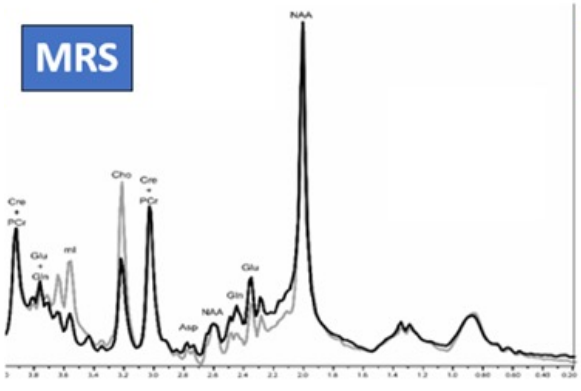
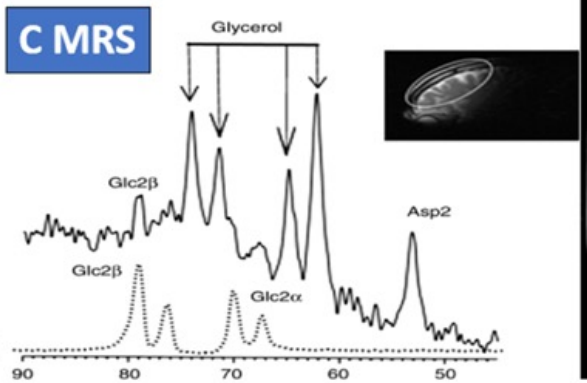
What can MRI tell us about the brain?

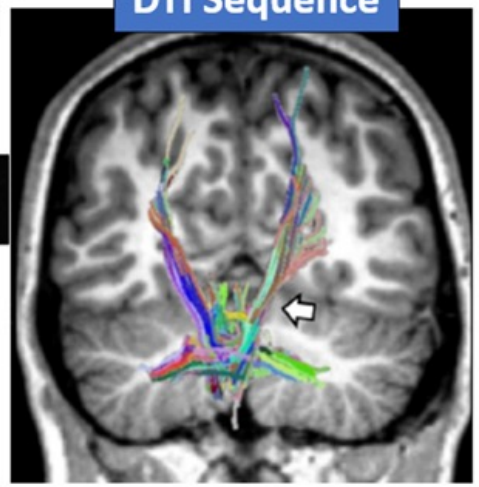












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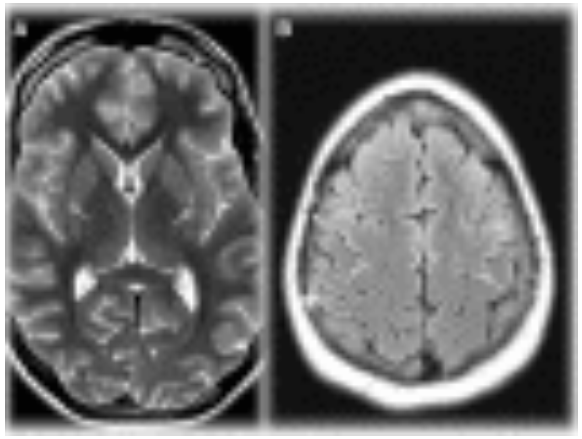
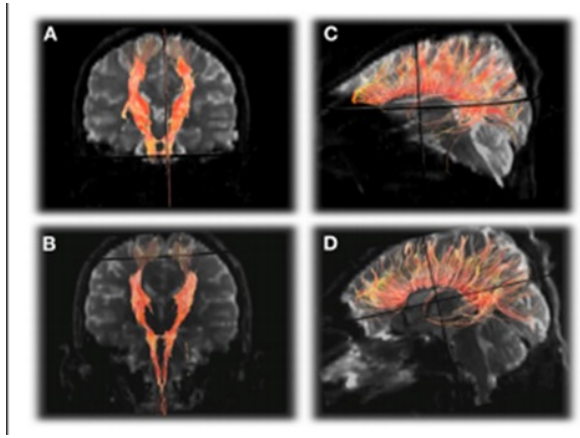
Recovery after HA

- Understanding recovery from HA
  - Opportunity to identify early biomarkers of injury and recovery
- Longitudinal imaging after HA
  - abnormal signal changes
    - posterolateral putamen
    - supplemental motor strip (SMA)
    - pre-motor cortex
    - post-central gyrus
  - cerebral hypoperfusion evolving to hyperperfusion





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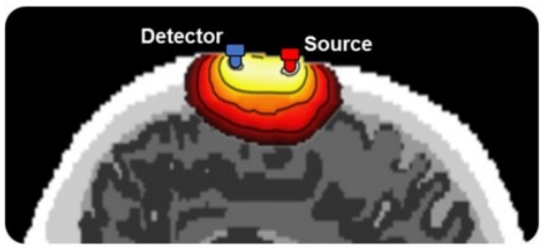
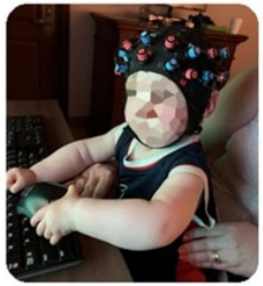
HA and the Brain

- In vivo investigations of the affected brain using multimodal neuroimaging combined with clinical and behavioral phenotyping hold promise
  - MR Spectroscopy
    - Proven as a tool to study biochemical aberrations
      - Elevated glutamine surrounding HA
      - Diagnose partial UCD
  - Functional MRI and Functional Near Infrared Spectroscopy (fNIRS)
    - Assesses local changes in cerebral hemodynamic levels of cortical regions,
    - Non-invasive technique
    - Surrogate to fMRI with better portability





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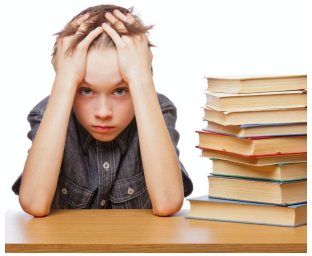
Patients who are treated still have cognitive problems

Earlier diagnosis, improved management, and nitrogen scavenger therapy have improved the lives of patients with UCD

However, many patients suffer from learning difficulties under the umbrella “executive function”

- Self-regulation/inhibition
- Working memory
- Cognitive flexibility
- Problem-solving, and planning



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What conditions have we studied?

- Our research focuses on OTC and Arg 1
  - noninvasive neuroimaging
  - neuropsychological testing
  - devices
- To understand the relationship between ammonia, glutamine, cognitive function, seizures, and specifically impact on development of working memory

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Female carriers of OTC

- Common belief
  - 85% of heterozygous females are asymptomatic based on history
  - 15% show symptoms ranging from behavioral and learning disabilities and protein intolerance to cyclical vomiting, stroke-like episodes, and hyperammonemic coma

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How has our research in the UCDC demonstrated otherwise?

- Improvements in brain imaging technology and the research done by the Urea Cycle Disorders Consortium (UCDC) have shown that both MRI scans (which show detailed images of the brain) and cognitive tests reveal similar results
- These results might not be very noticeable when the brain isn't under much stress or pressure

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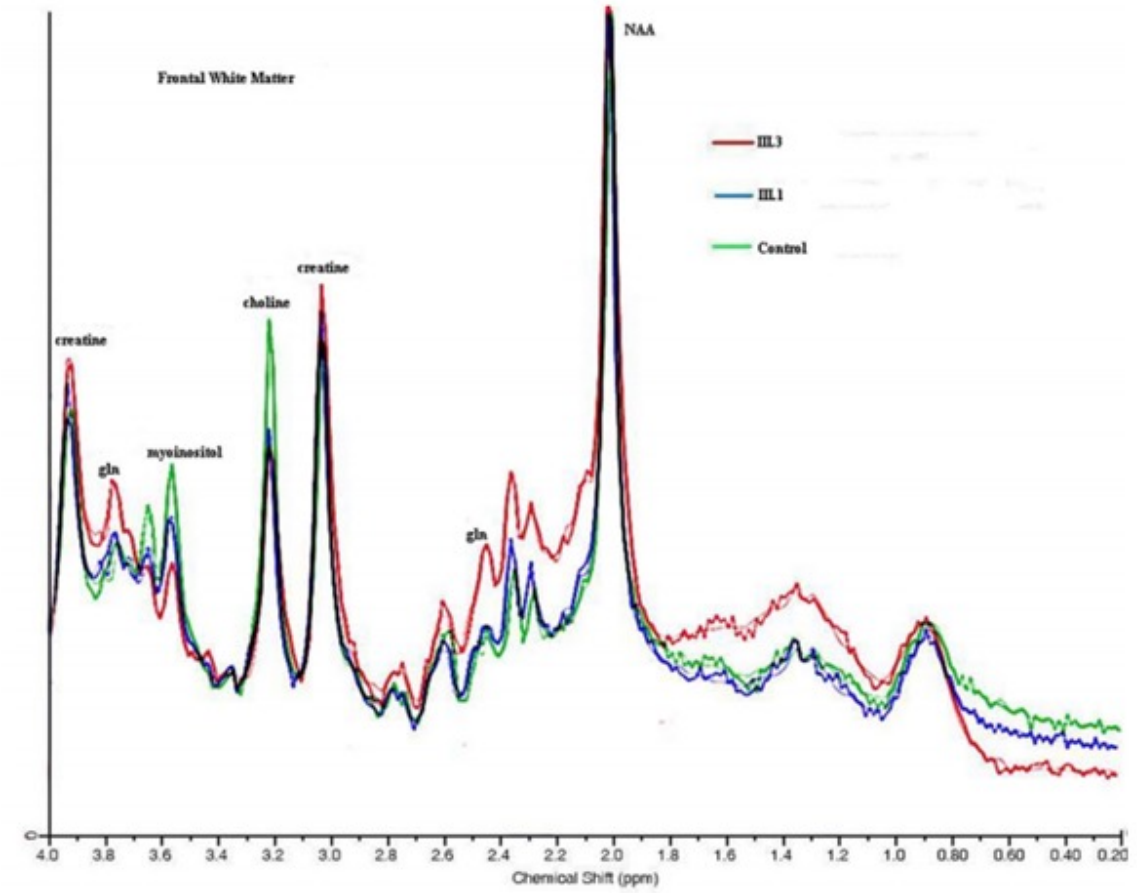
MRI spectroscopy: snapshot of brain chemistry



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Female carriers OTC

Table 2

Description of cognitive battery administered and the specific cognitive measures each task measures.

Cognitive Assessment	Academic	Executive Function	Verbal Memory	Simple Attention	Non-Verbal Memory	Motor Dexterity	Language
Stroop		X					
CTMT		X					
Brief		X					
Digit Span		X		X			
WASI	X		X		X		
VMI					X		
PA						X	
EVT							X
PPVT-III							X
WJ-III	X						X

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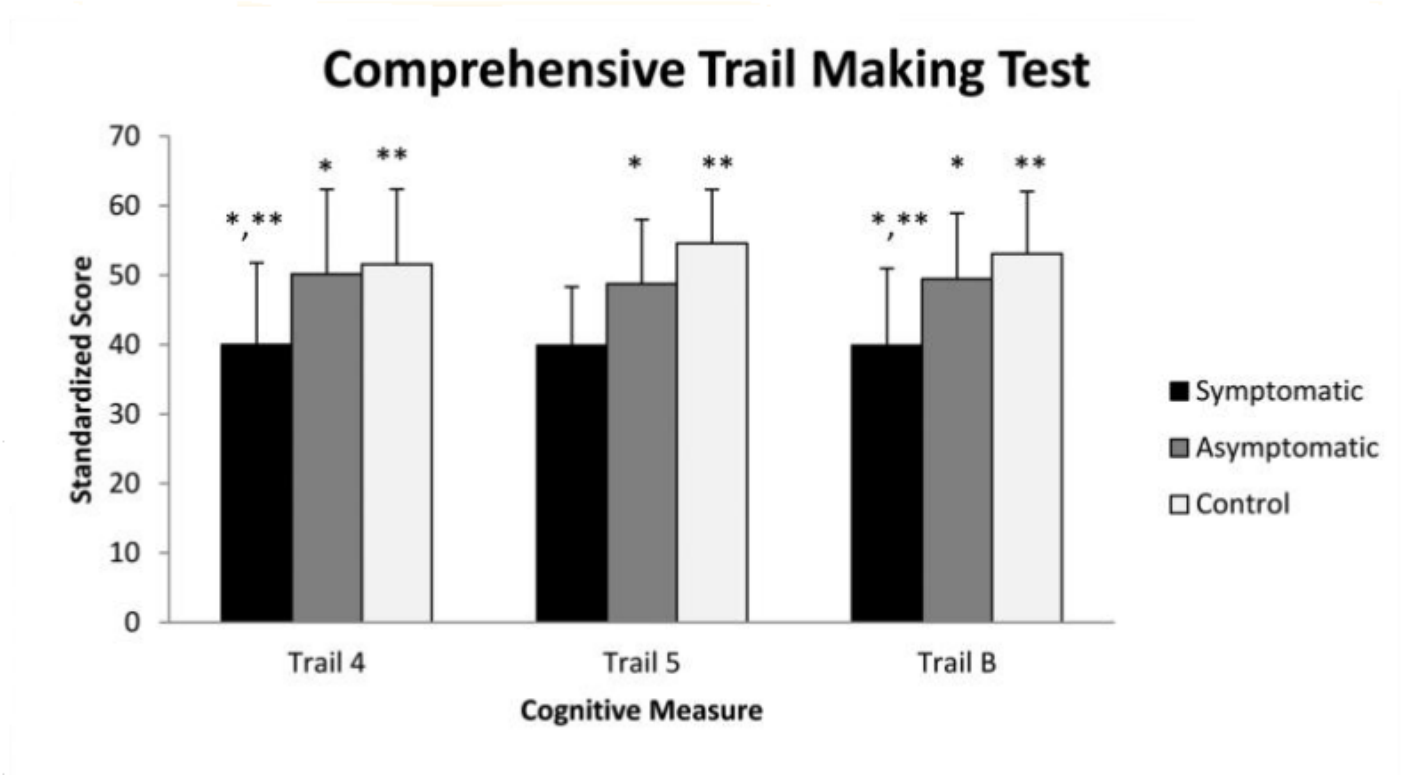
Female carriers OTC



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Female carriers OTC

- The discovery that “asymptomatic” female carriers of OTCD demonstrate cognitive deficits compared to the normative population helped to elucidate the many areas of the brain that are sensitive to HA, even in the absence of a clinically recognizable HA
  - When compared with protein tolerant siblings, female carriers were lower in performance and full scale IQ to a significant degree
  - struggle with motor dexterity and performance measures
    - driving

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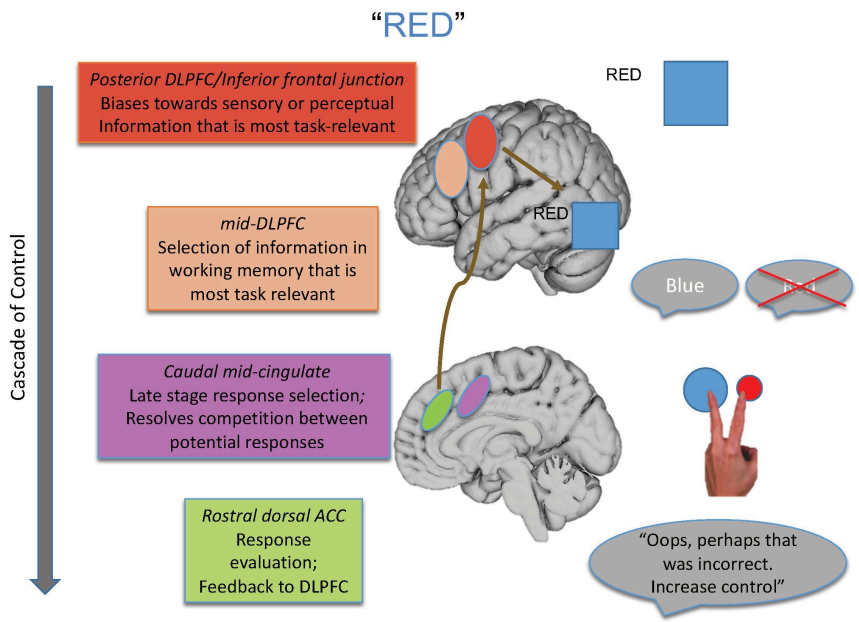
More obvious symptoms were uncovered when cognitive demand increases or there is superimposed illness or stressor



- In asymptomatic patients, hidden cognitive weaknesses have been identified that weren't detected before
  - when these patients were tested with a task called the Stroop task, which involves naming colors while ignoring words that describe different colors, they took significantly longer to respond compared to healthy individuals.

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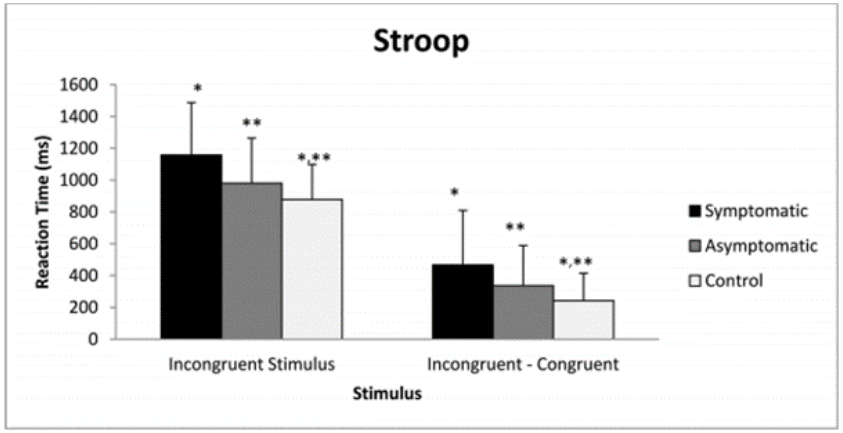
Female carriers OTC

- We believe that these patients only show difficulties in tasks that require planning and physical movement when those tasks become challenging. This pattern has also been noticed in brain imaging studies where patients were asked to perform memory tasks that got progressively harder.



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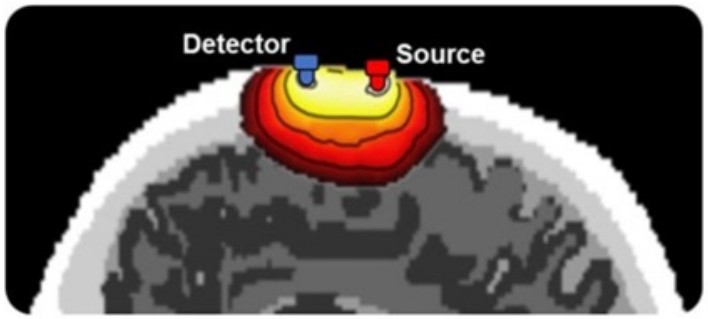
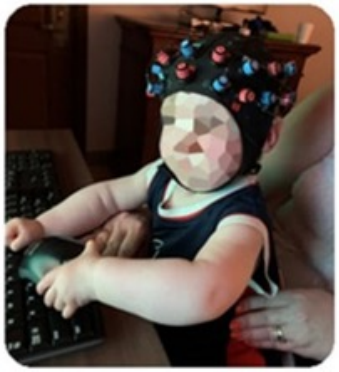
What about the babies?





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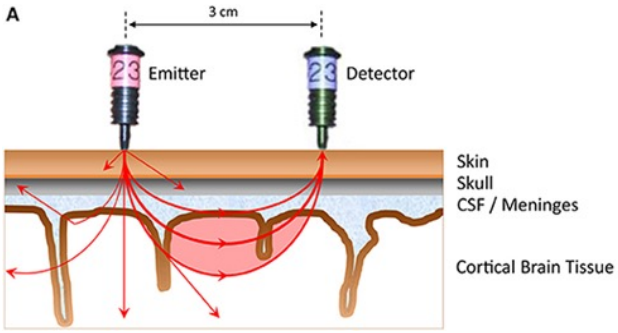

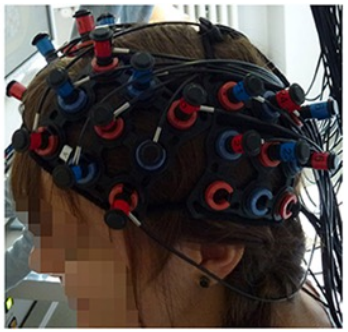

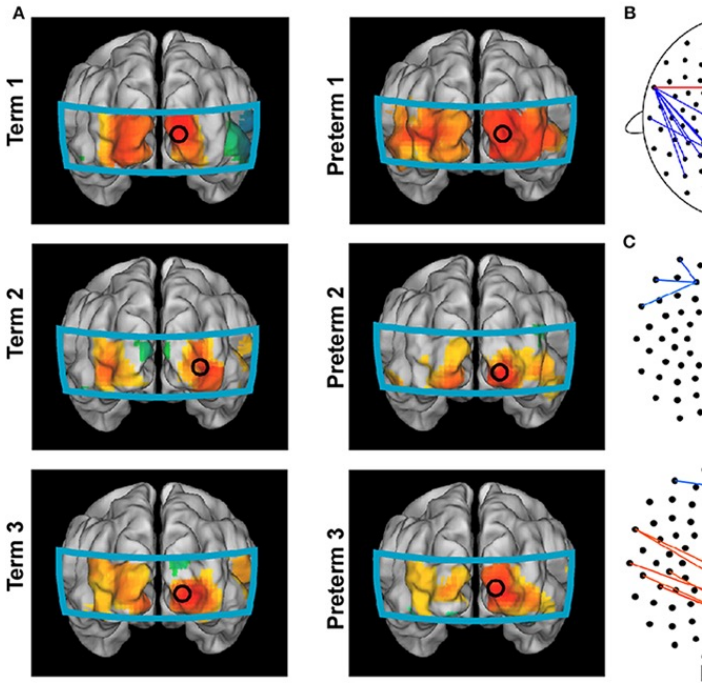

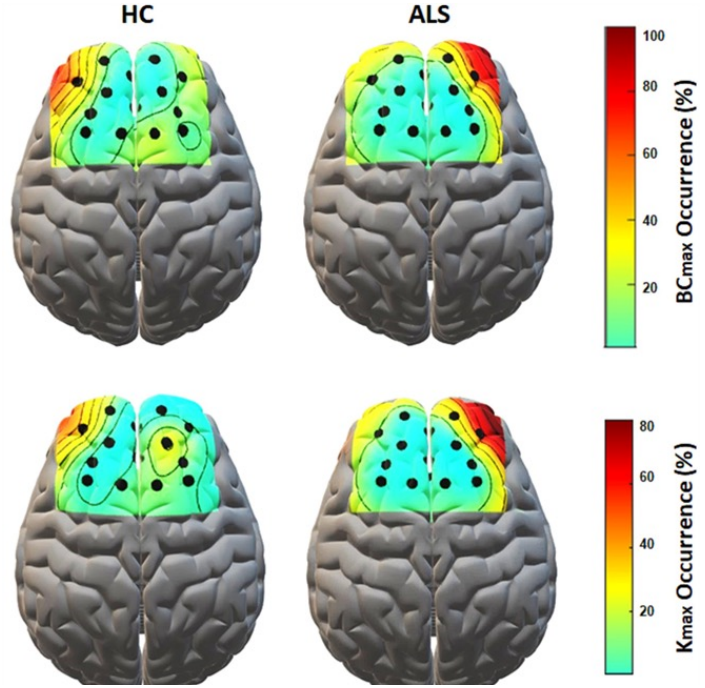

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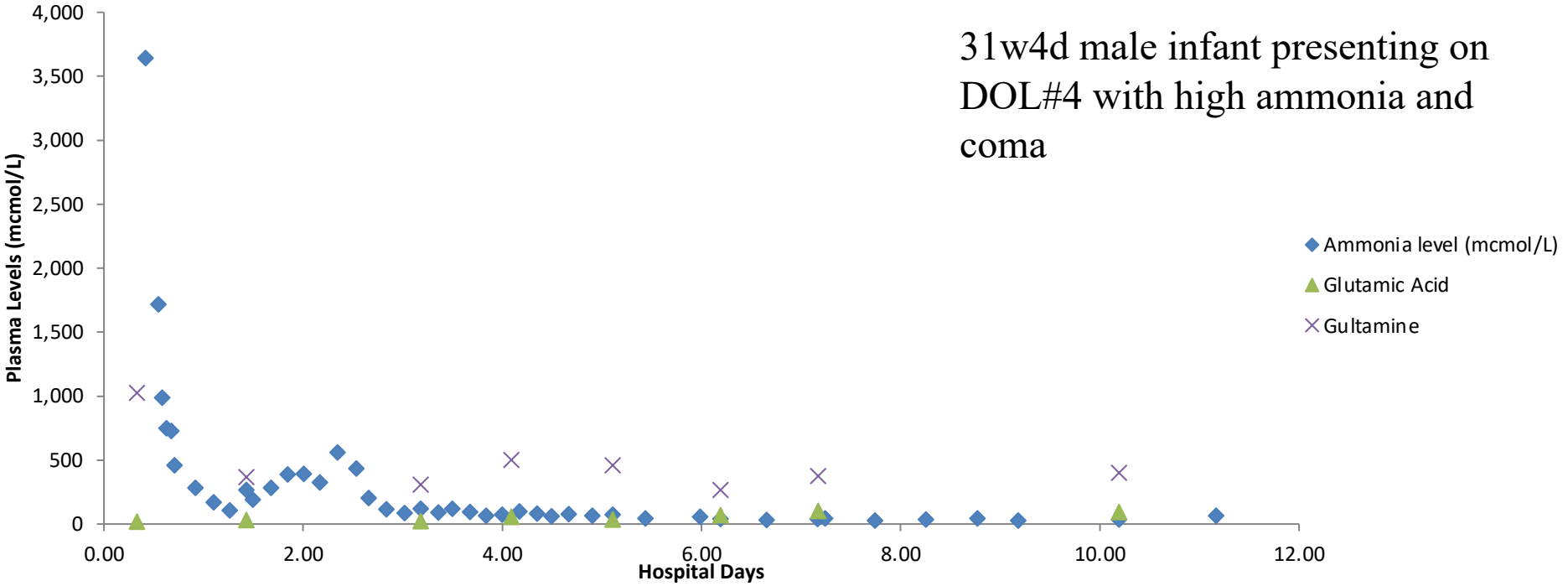
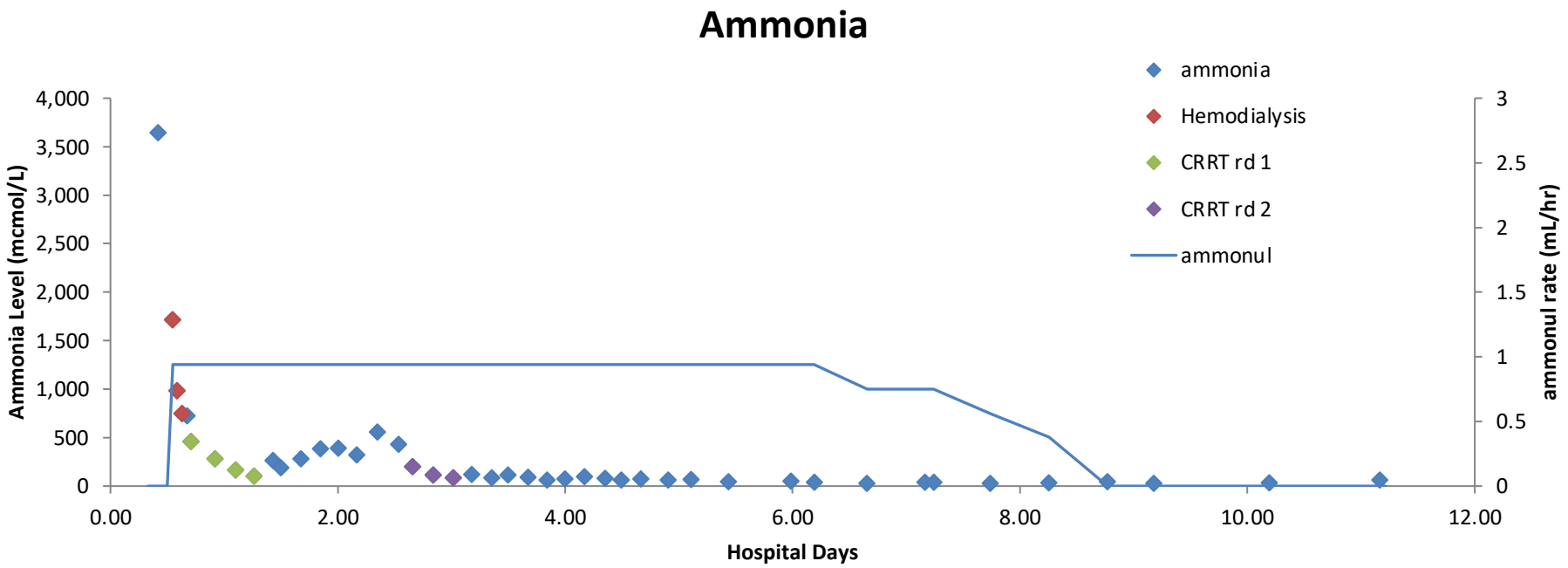
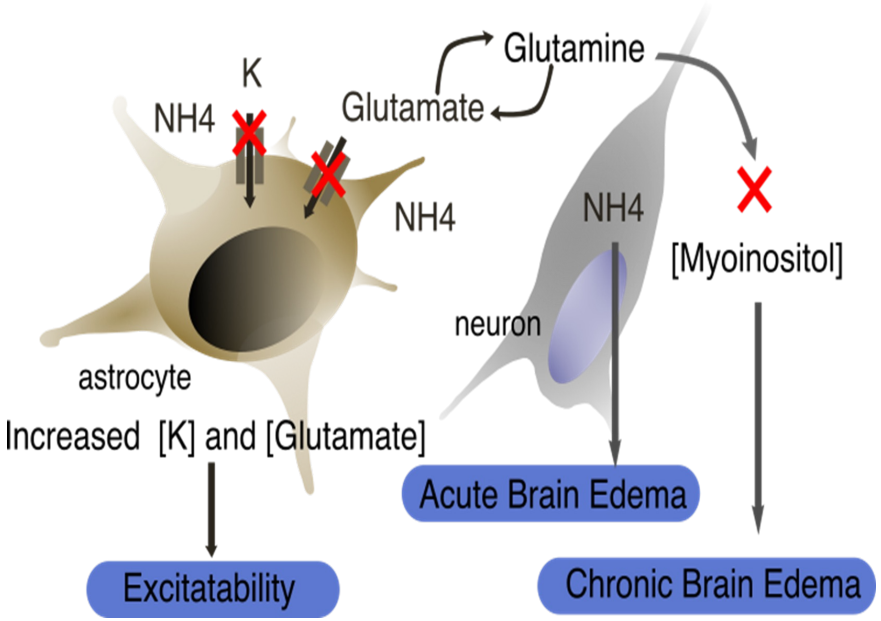
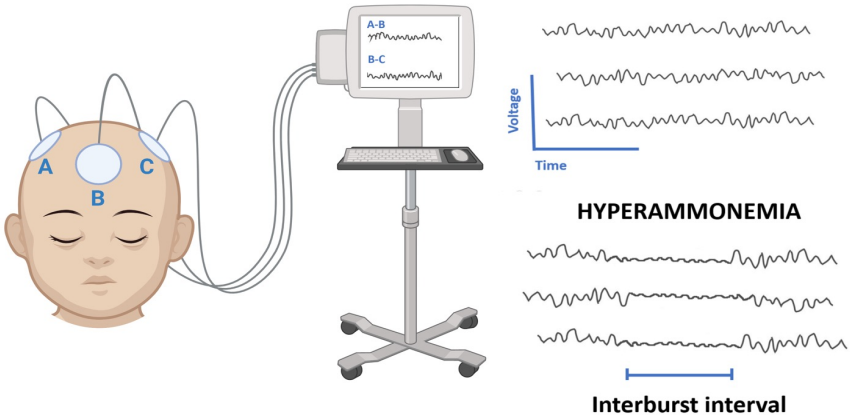
31w4d male infant presenting on DOL#4 with high ammonia and coma









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Results

- Continuous EEG monitoring revealed multiple silent seizures from the back of the brain
- We saw increase in delta power and a decrease in alpha and theta power during HA episodes.
  - Delta activity on electroencephalogram (EEG) is considered a biomarker of homeostatic sleep drive
  - Delta power is often associated with sleep duration and intensity

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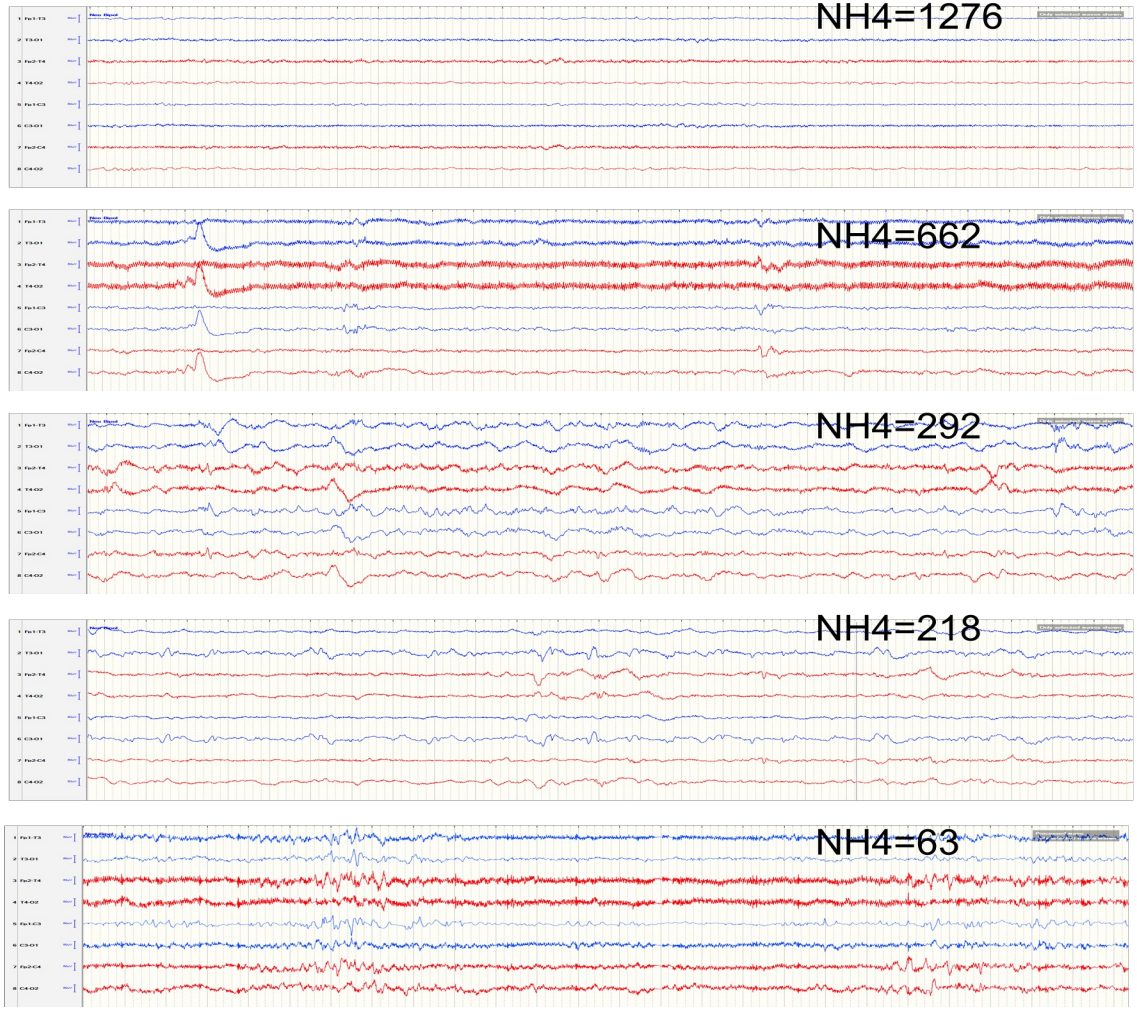
EEG Features During Resolving Hyperammonemia



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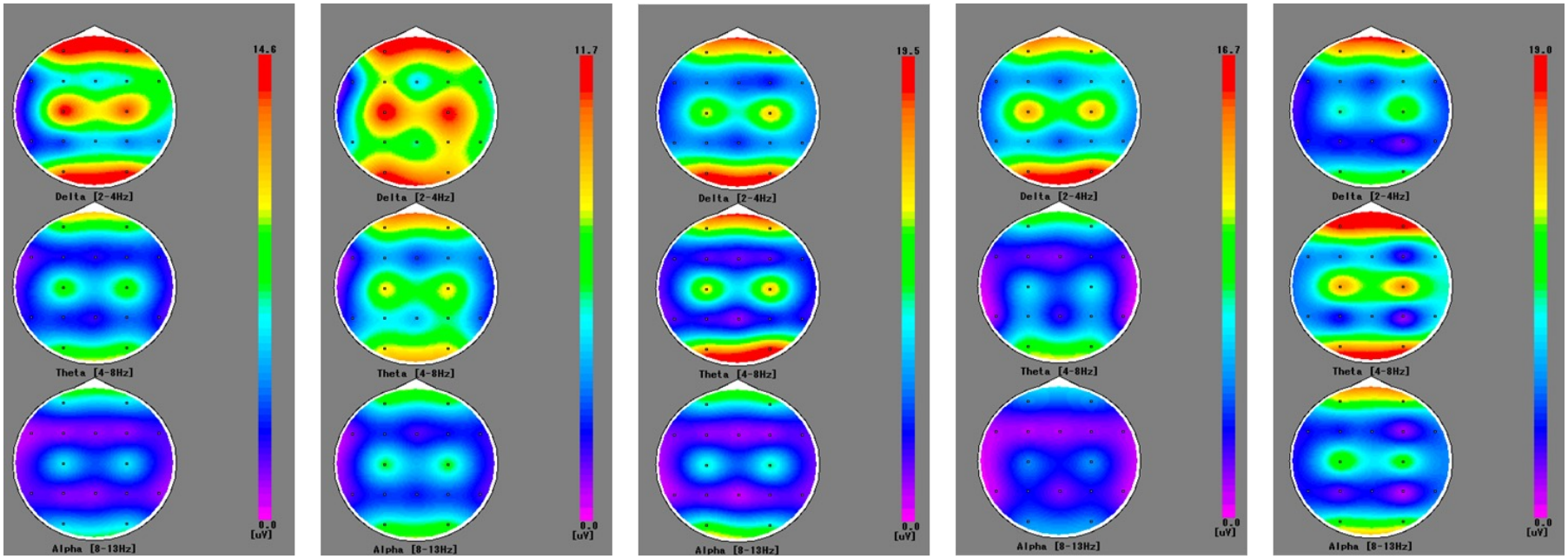
A decrease in ammonia level was correlated with a decrease in delta power and an increase in alpha and theta powers in the anterior head region



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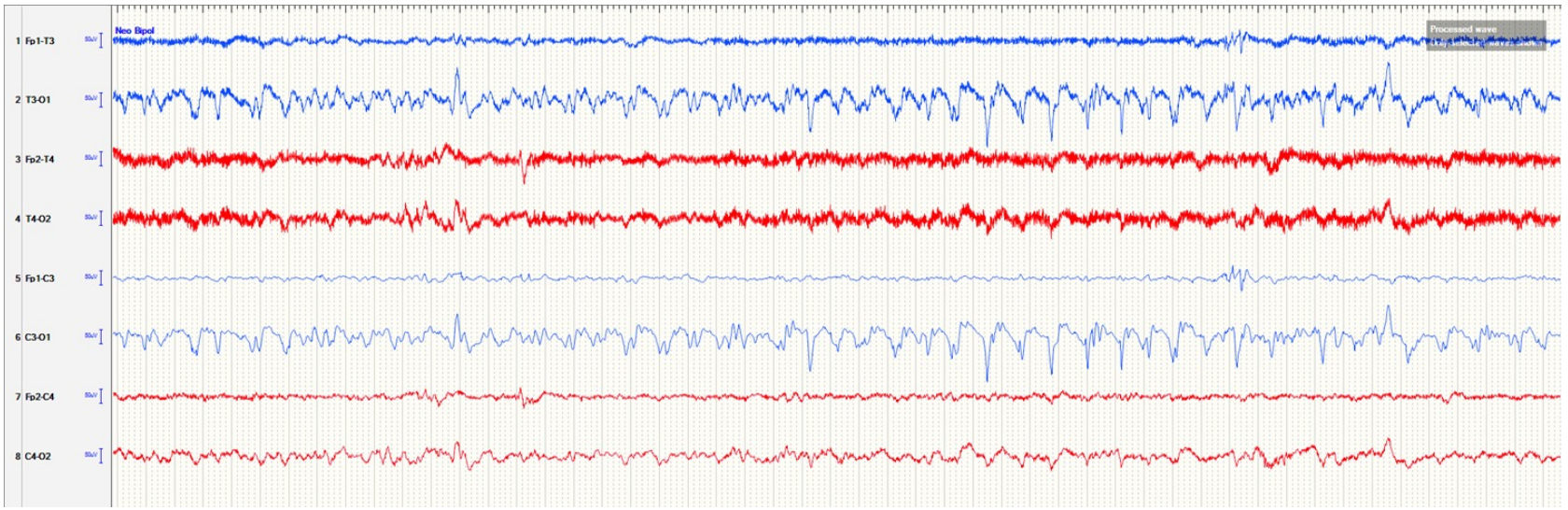

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How does that information help us?

- The presence and severity of EEG abnormalities in neonates with IEM can provide prognostic information regarding long-term neurodevelopmental outcomes
  - Persistent or evolving EEG abnormalities despite treatment may indicate ongoing brain injury and increased risk of cognitive impairment or epilepsy
  - Conversely, normalization of EEG findings may suggest a more favorable prognosis with appropriate management.

What about a complex executive function task such as driving?

- Driving requires an assortment of cognitive skills including executive functioning, information processing, visual processing, and memory
  - drowsiness, distraction or lack of attention, sleepiness, fatigue, and anxiety are reported as the main reasons of car accidents
- To better understand driver behavior and the sources of driver distraction, researchers have attempted to develop integrated driver models that capture driver behavior in a computational manner
  - These models provide insight into the sources of distraction by elucidating the exact processes by which a driver attends to the external environment, processes this information cognitively, and then reacts and manipulates the environment.

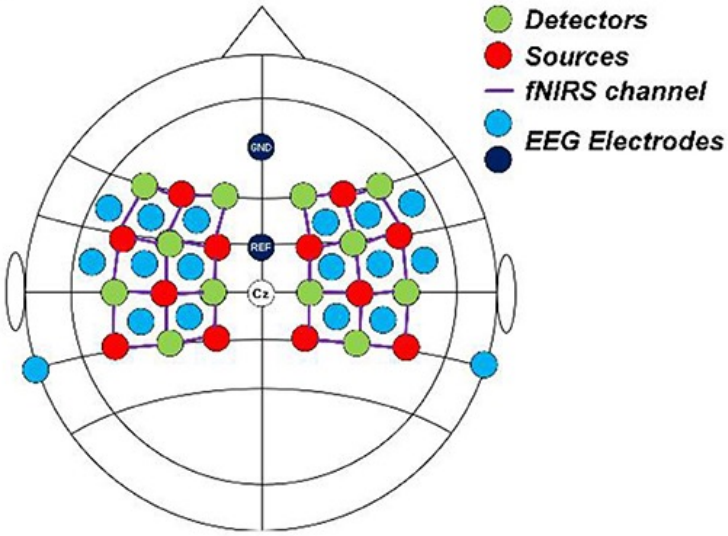
Complex real world functions: Driving

- Several research groups studied driving performance using different driving models
- Some of these works are using fNIRS that we will be using their results for understanding the outcomes of this study
- Our objective in this project is to provide an examination of biomarkers that should be considered in investigating driving performance in drivers with cognitive impairments due to UCD.

What about driving?

A

B



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The Driving challenge

The driving task will consist of several scenarios:

1. First level: This level consists of gentle curves on a simple roadway

   Subjects experience driving with the lowest level of demand and are required to respond only to operational-level driving tasks.

2. Second level: Subjects experience a higher level of demand. They will drive through a roadwork section with a narrow road

   This is considered as an intermediate level of demand.

3. Third level: In this level, subjects experience one step higher level of demand than level 2. They will experience a forced lane change and, they were required to execute an additional lane change if a discriminative stimulus (activation of the brake lights on a lead vehicle) was presented

   This decision rule was included in the pre-drive instructions. The addition of this working memory task was designed to result in the highest level of demand in this scenario.

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In Memory of Taeun Chang, M.D.

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Kettering family foundation

Come join our studies!!
Contact Alexa Taylor, senior research coordinator
ataylor4@childrensnational.org

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