Longitudinal studies of brain structure and function in MPS disorders: Lysosomal Disease Network

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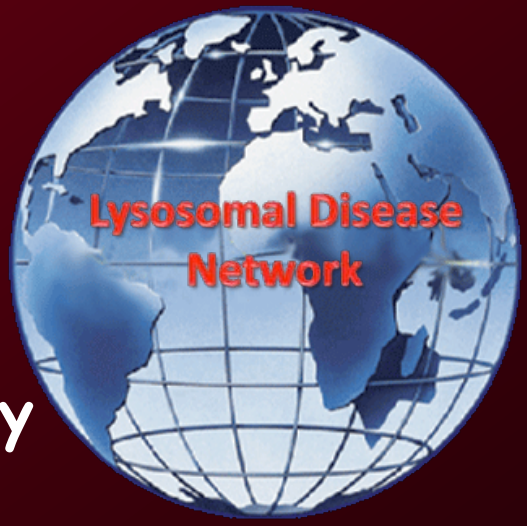

24th Annual National MPS Society
Family Conference

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Disclosures

- This research has (had) support from Lysosomal Disease Network (U54), MPS Society, Genzyme, Shire HGT, Biomarin, Ryan Foundation, and the Minnesota Medical Foundation

Objectives of Longitudinal Study of Brain Structure & Function in MPS disorders

- to identify abnormalities in brain structure and function over time
  - in treated and untreated MPS patients
- To identify distinct neuroimaging and neuropsychological patterns for each MPS disorder
- to develop quantitative measurements of change.
- to examine the degree to which risk factors influence brain and QOL outcomes
- To establish risk/benefit analysis for treatments

Coordination with other LDN studies

- Patricia Dickson – Harbor UCLA - Intrathecal ERT for cognitive decline in MPS I
  - Provide cognitive and MRI eligibility and treatment effects of intrathecal enzyme

- Lynda Polgreen - UMN - Longitudinal study of bone disease and the impact of growth hormone treatment in MPS I, II, and VI
  - Provide cognitive and MRI treatment effects – growth hormone

Methods

- 75-100 children/adults will be enrolled/followed in 8 centers over 5 years; 50 MPS I, 25-30 MPS II, 20 MPS VI.
- Seen yearly for a total of at least 3 or possibly 4 follow-up visits.
- Data: Quantitative neuroimaging (DTI, volumetrics) and neuropsychological tests, and medical history
- Samples collected for a biomarker developed by Lorne Clark (HCII-T)
- MRI data analysis (volumetrics and DTI) will be analyzed at the University of Minnesota through the neuroimaging core of the LDN.

Core Study Centers

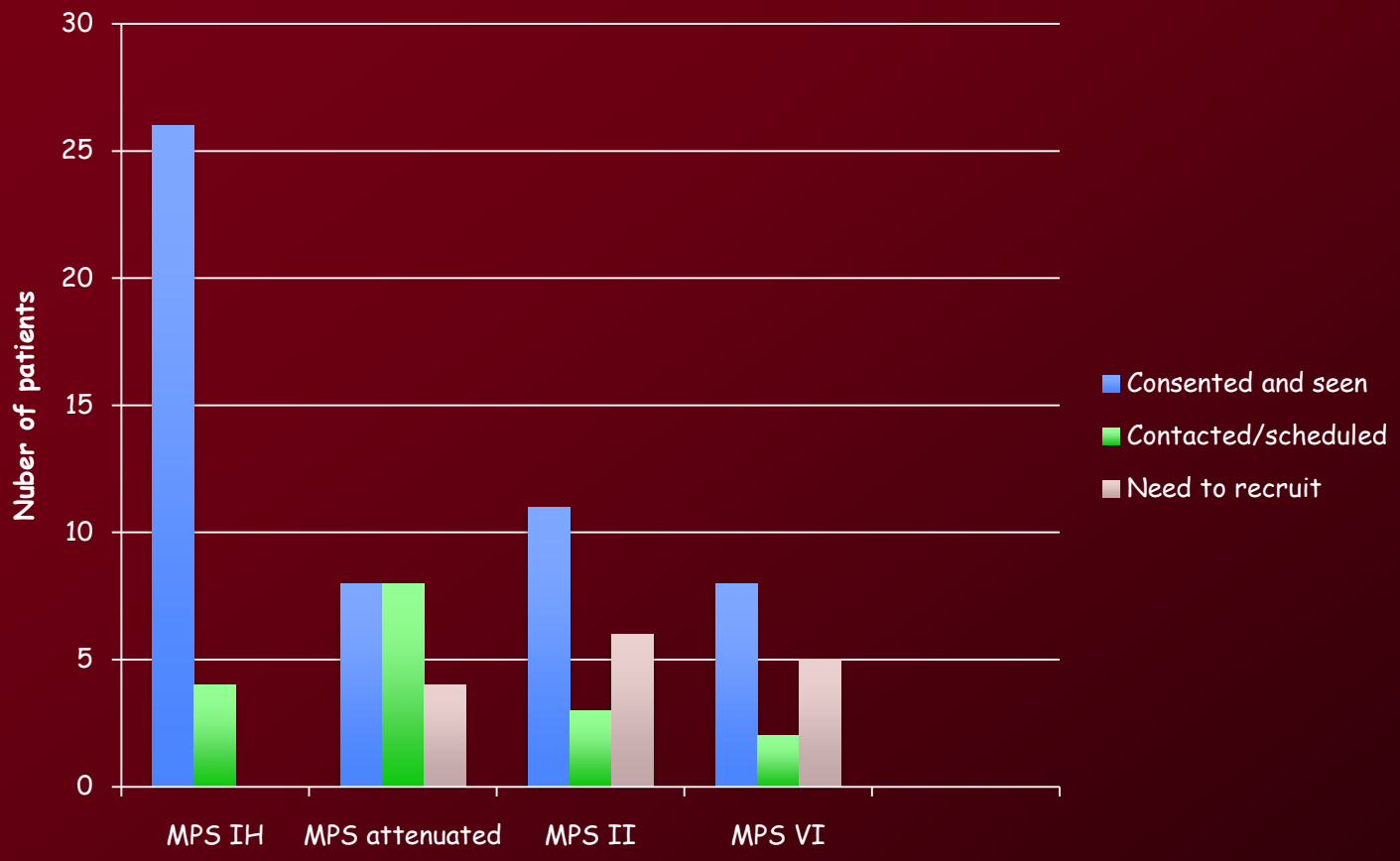
Minnesota*

Boston Children's
Emory
NYU
Oregon Health Science Univ.*
Oakland Children's*
Toronto: Hospital for Sick Children*
Utah

*activated

- Centers can be added if they have the resources to perform these studies (Siemans 3T Trio scanner) and NP testing
- Other centers can collaborate in data collection.

Recruitment for MPS Longitudinal Study as of September 30, 2010

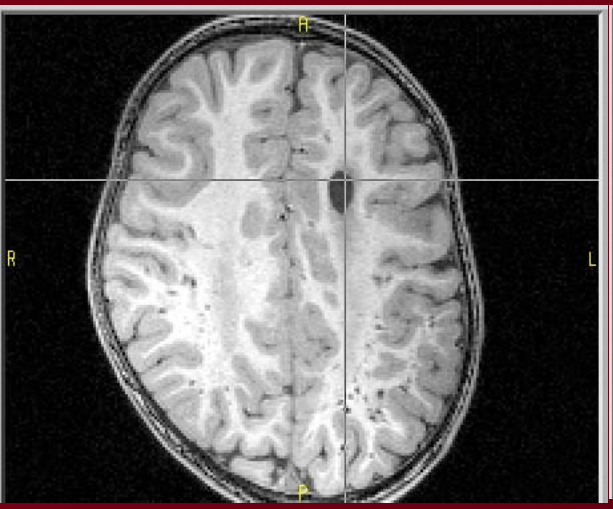


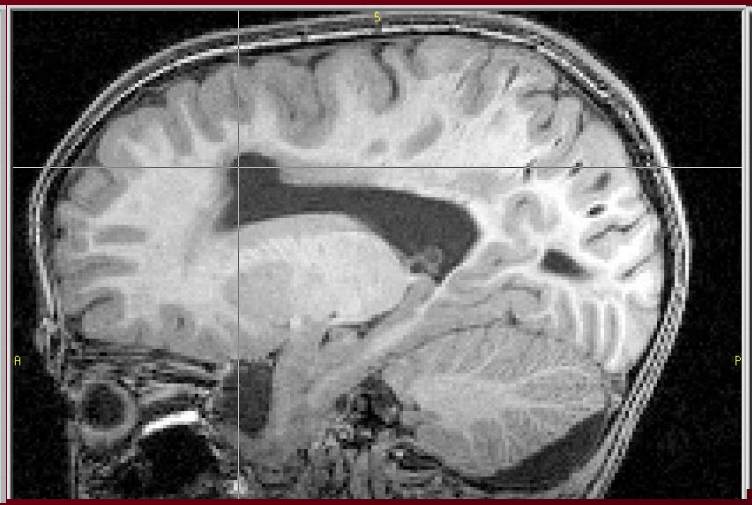
Participants recruited and data collected as of 9/30/10

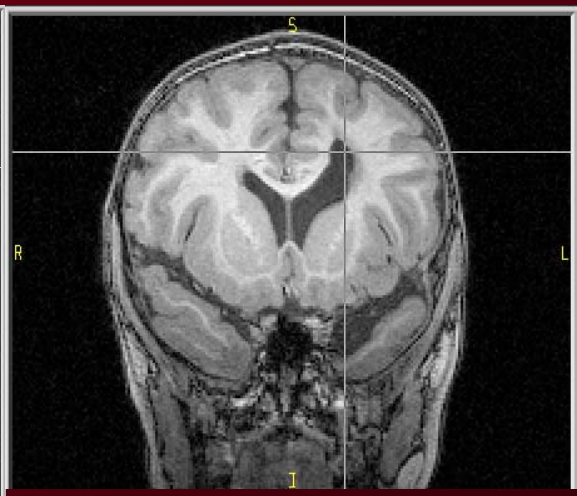
Diagnosis	N	Median Age	Mean IQ	Treatment
MPS I H	26	6.6	75	3 pre-HCT , 1 ERT, 12 HCTonly, 10 HCT+ERT
MPS I attenuated	8	13.9	94	ERT - all
MPS II	11	10.9	93	ERT - all
MPS VI	8	16.8	103	4 HCT, 2 ERT+ 2failed HCT
Total	53	10.2	85	

CORRELATION OF FUNCTION WITH CLINICAL SCANS IS POOR

7 year old boy with MPS II





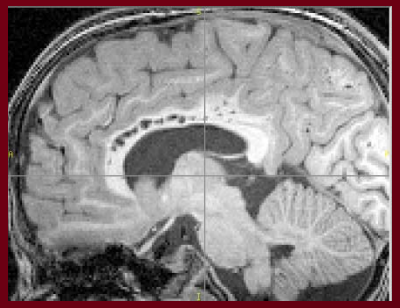


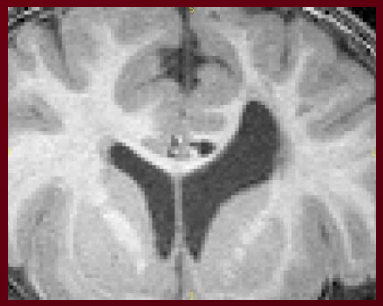
IQ = 128
No cognitive abnormalities

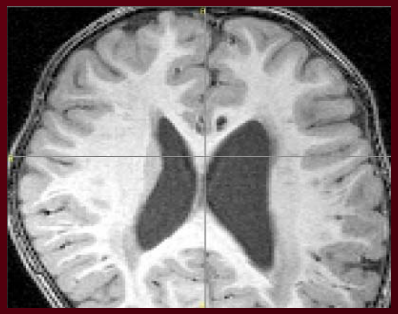
CORRELATION OF FUNCTION WITH CLINICAL SCANS IS POOR

Image Examples- MPS II

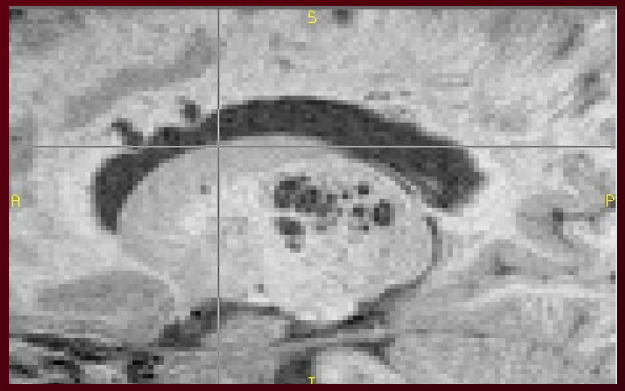
Abnormal appearance of a brain of a 7 ear old MPS II patient who has an IQ of 128

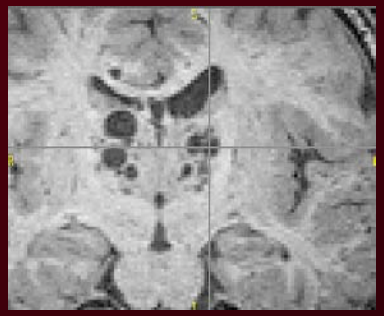






Virchow Robin spaces in thalamus; this 8 year old MPS II patient has an IQ of 93





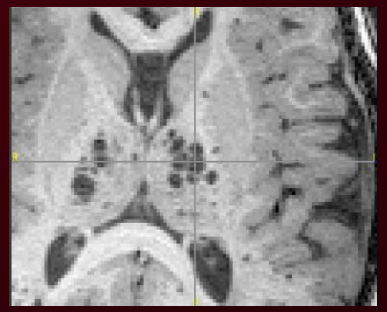


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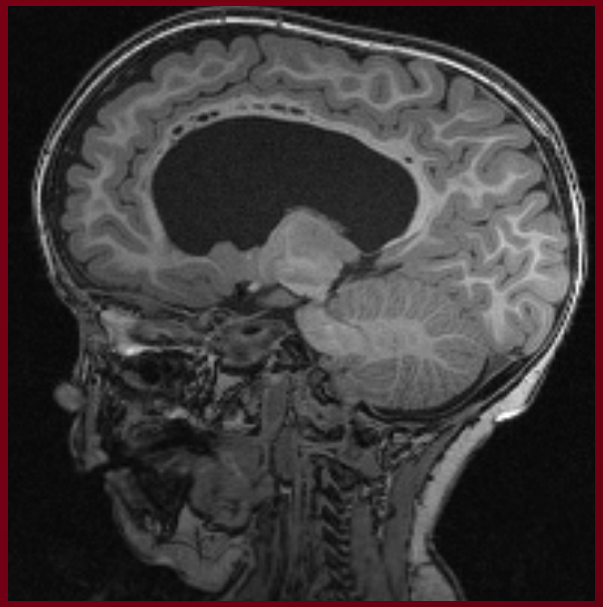
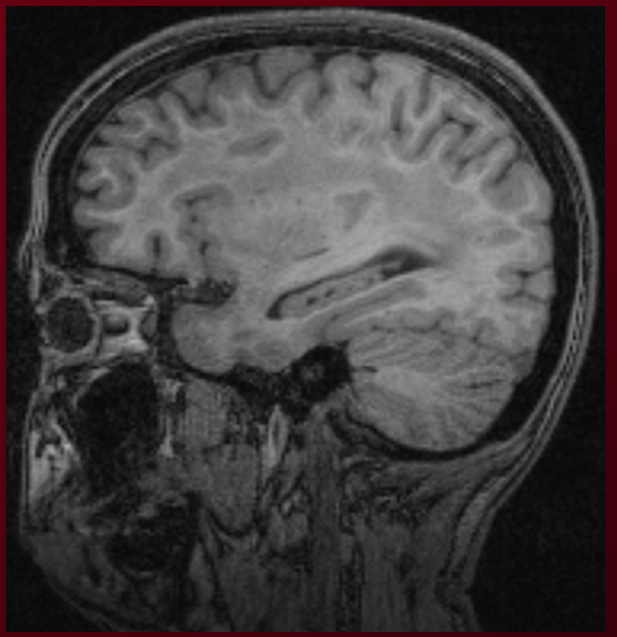
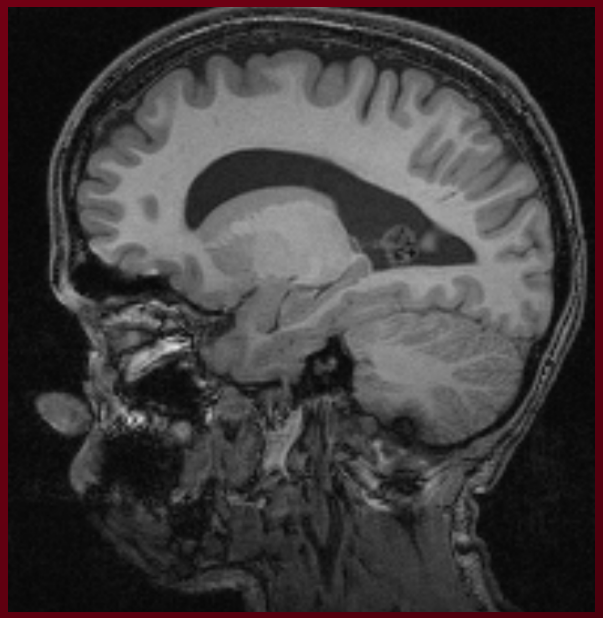
Image Examples- MPS I



2.5 year-old girl with MPSIH. Early HCT.
All cognitive functions average,





14 year-old boy with MPSIH. Early HCT.
Cognitive, memory, attention low average, visual spatial below average,
.

16 year-old girl with MPSIA.
Cognitive, visual spatial, memory (long and short term) impaired (attention test – unable to do.

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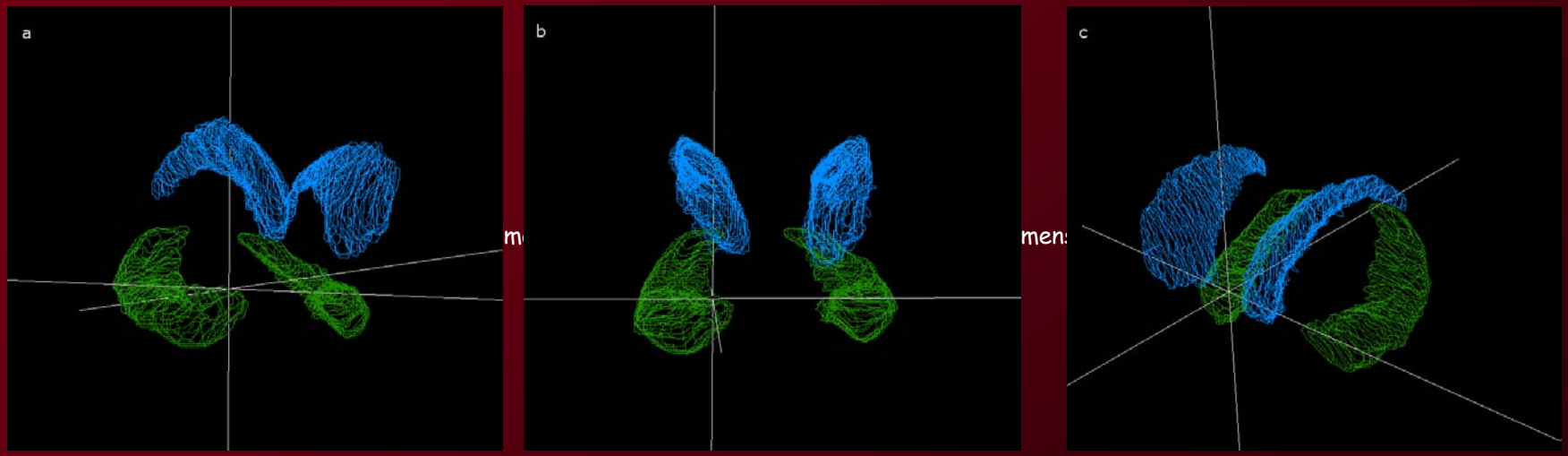
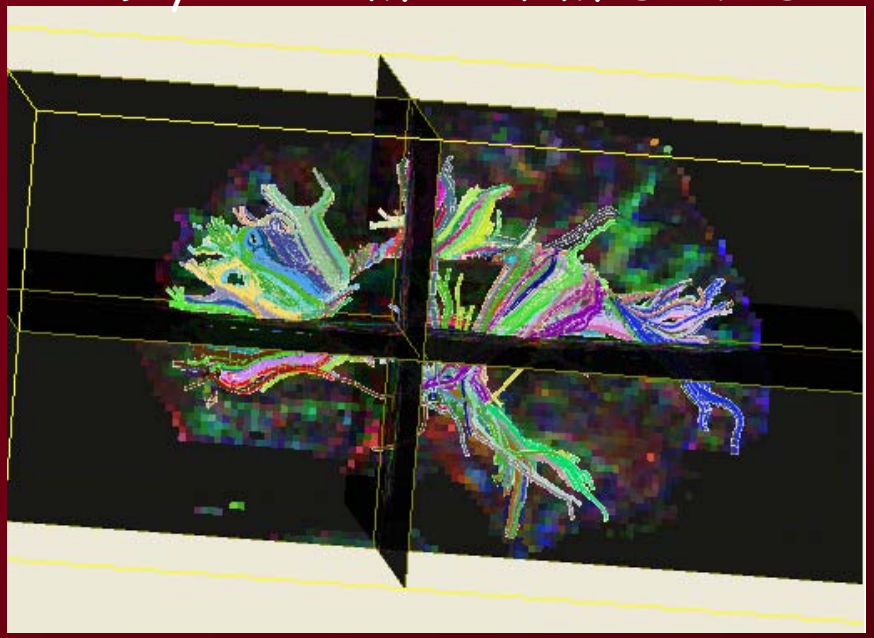
Imaging of hippocampus and caudate in three dimensions

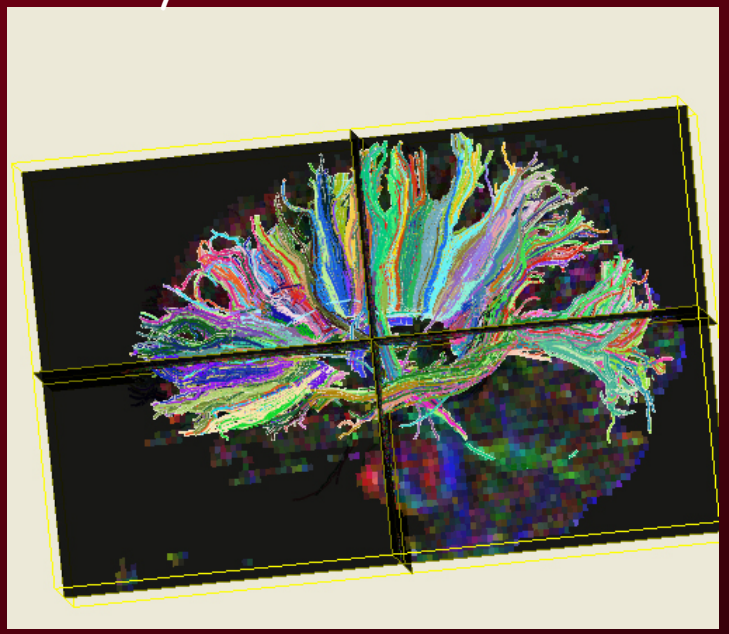


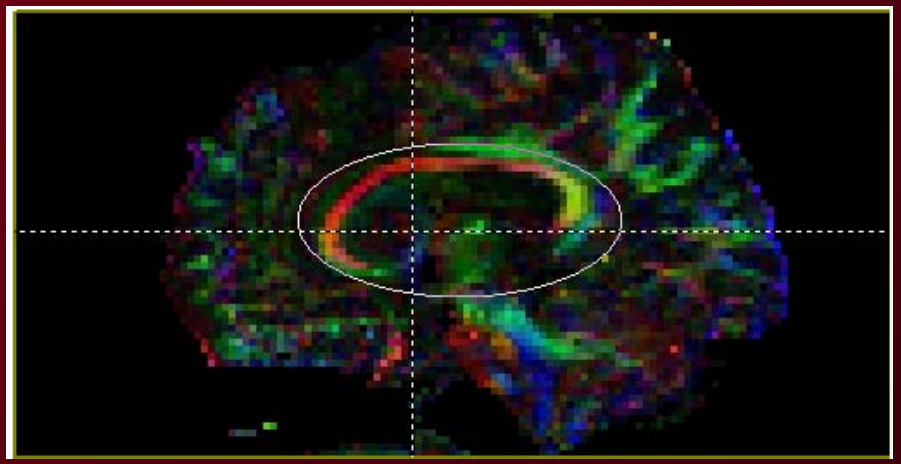
Fiber tracking: region of interest over the corpus callosum

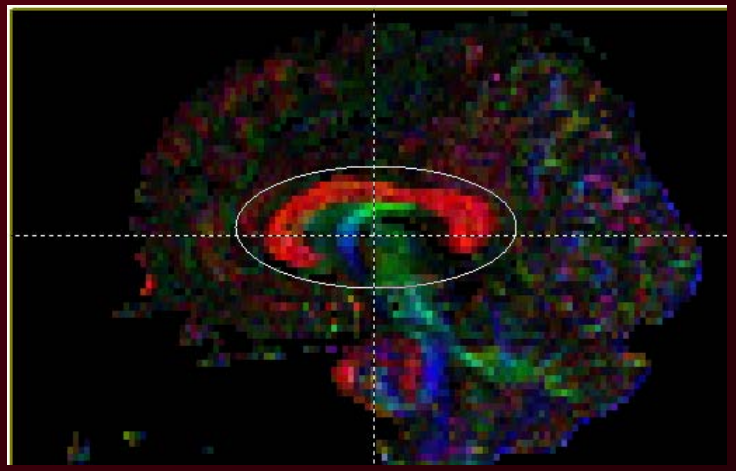
9-year-old Male w/ MPS I H-S



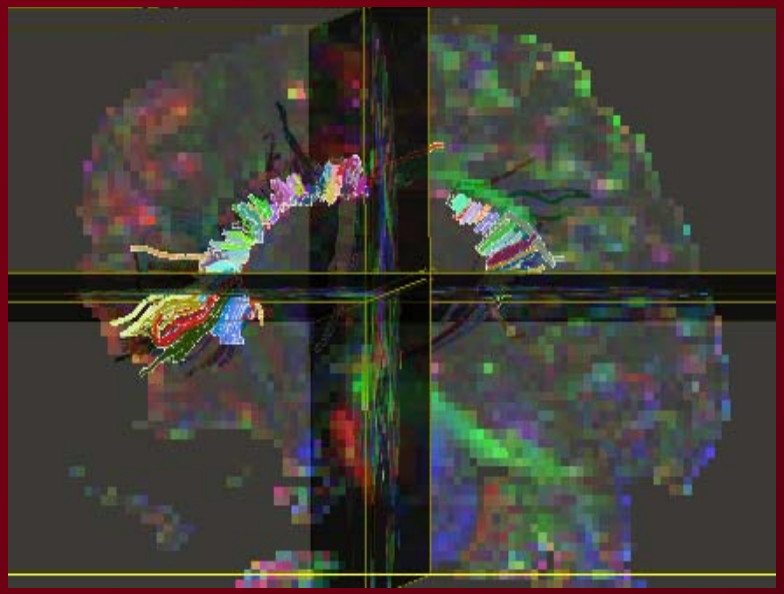
9-year-old Male Control

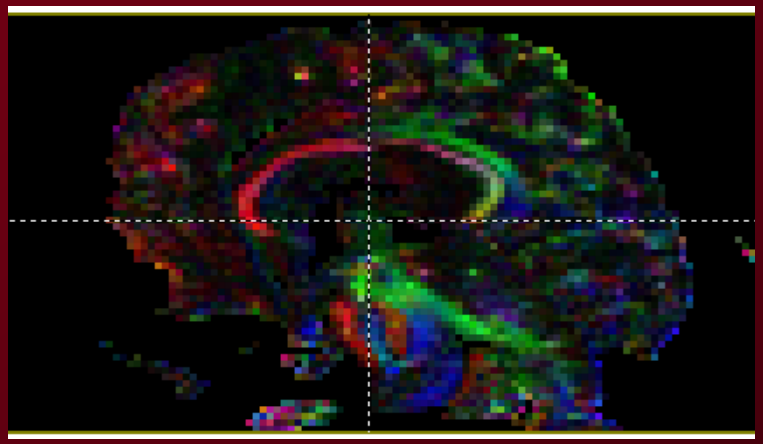




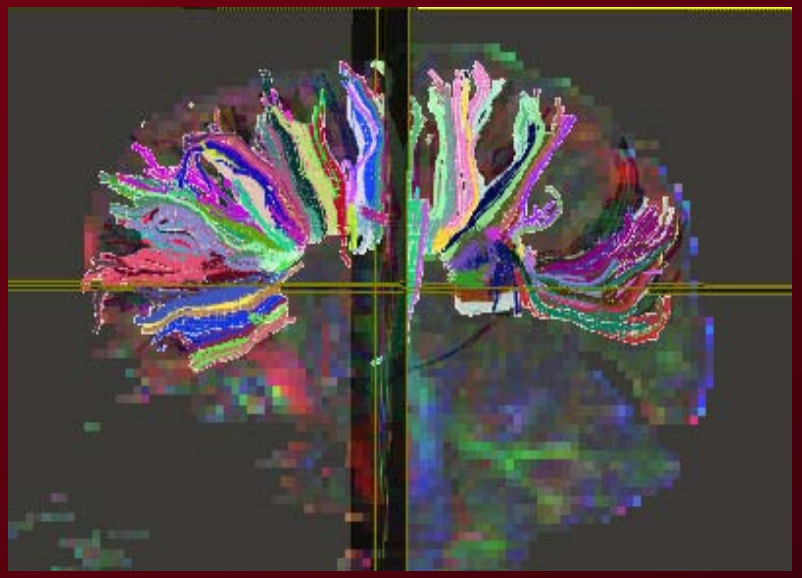


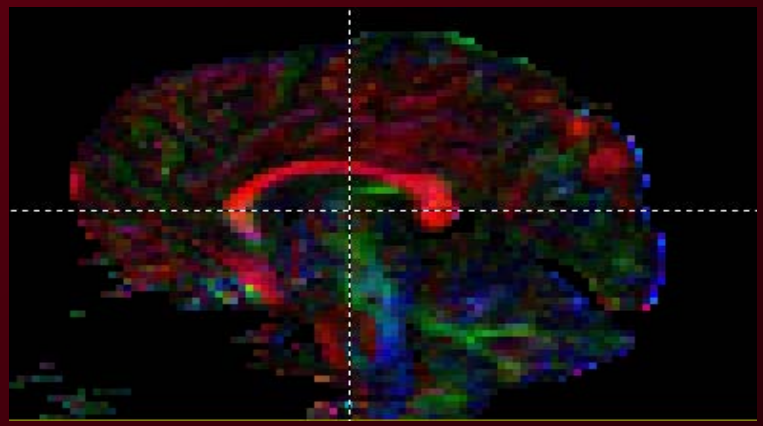
10 yr female $MPSI_{sev}$





10 yr female control





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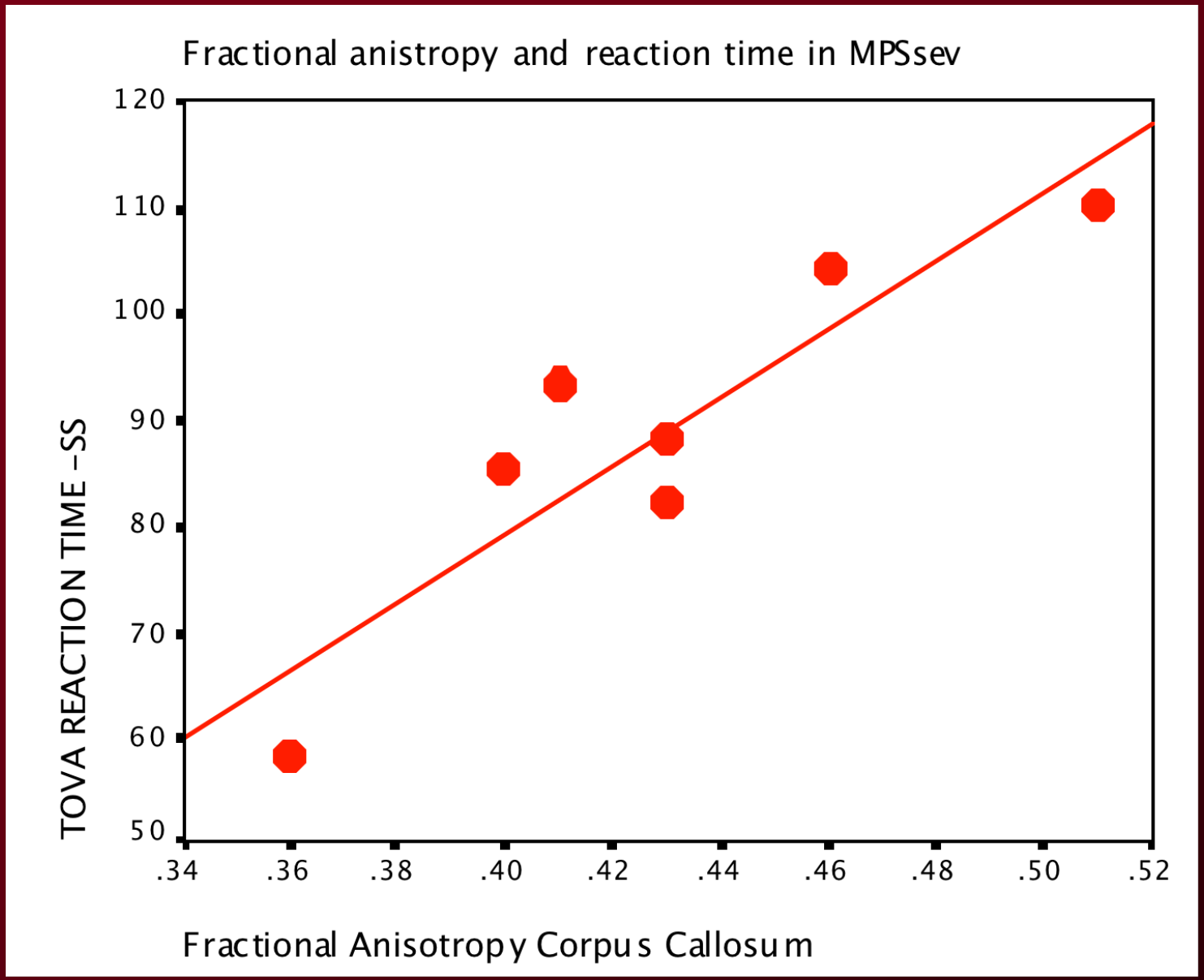
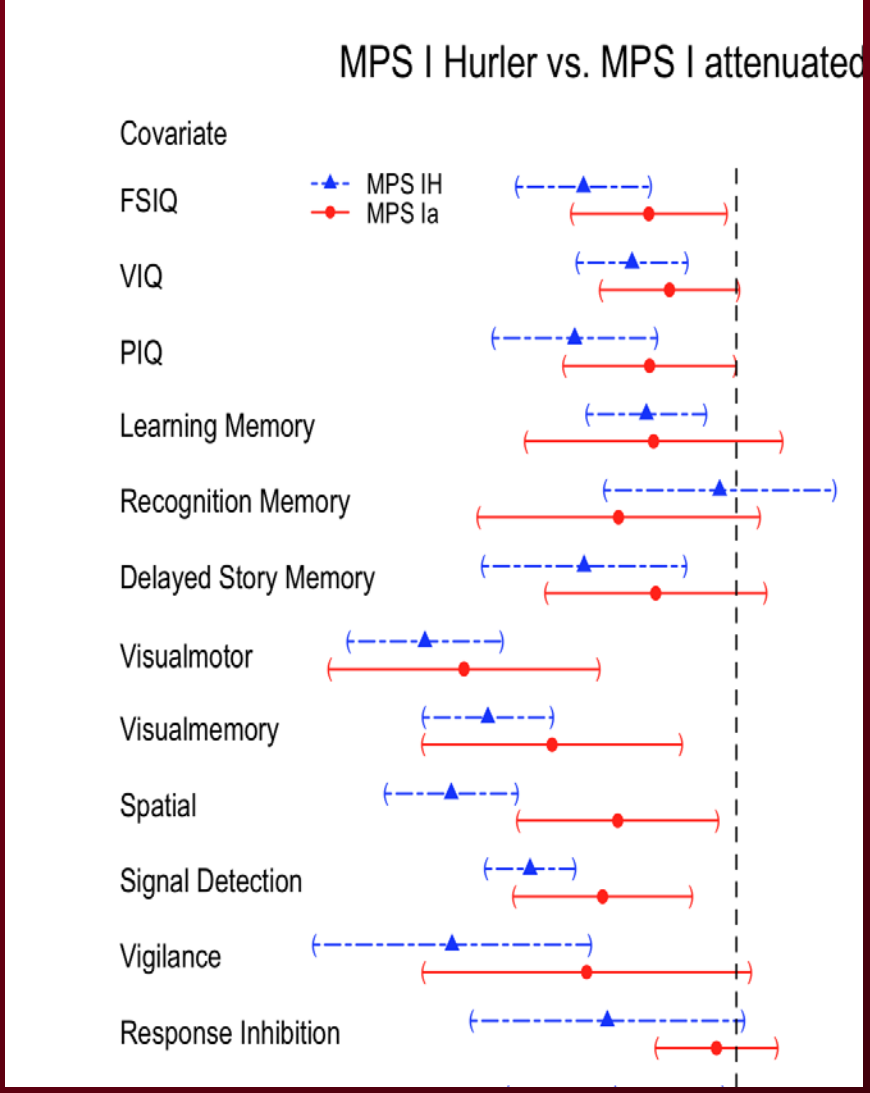
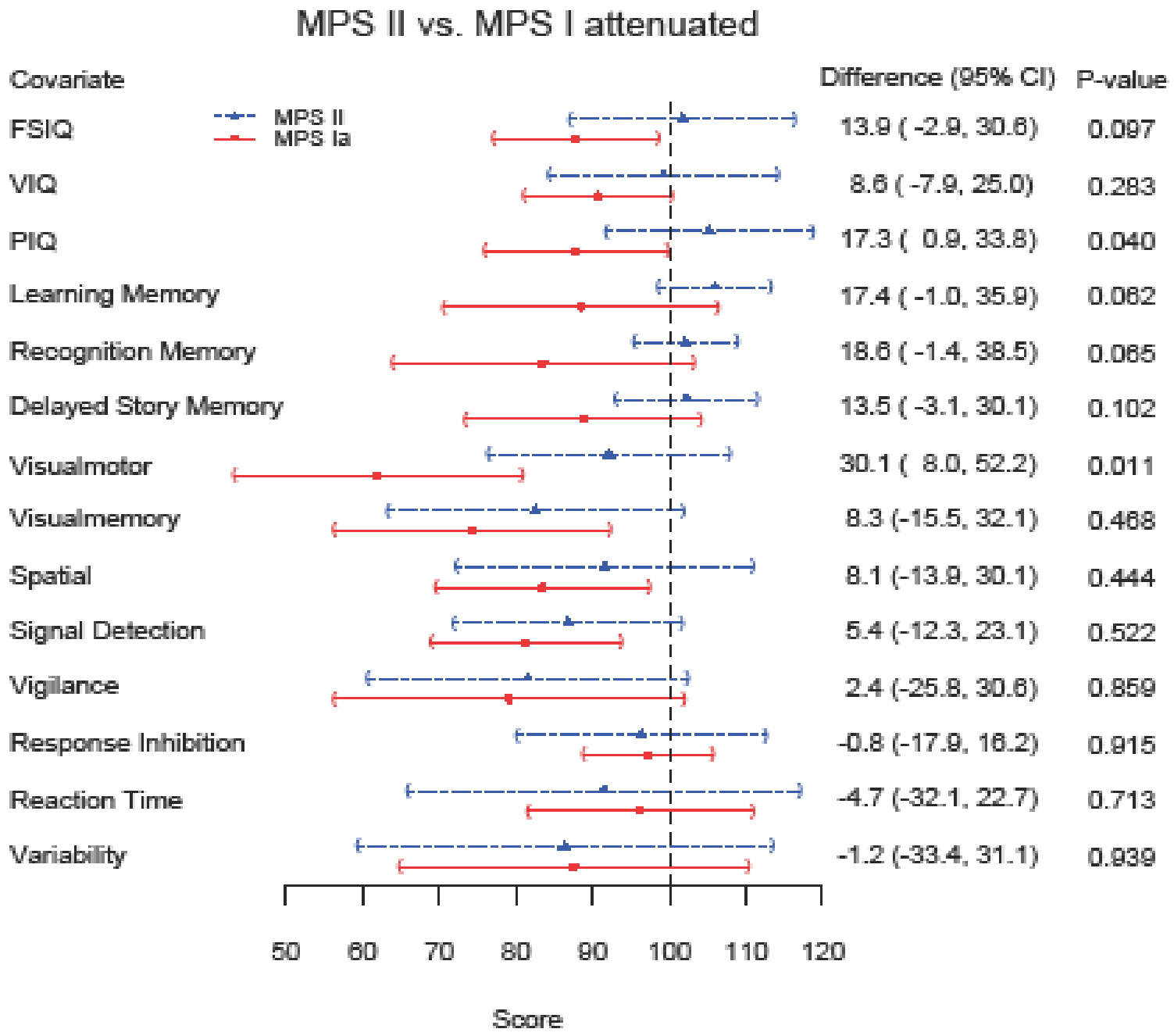

Fractional anistropy and reaction time in MPSsev
TOVA REACTION TIME –SS
120
110
100
90
80
70
60
50
.34
.36
.38
.40
.42
.44
.46
.48
.50
.52
Fractional Anisotropy Corpus Callosum


MPS I Hurler vs. MPS I attenuated
Covariate
MPS IH
MPS Ia
FSIQ
VIQ
PIQ
Learning Memory
Recognition Memory
Delayed Story Memory
Visualmotor
Visualmemory
Spatial
Signal Detection
Vigilance
Response Inhibition


MPS II vs. MPS I attenuated
Covariate
Difference (95% CI)
P-value
MPS II
MPS Ia
FSIQ
13.9 (-2.9, 30.6)
0.097
VIQ
8.6 (-7.9, 25.0)
0.283
PIQ
17.3 (0.9, 33.8)
0.040
Learning Memory
17.4 (-1.0, 35.9)
0.062
Recognition Memory
18.6 (-1.4, 38.5)
0.065
Delayed Story Memory
13.5 (-3.1, 30.1)
0.102
Visualmotor
30.1 (8.0, 52.2)
0.011
Visualmemory
8.3 (-15.5, 32.1)
0.468
Spatial
8.1 (-13.9, 30.1)
0.444
Signal Detection
5.4 (-12.3, 23.1)
0.522
Vigilance
2.4 (-25.8, 30.6)
0.859
Response Inhibition
-0.8 (-17.9, 16.2)
0.915
Reaction Time
-4.7 (-32.1, 22.7)
0.713
Variability
-1.2 (-33.4, 31.1)
0.939
50
60
70
80
90
100
110
120
Score

Initial studies have shown…

- **Cognitive abnormalities were found in all MPS I subjects, not just MPS IH (Hurler syndrome).**
- **Hippocampus volume may be a key site of neuropathology in MPS I associated with learning/memory impairments.**
- **White matter tract organization is affected in MPS I with MPS IH more impaired.**
- **MPS IH is associated with poor attention and processing skills.**
- ***Lower callosal FA in MPS IH likely results from HCT treatment (chemotherapy).***

Thanks to

- Kate Delaney – project coordinator/psychometrist
- Igor Nestrasil – imaging
- Alia Ahmed – Imaging
- Julie Eisengart – neuropsychological testing
- Rich Ziegler – neuropsychological testing
- Chet Whitley – PI LDN
- Brenda Diethelm-Okita – IRB/administration

and these centers…..

- Center for Neurobehavioral Development
- Center for Magnetic Resonance Research
- Clinical and Translational Science Institute
- Fairview University Imaging Center
- Minnesota Supercomputer Center