

Pilot studies and cross-sectional studies; how they inform natural history studies

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- Longitudinal Studies of Brain Structure and Function in MPS Disorders
E. Shapiro, P.I.
 - Lysosomal Disease Network U54NS065768
C. Whitley P.I. E. Shapiro, Co- P.I.
Also funded by Genzyme, ShireHGT, Biomarin, National MPS Society,
and Ryan Foundation.
 - Characterizing the Neurobehavioral Phenotypes in MPS III
M. Potegal, P.I., E. Shapiro, Co-P.I.
 - Lysosomal Disease Network
 - Shire Human Genetic Therapies
 - A 12-month Longitudinal, Prospective, Observational, Natural History
Study of Patients with Sanfilippo Syndrome Type A (MPS IIIA)
C. Whitley P.I., E. Shapiro, Co-P.I.
 - Shire Human Genetic Therapies

Value of pilot studies

- Pilot studies are
 - small scale (small N) preliminary studies to plan for natural history/longitudinal study
 - feasibility
 - measurement development
 - recruitment potential
 - time and costs
 - possible adverse events
 - effect size to determine size of sample
 - effect of age/developmental stage
- Pilot subjects usually not included in the larger longitudinal study
 - unrealistic in studies of rare diseases.
 - consider the effect of having a subject in a pilot study who is also in the larger research study

Value of cross-sectional studies

- Large single visit study
 - Stand alone study or associated with a natural history study
 - Baseline visit of a natural history study
- Ns usually larger than a pilot study
- Goals and results may be broader
 - Developing expertise
 - More fully developing a measure
 - Exploring a specific hypothesis
 - Validating a scoring system or other quantification
 - Identifying range of phenotypes by age at diagnosis and assessment
 - Identifying variables that may be important that were initially overlooked



Example-Lysosomal Disease Network study: 'Longitudinal Studies of Brain structure and function in MPS disorders'

- Pilot study to develop protocol to study brain
- MPS I, II, and VI: All patients now are treated
- Too late for a natural history study
- But we don't know about the evolution of brain disease in these patients
- Enzyme replacement does not affect the brain. Do we need to find better treatments of the brain?

Pilot Study

Brain structure and function in MPS disorders

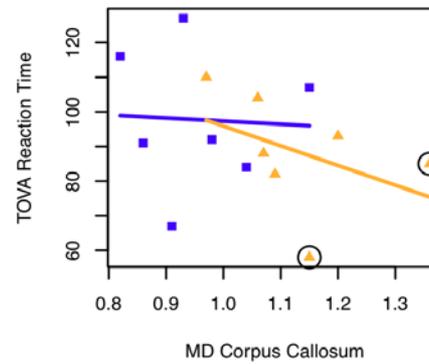
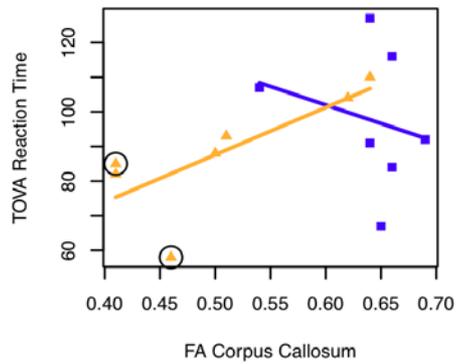
10 subjects with MPS I (attenuated forms) and 10 with MPS IH –

methods: neuropsychological tests of IQ, memory, attention, spatial ability; hippocampal volumes; diffusion tensor imaging

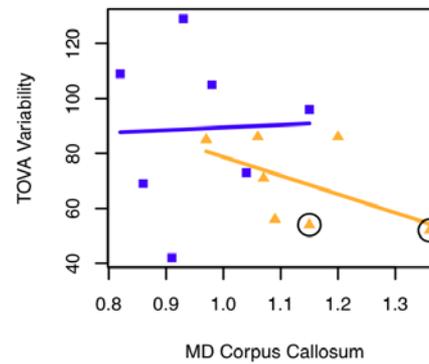
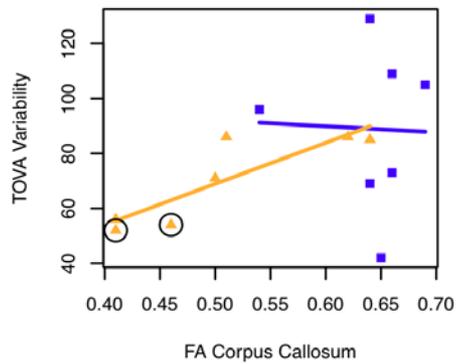
What was gained?

- **Developed expertise**
 - We began with Image J for manual tracing and evolved to Brains2. At the end of the pilot we demonstrated expertise and this expertise has spread to our ShireHGT sponsored natural history study as well.
- **Feasibility, ease of recruitment, time and measures**
 - Found that doing neuropsych and imaging could be done in one day
 - Had no trouble recruiting participants even though no benefit
 - Determined that imaging and neuropsych measures were appropriate
- **Results and unforeseen events**
 - Small sample gave misleading results on some variables- Image J
 - We found in the cross sectional first year study that Brains 2 is a better program
 - Problems with practice effects
 - Needed to change to measures with alternate forms
 - Upgrade in scanner after 7 participants in each group. Could only use 7 out of 10 participants in each group for DTI analysis.
- **Scientific results were strikingly different between our two groups**

Significant results from pilot study even with an N of 7



■ MPS IA
▲ MPS IH



Baseline - Cross sectional Study

(Longitudinal Studies of Brain Structure and Function in MPS Disorders)

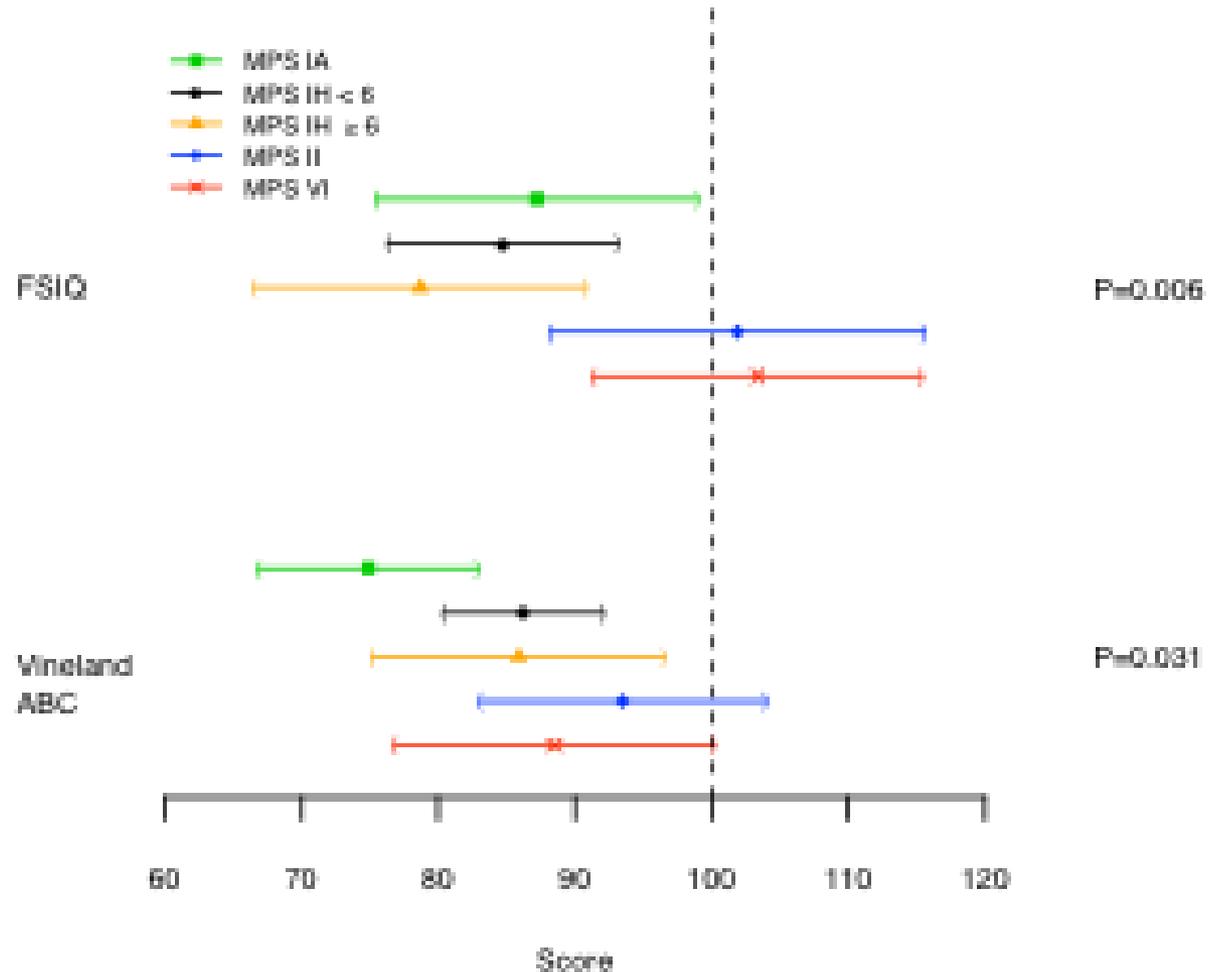
What was gained?

- Baseline results adjust and hone the measures
 - Multicenter study raises new problems
 - Quality control and training of sites
 - MRI comparability is an issue; developed techniques for statistical analysis
 - After enrolling 100 patients with MPS disorders new mid-study questions have emerged....
 - Emotional/behavioral abnormalities need more intense study
 - DNA mutation data assumes more important in outcome – needed to raise funds to do that
 - Problems of orthodontic braces, programmable shunts, and cochlear implants emerged, preventing acquisition of MRI data
 - All patients are treated with either HCT or enzyme; handling this requires stratifying by treatment and years since starting treatment.
- Surprising findings
 - MPS I and MPS VI patients who have undergone HCT compared to those on enzyme have decreased brain size but equivalent IQ. Storage material in brain? How can we pursue this? Resting fMRI?
 - Adaptive skills in attenuated MPS I surprisingly low? Related to age at first treatment? Or disease severity (age of onset)?
 - Complex relationship of hippocampal size and memory in MPS patients which needs to be teased apart

Cross sectional data – baseline

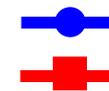
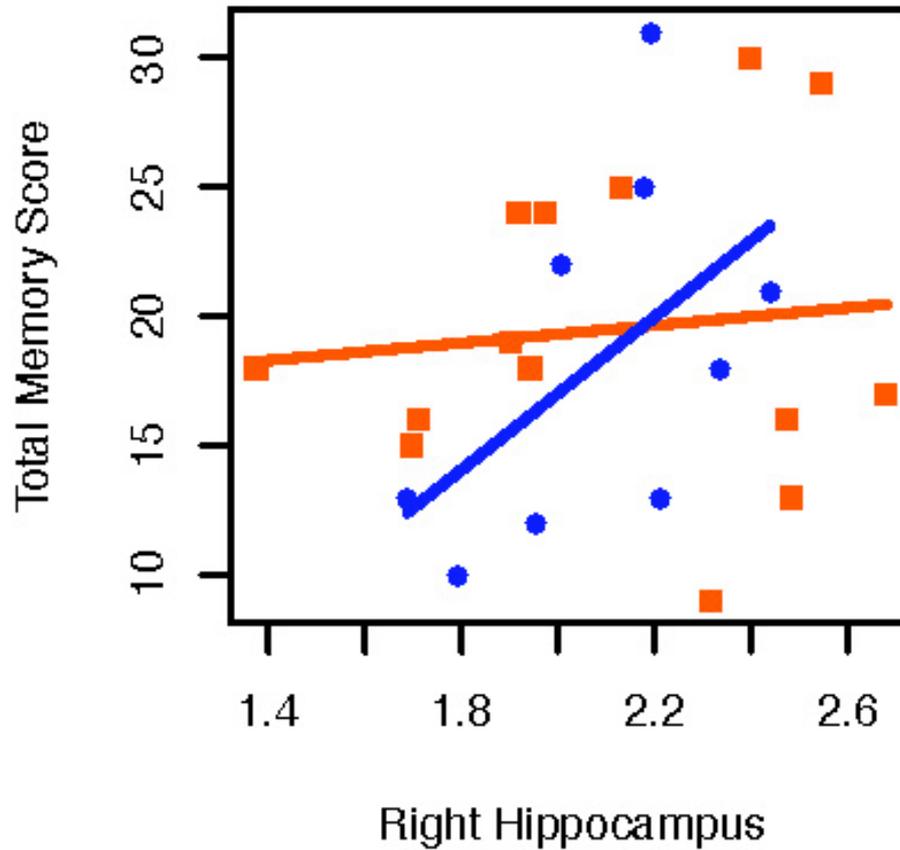
Surprising result - poor adaptive skills in the attenuated forms of MPS I

MPS IA, MPS IH, MPS II, MPS VI



Hippocampus and memory in MPS I

Why is there a relationship in MPS IH and not in attenuated patients?



MPS IH n=9
MPS IA n=14



ShireHGT sponsored study ‘A 12-month Longitudinal, Prospective, Observational, Natural History Study of Patients with Sanfilippo Syndrome Type A (MPS IIIA)’

- Pilot Study: Development of disease-specific behavior rating scale
- Associated cross-sectional study: (sponsored by the Lysosomal Disease Network and ShireHGT) to explore the behavioral phenotype
- Baseline cross-sectional study: What has it taught us?

Pilot study

Development of a Disease-specific Behavioral Scale in Sanfilippo Type A

- Sanfilippo syndrome is associated with very abnormal behavior, not well characterized.
- Observations of children and clinical descriptions led us to think they might have a Klüver-Bucy-like syndrome.
 - Developed a disease specific scale from observations, from clinician input, and from the literature.
 - First iteration of this scale sent to 50 parents of patients with MPS III anonymously through the National MPS Society.
- We chose 10 patients to interview and walk through the scale for us to hone and improve it.

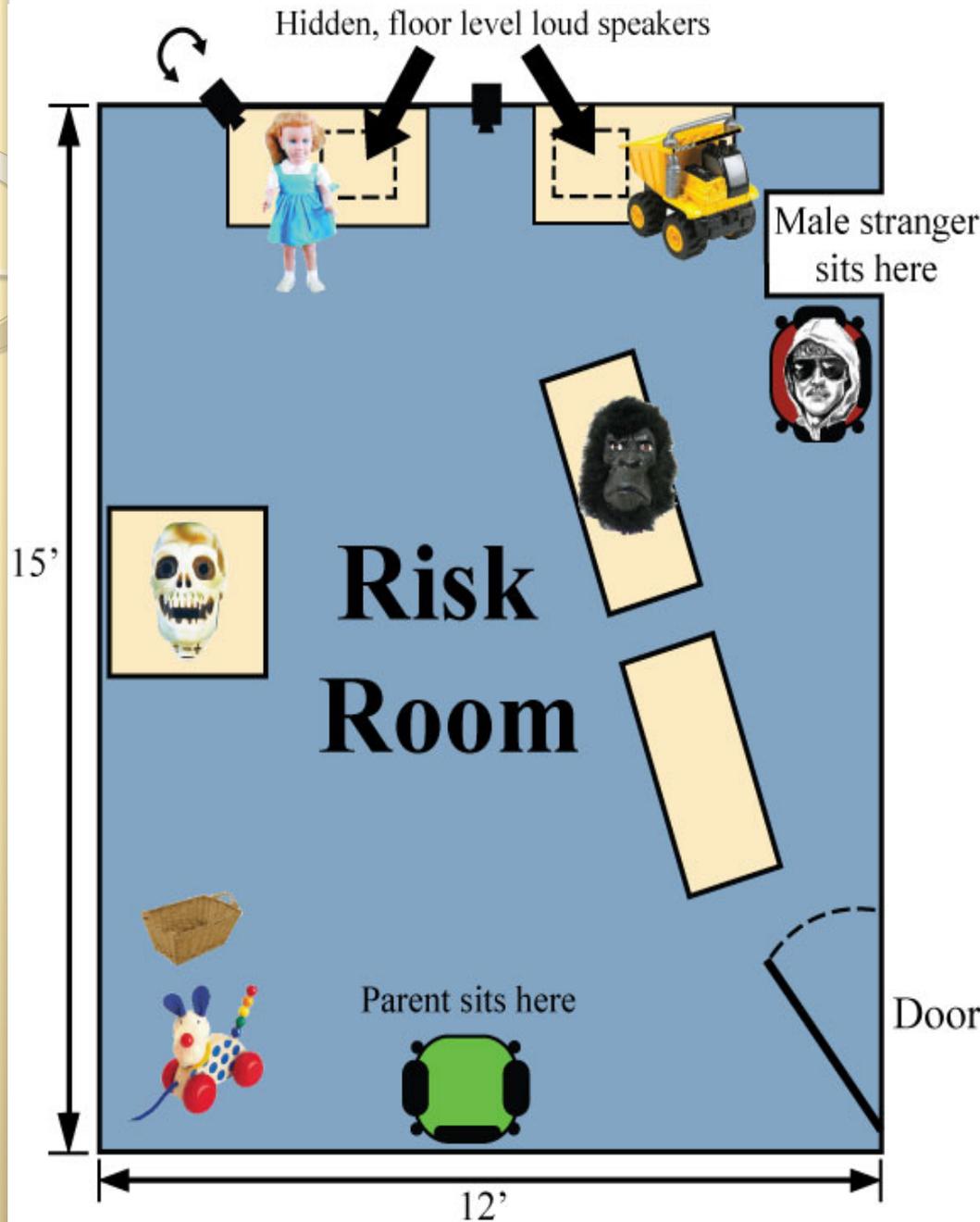
What was gained?

- Now used in the MPS III A Natural History Study; and although it is still being refined, it has proven useful in corroborating our observations of specific behaviors in MPS III and especially the Klüver Bucy-like symptoms.



Cross sectional study associated with Natural History Study Characterizing Neurobehavioral Phenotypes of Sanfilippo syndrome

- At baseline visit of the natural history study we carried out associated cross-sectional study:
 - we examined the Klüver-Bucy-like behaviors in a behavioral laboratory setting- we compared the MPS IIIA to MPS I Hurler patients
 - we examined fear, startle response, activity level , and social reciprocity in this 10 minute ‘risk room’ paradigm.
 - We also examined ‘autistic’ like symptoms using a standard autism measure, the ADOS.



Phases:

1. Exploration

(≤ 10 minutes)

locomotion, mask contact

2. Startle

(3 90dB sounds)

whole body response

3. Attachment

(30 sec departure)

response to parent's return

4. Compliance (≤ 5 trials)

1 item clean-up demand

Behavioral Results “Risk Room” (diagnosed under age 6 data only)

Covariate	MPS I	MPS III (Diagnosed < 6 yrs)	
	(N=8) Estimate (95% CI)	(N=22) Estimate (95% CI)	P-value*
Locomotion Move-away Latency (sec)	161.7 (-76.2, 399.5)	43.8 (3.7, 83.9)	0.263
Locomotion Percent Time	10.0 (-2.3, 22.3)	57.2 (41.8, 72.6)	<0.001
Next to Mother Percent Time	71.5 (41.7, 101.3)	34.3 (20.2, 48.5)	0.022
Touch Mask (%)	0.0 (0.0, 48.3)	68.2 (45.1, 85.3)	0.012
Approach Stranger (%)	83.3 (36.5, 99.1)	40.9 (21.5, 63.3)	0.167
Startle (%)	75.0 (35.6, 95.5)	22.7 (8.7, 45.8)	0.028
Hold/return to Trigger Toy (%)	16.7 (0.9, 63.5)	80.0 (55.7, 93.4)	0.018
Reunion Score	3.7 (3.1, 4.2)	2.3 (1.8, 2.9)	<0.001
Clean-up Compliance (%)	87.5 (46.7, 99.3)	36.4 (18.0, 59.2)	0.039

* Comparison to MPS I group

Neurobehavioral study of Sanfilippo Syndrome

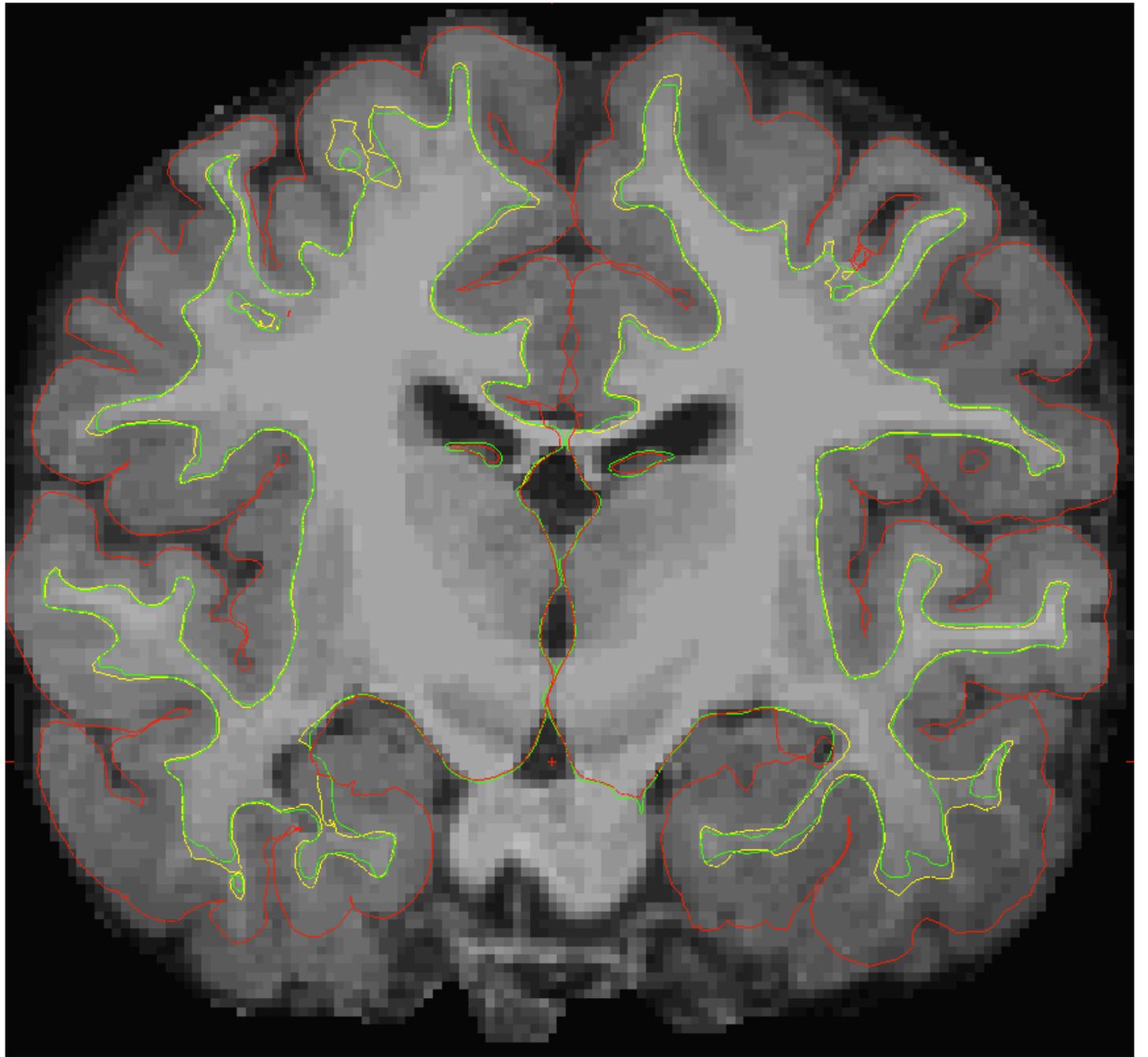
What was gained?

- Confirmed Klüver-Bucy – like syndrome
- Confirmed autism symptoms in middle stage of disease
- These findings suggested abnormalities might be localized to the amygdala. Preliminary evidence suggests that the amygdala may be a critical part of the brain in Sanfilippo syndrome. We are now examining percent change in amygdala volumes over time in the natural history study.
- Cross sectional studies can inform a natural history study

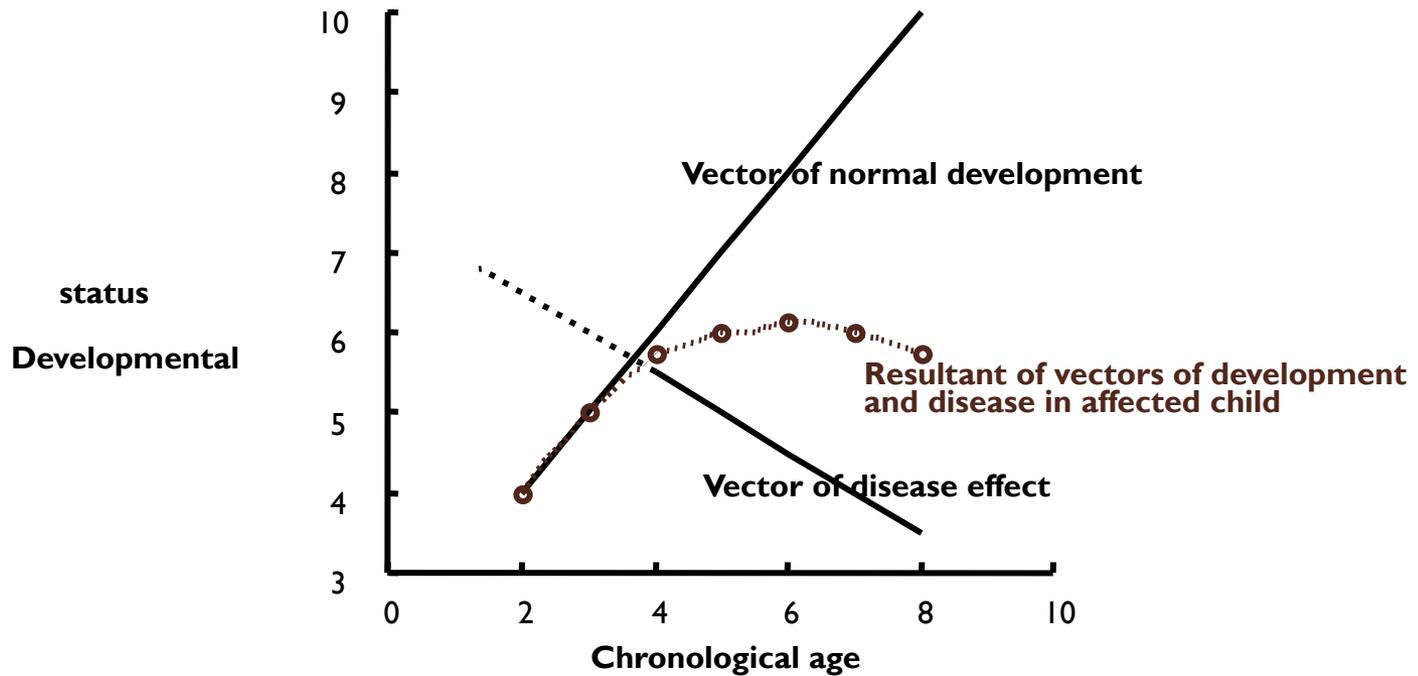
Cross-sectional study baseline of Sanfilippo A Natural History study

What was gained?

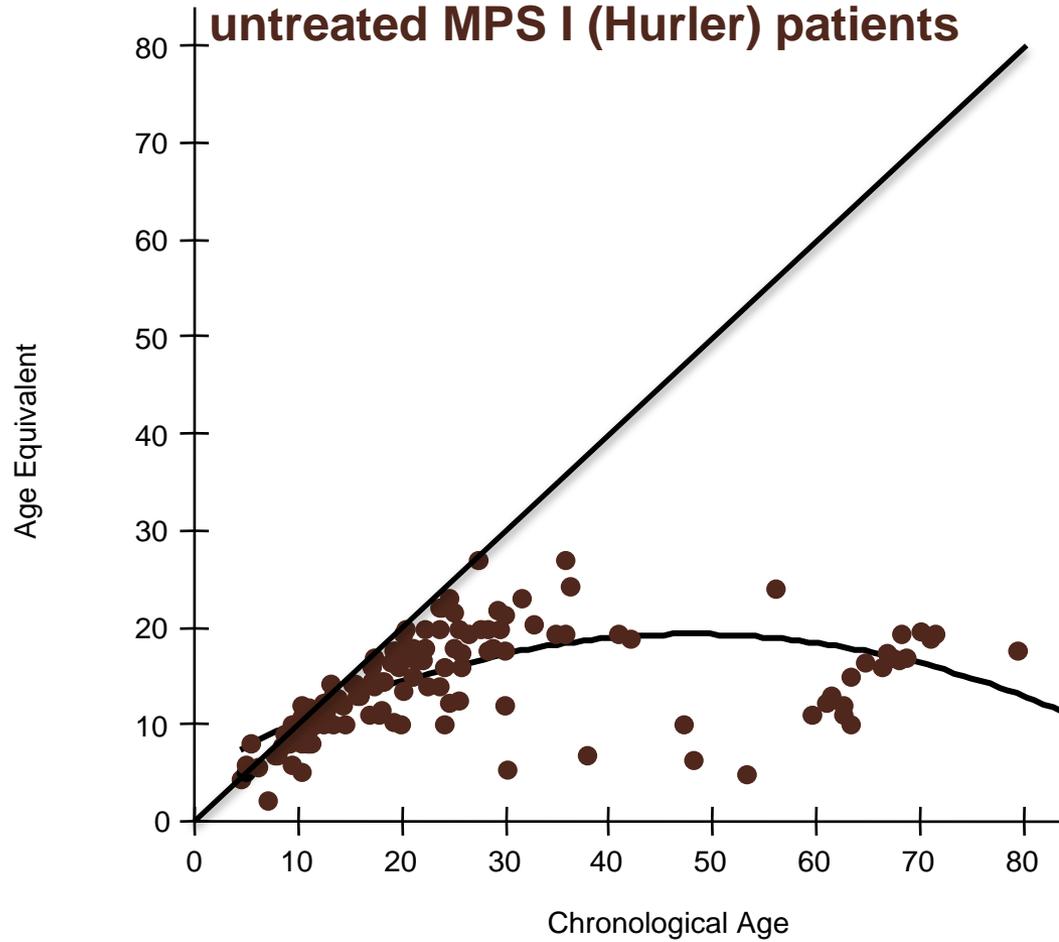
- Results of cross-sectional studies inform future directions
 - we found we could obtain accurate measurement of cognitive function in very impaired/demented children; validated methods
 - Initial cross sectional results provide a proxy for longitudinal study regarding rate of decline and association of brain volumes and cognitive functioning – now we now it works!
 - Unexpected findings
 - Ceiling of cognitive development in early diagnosed children- importance of developmental trajectory of the disease.
 - Unexpected challenges
 - Need to develop methods for gray-white delineation in younger children
 - Need to acquire control scans of typically developing children over one year period to determine a rate of change.



Hypothetical effects of disease and normal development on growth trajectory

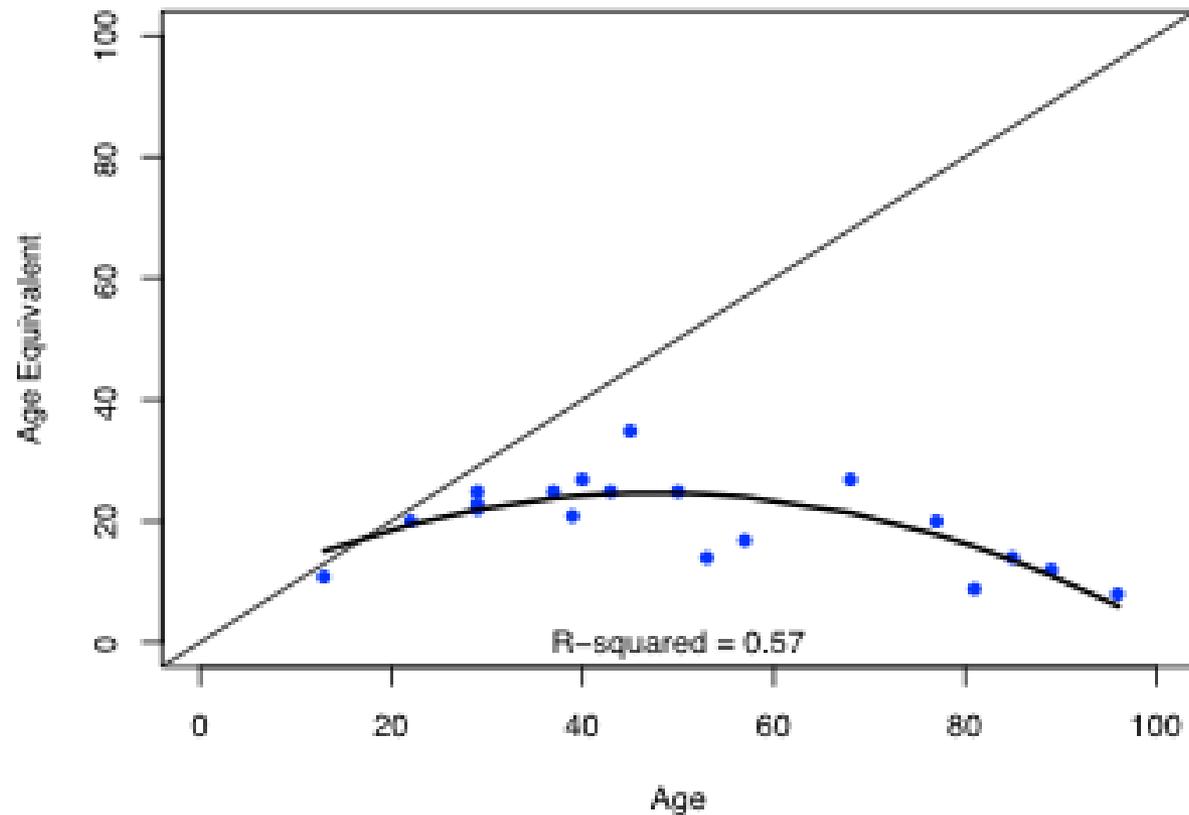


Age/Bayley and Mullen Age Equivalents for untreated MPS I (Hurler) patients



Unexpected finding

Children with classic form do not develop past a 3 year cognitive age equivalent.
Generates hypotheses about the neural basis of cognitive decline



Conclusions

Pilot and cross-sectional studies prior to a natural history study provides opportunity to

- Develop and validate of new measures and techniques; opportunity to test them for later natural history studies and clinical trials
- Provide feasibility information
- Develop expertise
- Provide recruitment potential
- Provide information about time and costs
- Possible obstacles to data acquisition
- Determine effect size to estimate size of sample needed
- Obtain significant new information especially the developmental growth trajectory
- Develop new hypotheses based on unexpected results