The Cerebra Centre for Neurodevelopmental Disorders

UNIVERSITY OF BIRMINGHAM

E·S·R·C ECONOMIC & SOCIAL RESEARCH COUNCIL

Assessing Cognition in metabolic disease

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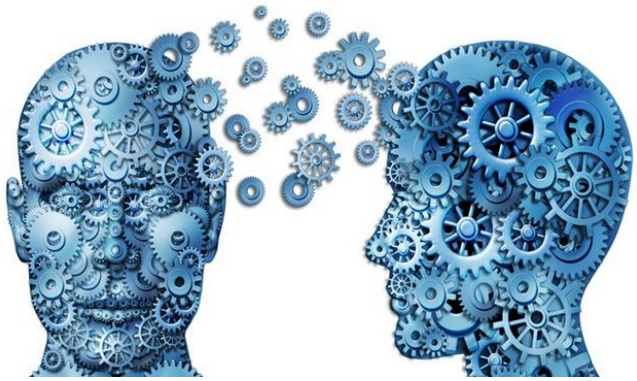
Why cognition?



- Important clinical sign
  - Treatment decisions can be influenced by when cognition is to be affected
- Important for a full understanding of behaviour
  - What are the challenges that individuals with disease are likely to face?
- Important for diagnosis, treatment decisions and disease tracking
- Theoretically important for understanding biochemical systems that support cognition

Methodological challenges

- What is the best way to assess neurodegenerative diseases?
  - Limited time with patients (need limited number of assessments)
  - Limited number of patients (need methods that work with small samples)
  - Moving target – neurodegenerative diseases in children must be assessed against capacities in controls that are changing

Two brief examples…

- Early signs -- Eye-movements in Niemann-Pick C

- Different profile of abilities affected in different diseases
  - Morquio (MPS-IVa)

  - Tyrosinemia Type III

Diseases

- Niemann-Pick C –
  - Lysosomal storage disorder that affects transport of cholesterol.
  - Infant, childhood and adult onset.
  - The earlier onset > more rapid progression
  - Currently treated with miglustat

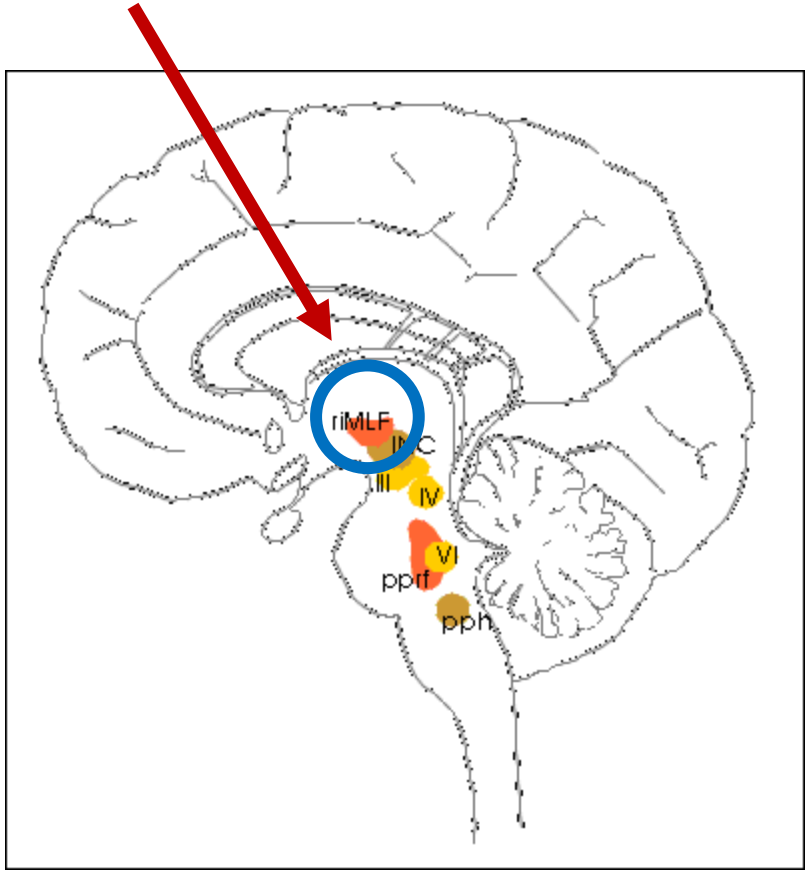
- Treatment: Miglustat – stabilizes disease, but not a cure
  - Expensive
  - Side effects

- Questions:
  - When is the best time to start treatment?
    - When cognitive effects are beginning
    - Before degeneration has gone too far
    - But not before it is needed.

  - How is treatment affecting disease progression?
    - Need sensitive measures

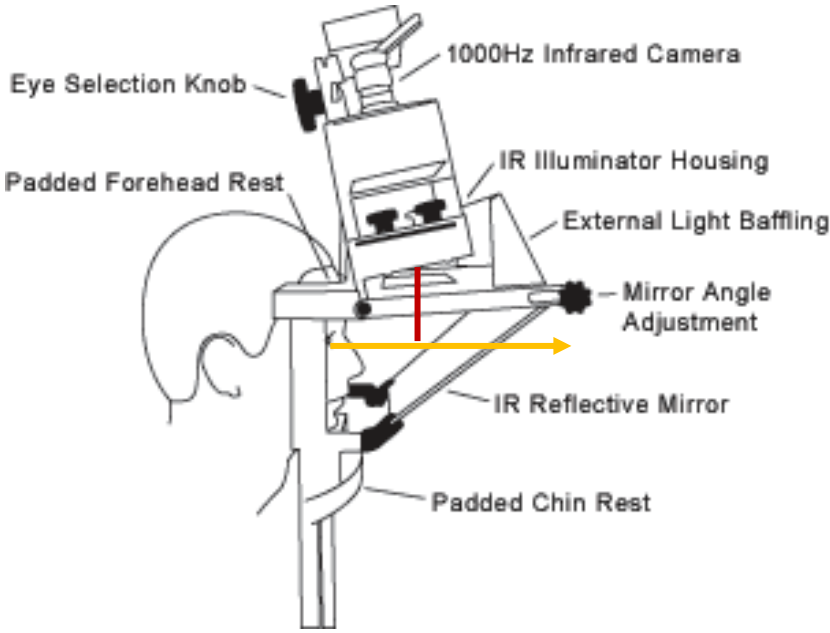
Eye movements in Niemann-Pick

- Characteristic sign: eye-movements slow and then stop
- Vertical movements affected before horizontal
- Caused by damage to very specific brain stem nuclei (riMLF, PPRF)
- Changes are *eventually* apparent in a bedside neurological exam



Can we detect changes earlier?

- Eye-tracking
  - Measure eye position 1000 times per second
  - Modern eye trackers make this feasible



Simple tasks

- Saccade – look at a target when it moves
- Fixation – keep looking at a target until it disappears (sustained attention)
- Memory guided saccade
  - Target flashes
  - DON'T LOOK
  - Remember where it was
  - On signal, look where target used to be
- Smooth pursuit
  - Follow a moving target around the screen

Two groups of patients

- Already on treatment
- Untreated

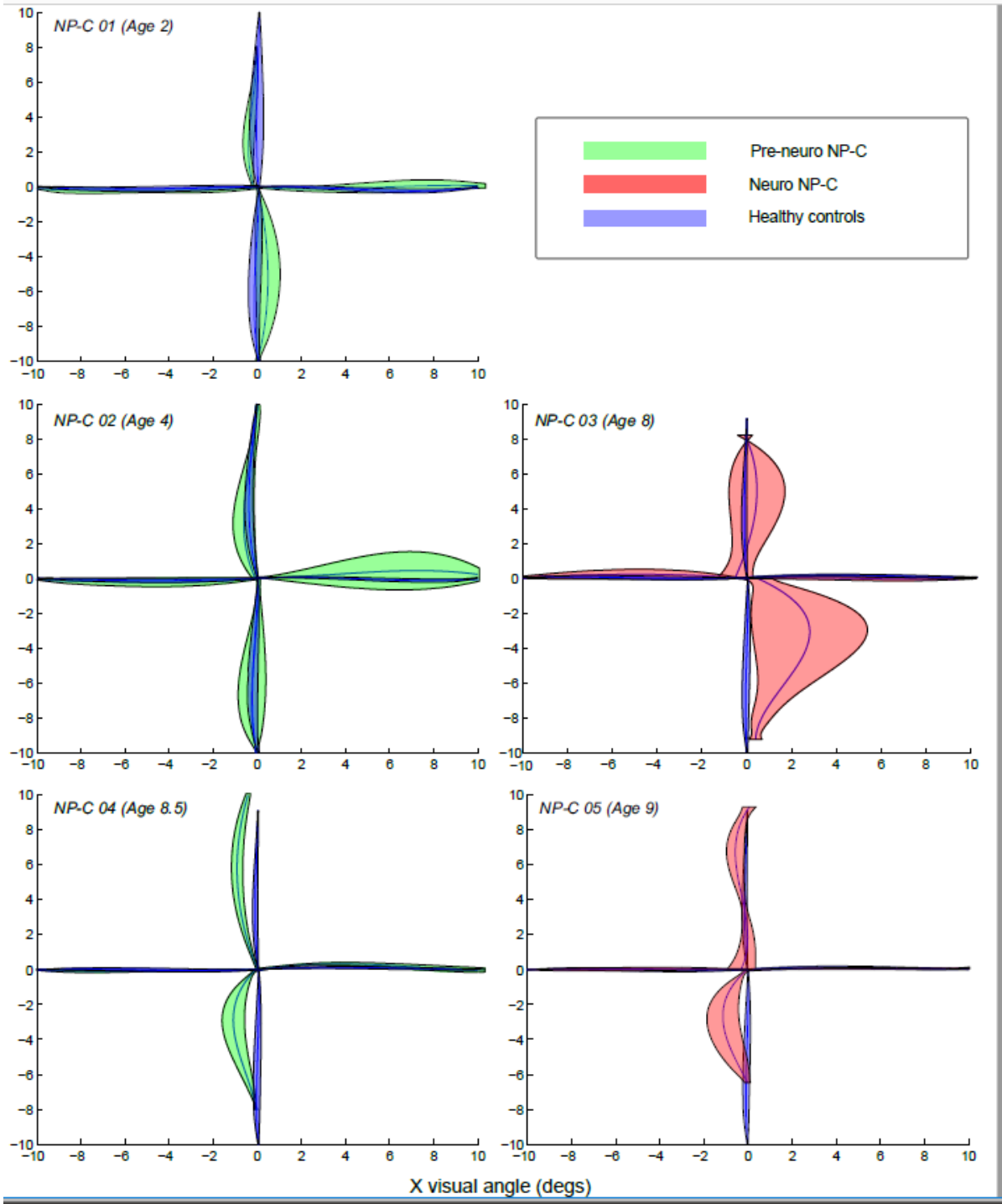
Results

	Patient Number	Age (Years)	Neuro Involvement	Vertical movements					
				Saccade Onset		Saccade Velocity		Saccade Curvature	
				D	U	D	U	D	U
untreated	NP-C 01	2	No	-	-	-	-	-	-
	NP-C 02	4	No	-	-	-	-	-	-3.19
	NP-C 04	8.5	No	-	-	-2.37	-	-2.28	-3.26
treated	NP-C 03	8	Yes	-2.17	-	-3.1	-2.83	-26.74	-16.37
	NP-C 05	9	Yes	-	-2.16	-4.11	-3.36	-5.65	-2.6

- Treated patients show widespread effects
- Untreated patients can have slower saccades and curved saccades

Early signs

- Slowing
- Curvature
- In vertical saccades are early signs



Example 2 – Morquio (MPS-IVa) and Tyrosenimia III

- Tyrosinemia III thought to cause cognitive impairments (e.g. based on treated Tyrosinemia I), but not well documented.

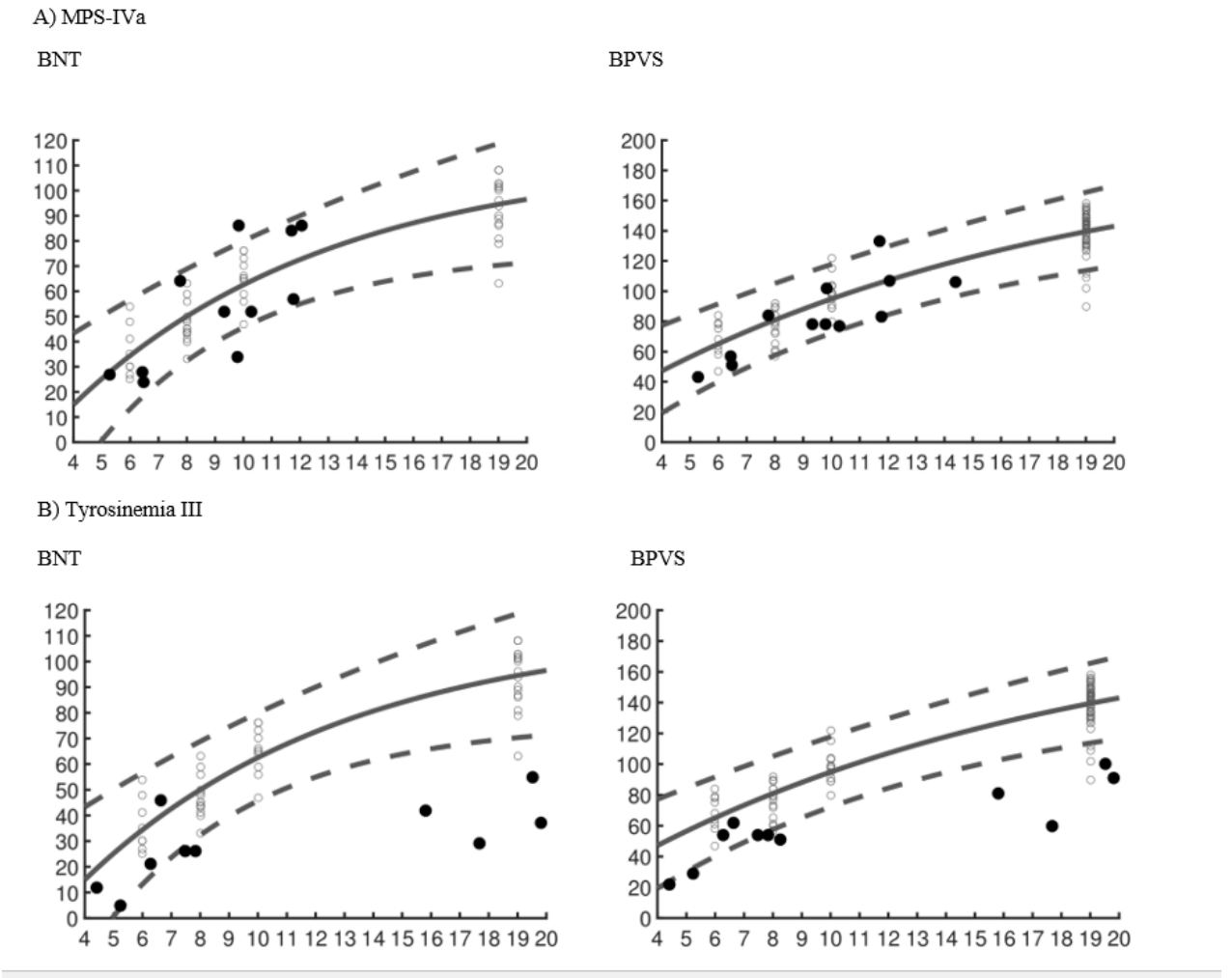
- Morquio not thought to cause cognitive impairments
- Questions: Would there be cognitive changes
- Would different diseases have different profiles?
  - Or would there be homogeneous general decline?

Contrast domains:

- Language – BPVS (receptive) Boston Naming Test (productive)
- Attention – Visual search, Saccade task, fixation tast.

Result -- Language

- MPS-IVa not affected
- Tyrosinemia III affected (esp older individuals)



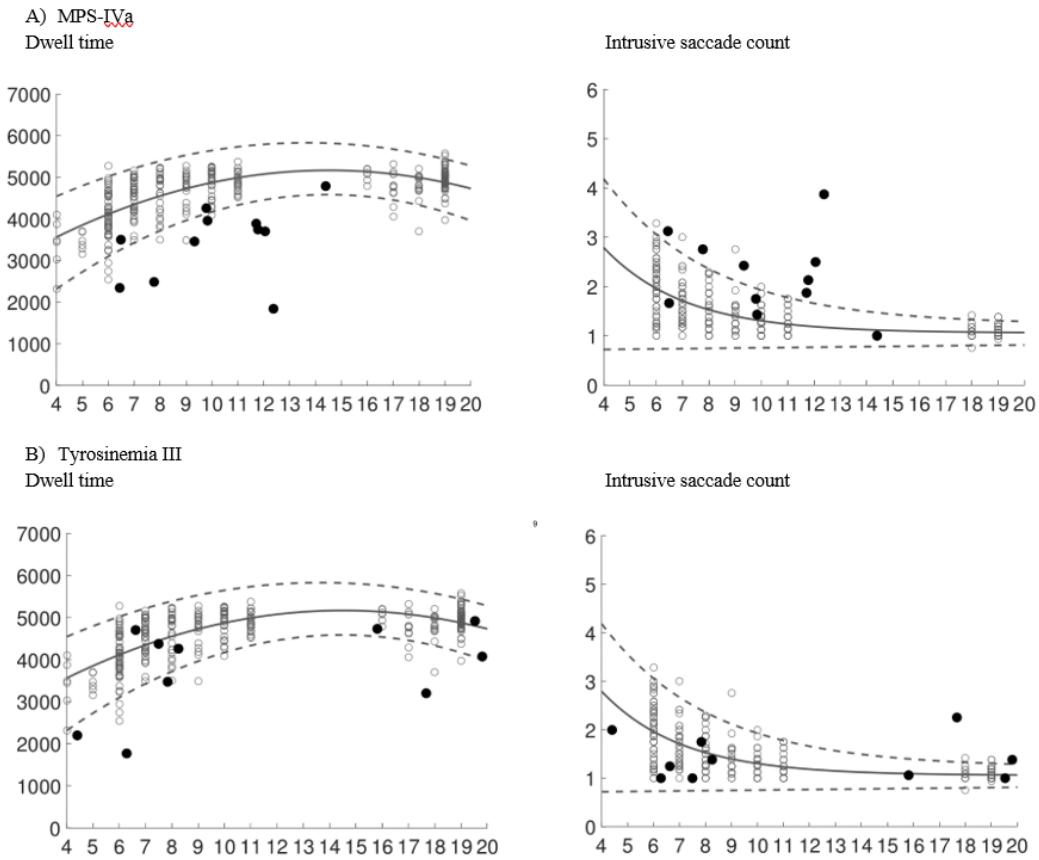
Result – Sustained attention (fixation task)

MPS-IV clearly affected

Tyrosinemia III mild problems

Dwell time

Intrusive saccades



Tyrosinemia III / Morquio (MPS-IVa)

- Both disease had cognitive effects
- Language clearly affected in Tyrosinemia III
- Both had problems with sustained attention, but this was clearer in Morquio
- Disease profiles were not the same
  - Not homogeneous decline
- Language/sustained attention are good candidates for tracking disease progress or treatment effects (note age-related decline in T3)

Summary

- Cognitive assessment is possible in these groups
- Simplified tasks with variable difficulty
- Special methods for comparing data using developmental trajectories and statistical models
- Profiles across diseases were not uniform
- Best measures are candidates for disease tracking, assessing treatment or diagnosis

Thank you…

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