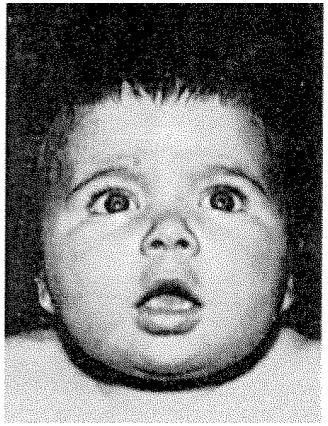
Abnormal Corpus Callosum Morphology in Congenital Hypothyroidism

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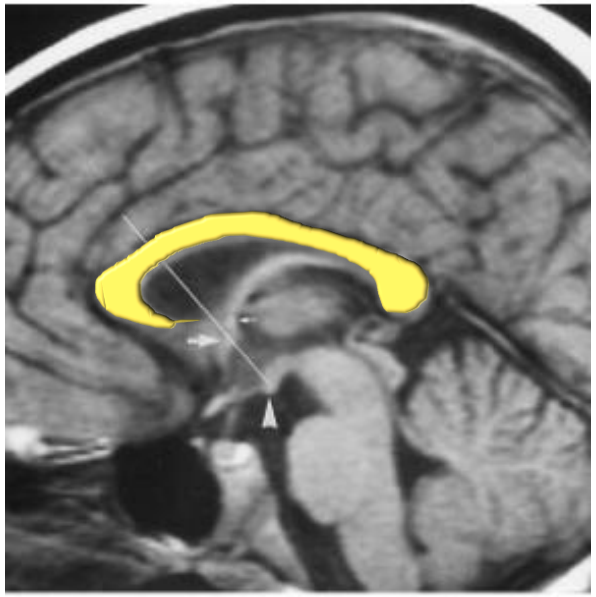
AMERICAN THYROID ASSOCIATION ANNUAL MEETING

SAN JUAN PUERTO RICO, OCTOBER 2013

Disclosure

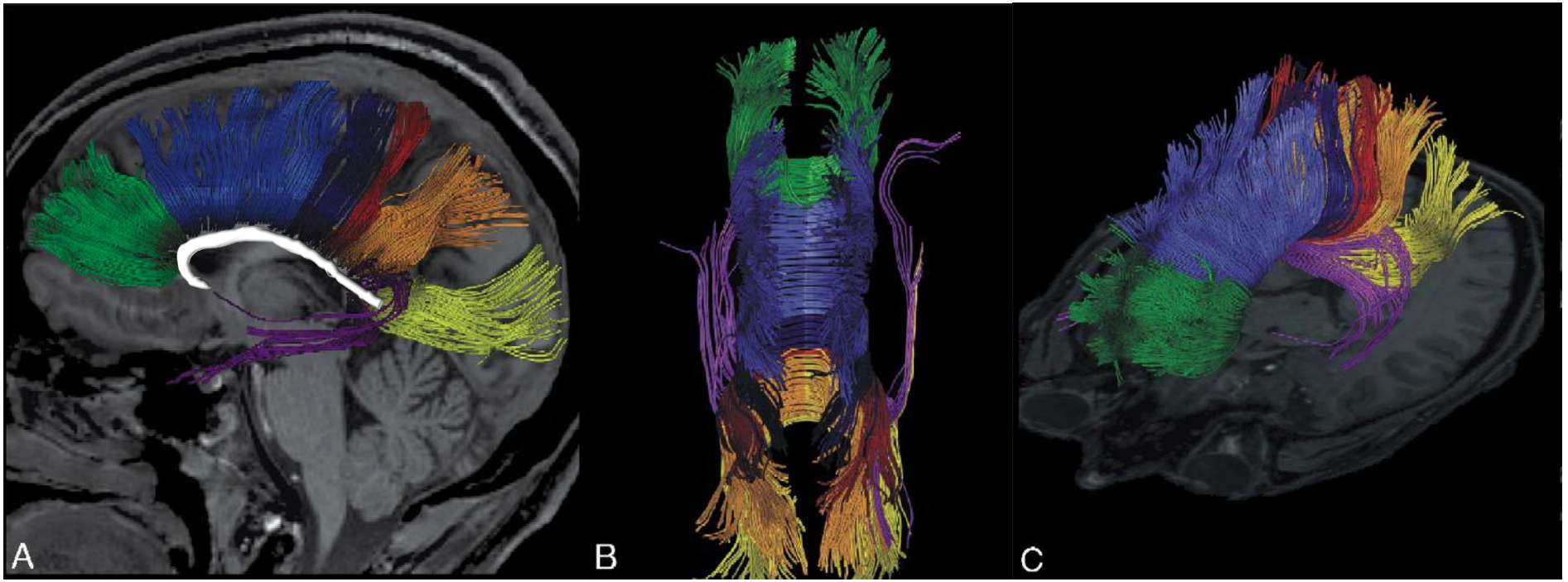
I have nothing to disclose

Corpus Callosum



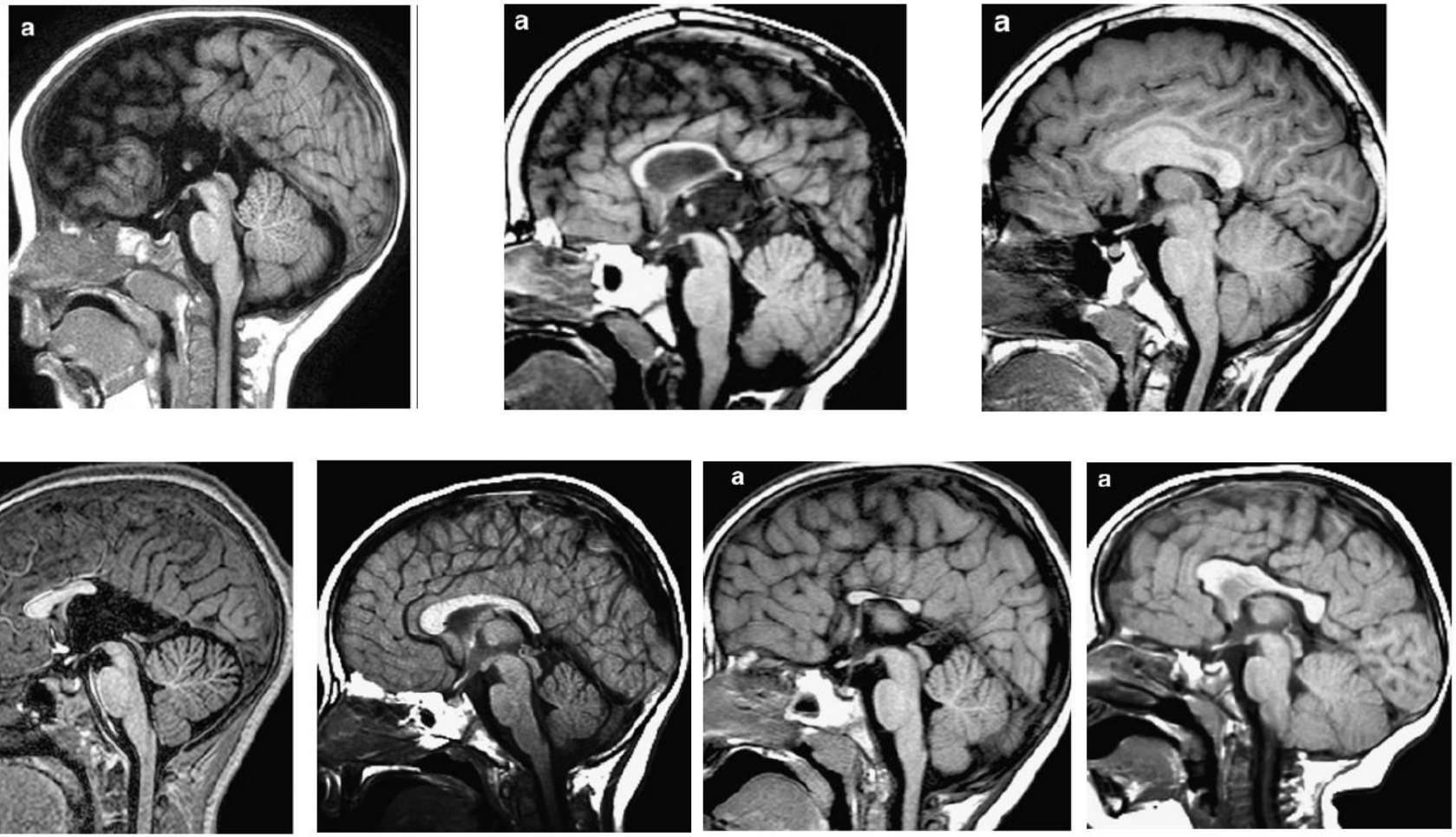
- Largest white matter (WM) tract in brain
- Transfers information between hemispheres
- Needed for many functions (e.g., bimanual coordination, social communication, complex reasoning)

Corpus Callosum



Hofer & Frahm (2006) NeuroImage 32:989-994

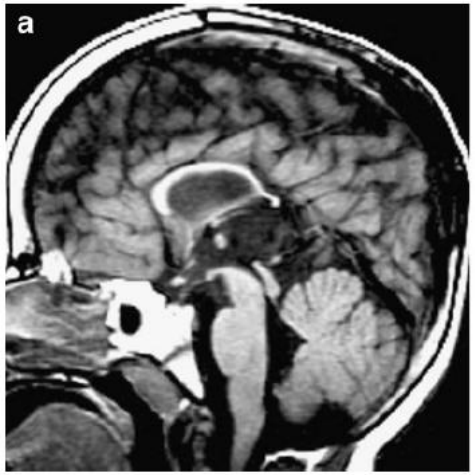
Corpus Callosum Abnormalities



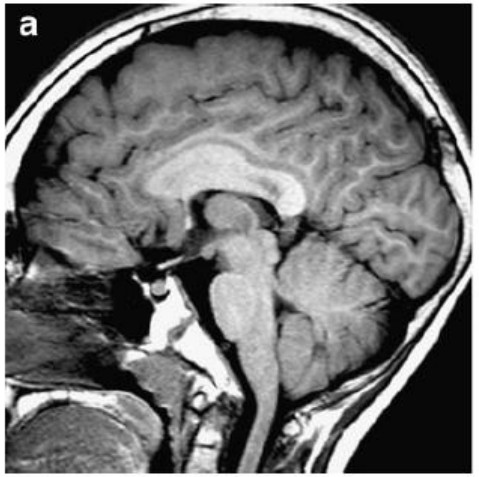
Raybaud, C. (2010) Neuroradiol 52:447-477

Corpus Callosum Abnormalities

fetal alcohol syndrome



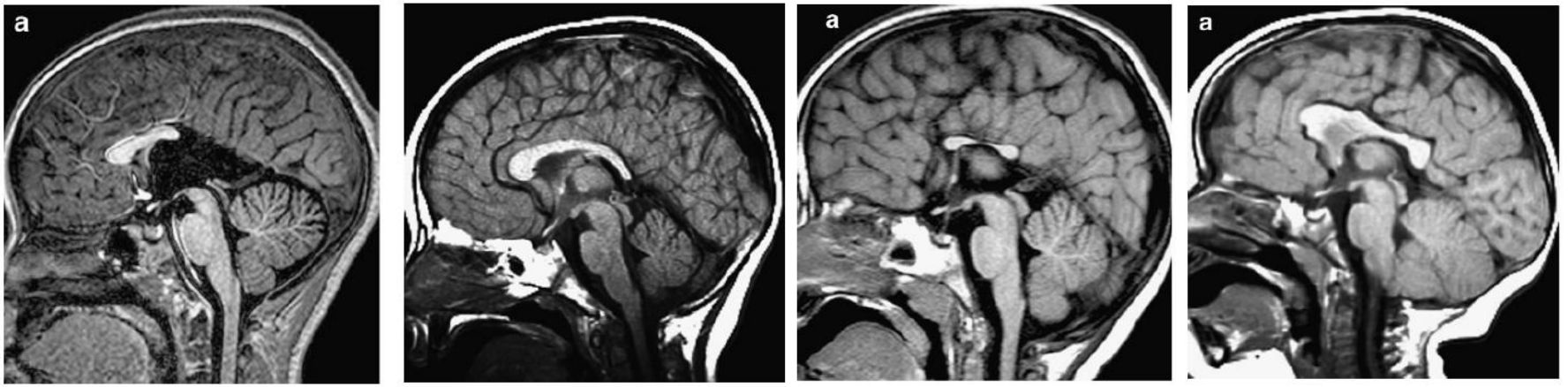
Turner syndrome
ADHD
prematurity



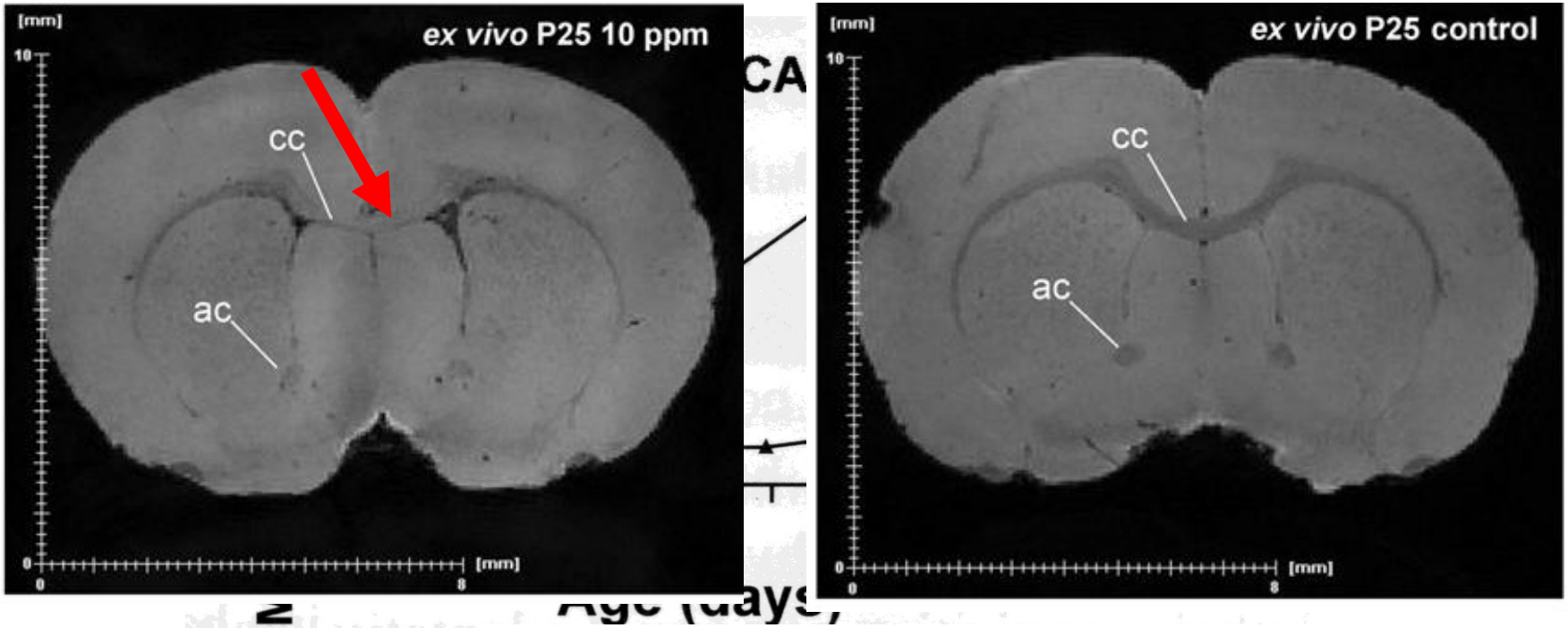
autism

Corpus Callosum Abnormalities

- Down syndrome
- Williams syndrome
- 22q11.2 syndrome



Thyroid hormone is essential for corpus callosum development



Powell M.H. et al (2012) Neurotoxicol 33: 1322-1329

Berbel P et al (1994) Behav Brain Res 64: 9-14

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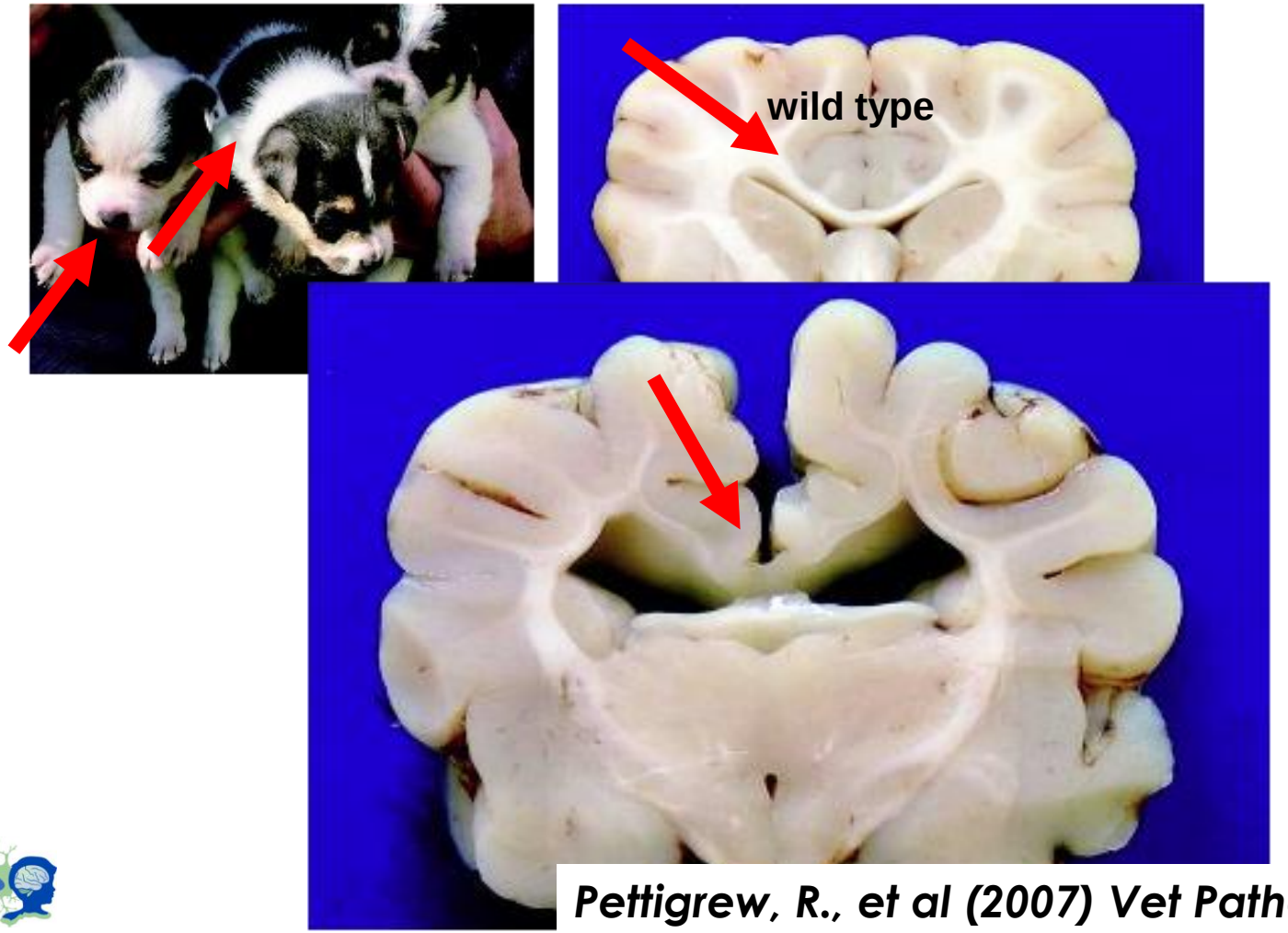
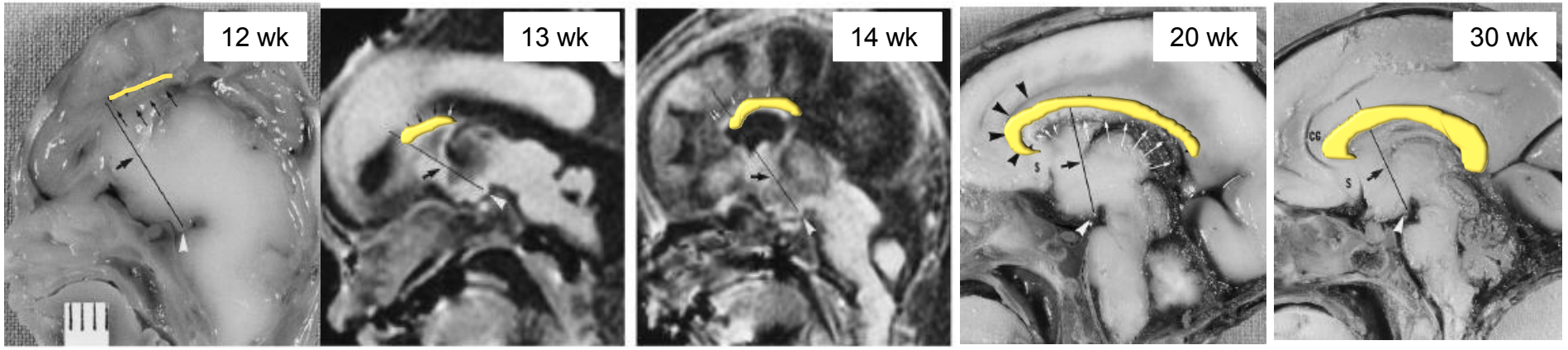


Pettigrew, R., et al (2007) Vet Pathol 44:50-56

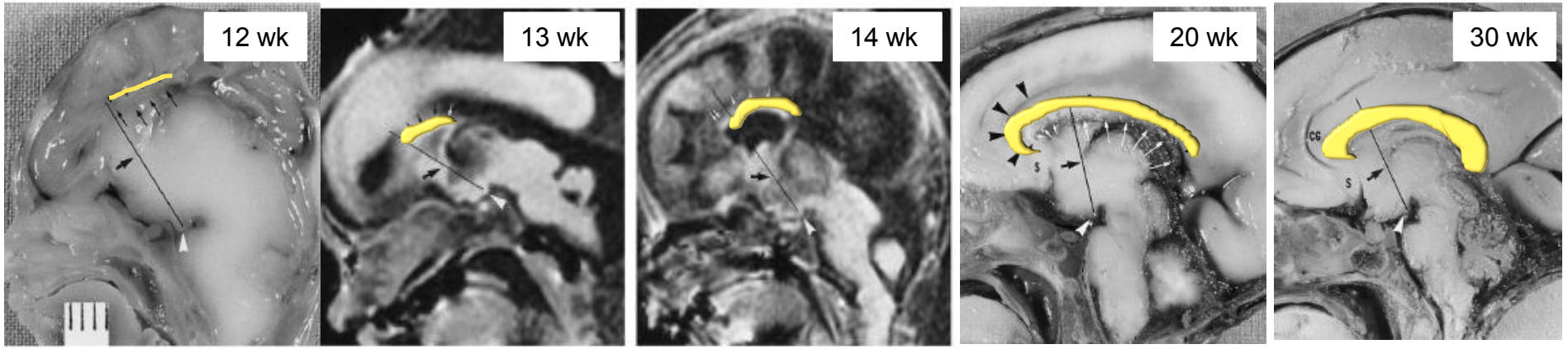
Corpus Callosum Development

- Undergoes major development in gestation and postnatally
  - period of exuberant axonal growth
    - bidirectional & inside-out pattern
    - anterior before posterior



Corpus Callosum Development

- Undergoes major development in gestation and postnatally
  - period of exuberant axonal growth
  - exuberant axonal pruning
  - myelination



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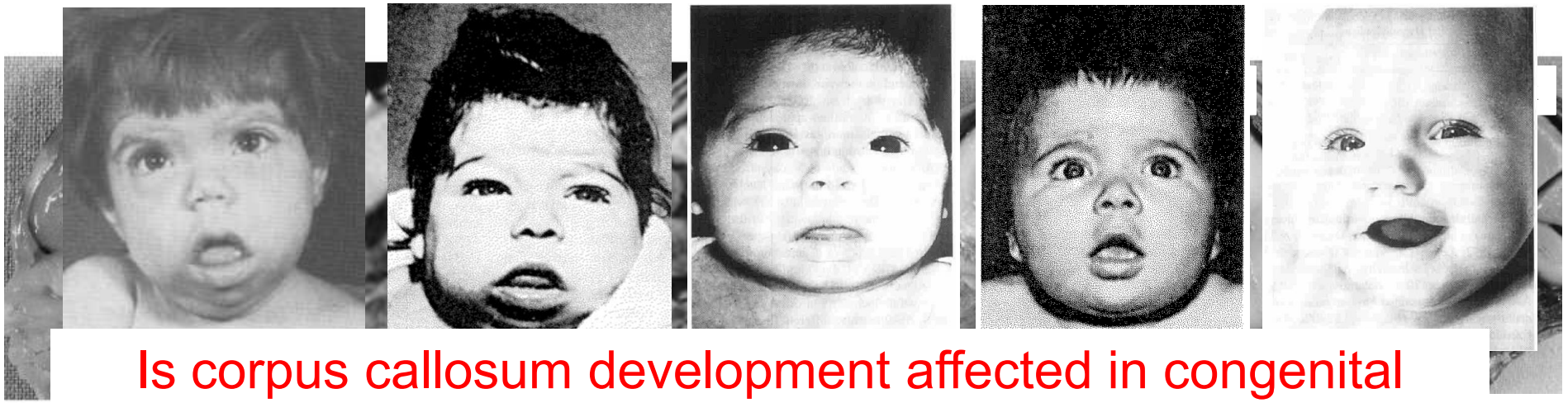
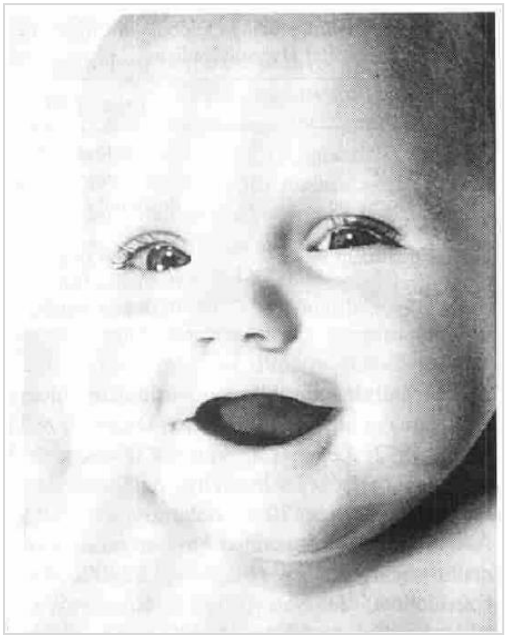
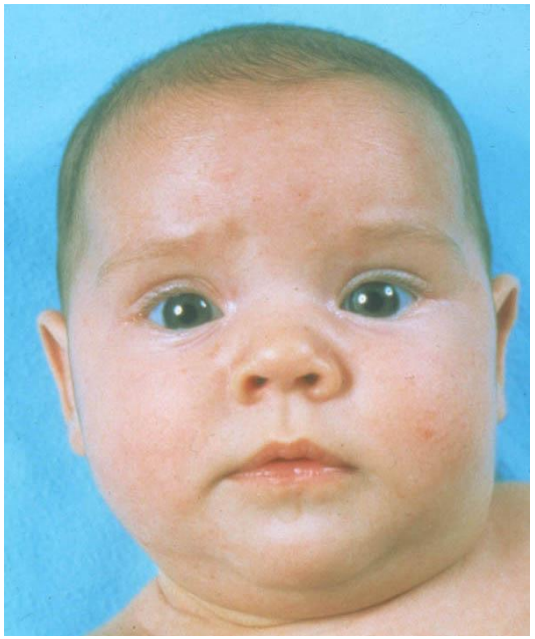


Is corpus callosum development affected in congenital hypothyroidism (CH)?





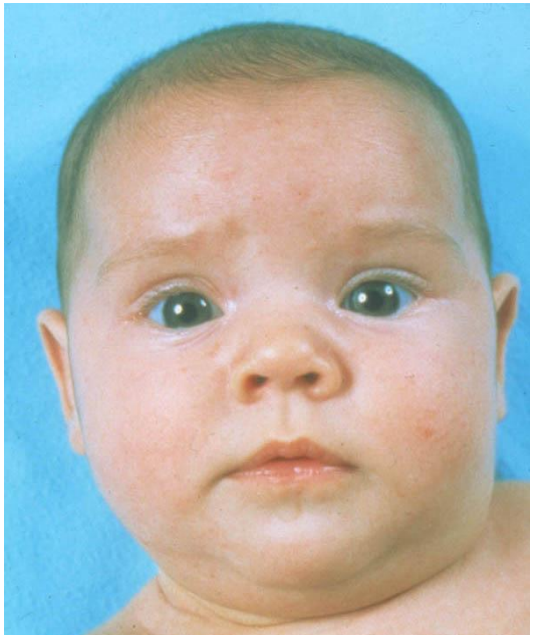
- Experience a circumscribed period of thyroid hormone deficiency
  - reflects etiology, severity of hypothyroidism at diagnosis, treatment factors (age, dose)

3 Research Questions

1. Is corpus callosum morphometry and morphology affected in congenital hypothyroidism (CH)?
2. Are corpus callosum abnormalities associated with disease severity and treatment?
3. Are effects correlated with (suboptimal) outcome?

Sample: CH

- N=41
- 9 to 16 yrs (mean=12.4 yrs)
- 11 athyrosis, 21 ectopic, 6 dyshormonogenesis, 3 unknown
- Median Rx onset=13 days
- Median TSH@diagnosis=311 mU/L
- Mean T4@diagnosis=53.9±36.2 nmol/l

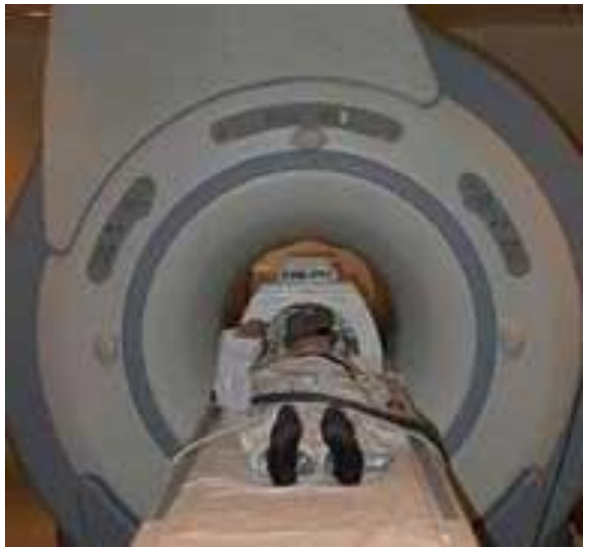


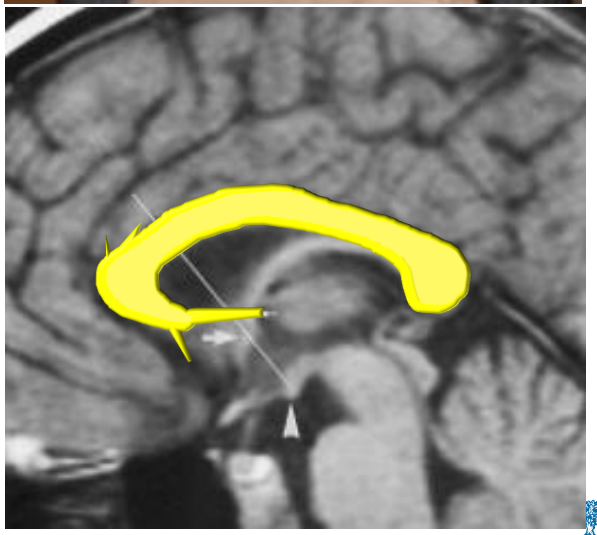
Sample: Controls

- 42 youth matched with CH for:
  - age (mean=12.0 yrs)
  - sex
  - socioeconomic status

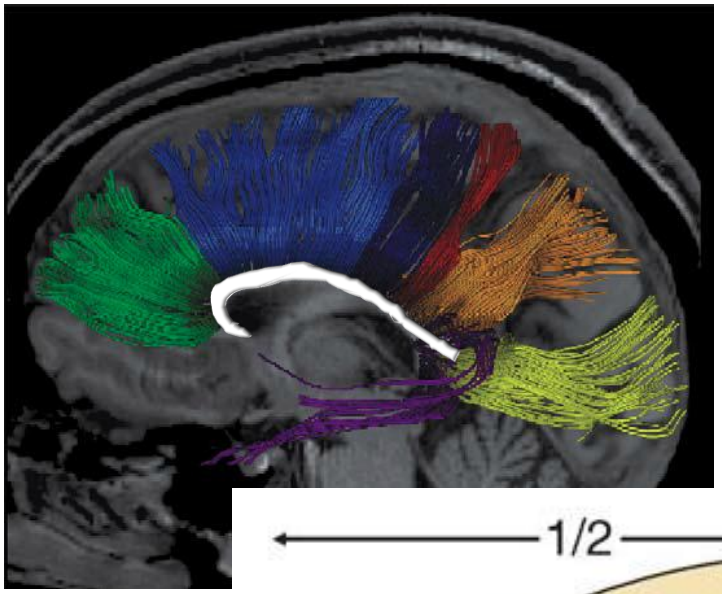
Procedures

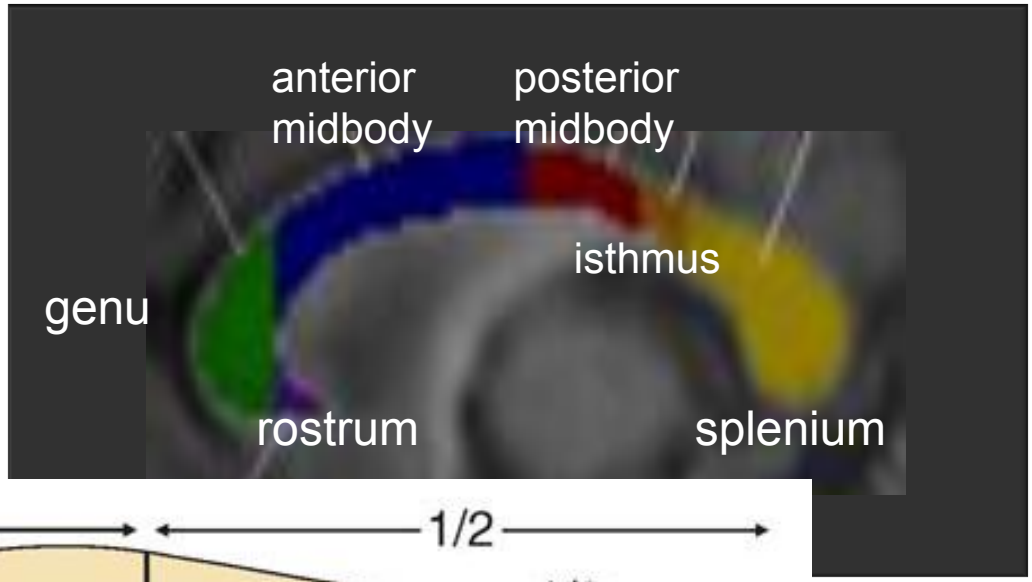
- Day 1: 4-hour neuropsychological evaluation
- Day 2: 1-hour MRI scan in 1.5 Tesla magnet
  - 7-min axial T1 FSPGR sequence (*TR/TE=10.3/4.2 ms, inversion time=400 ms, flip angle = 20^0, slice thickness = 1.5mm)*
- Corpus callosum manually traced and measured using Analyze 9.0

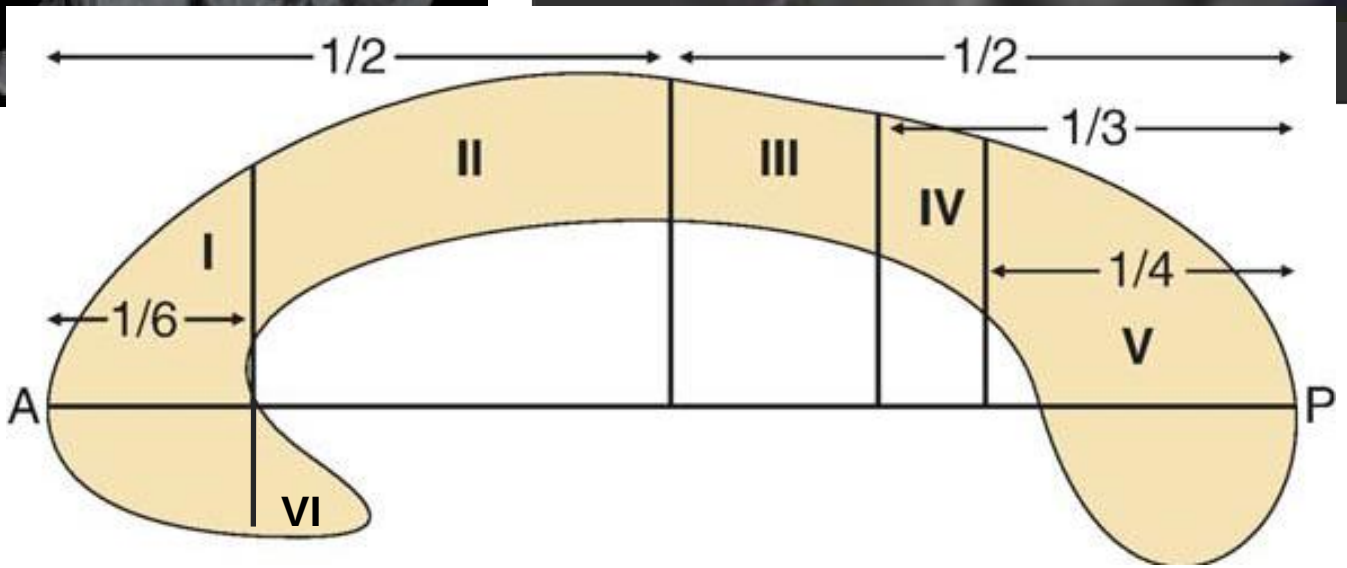




Quantitative Approach







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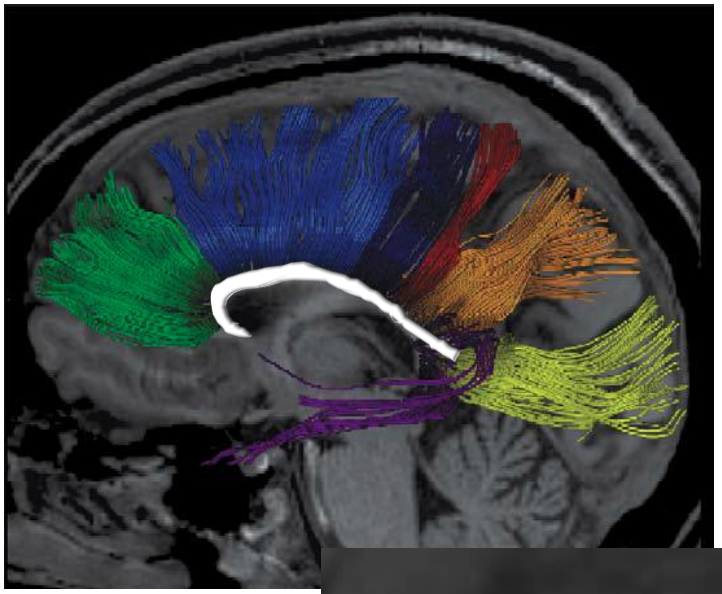
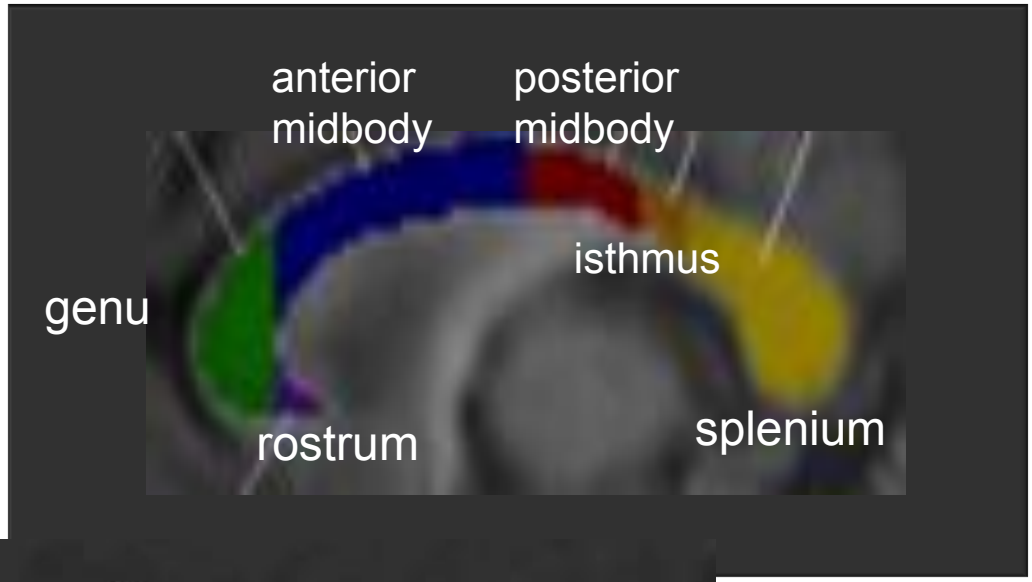
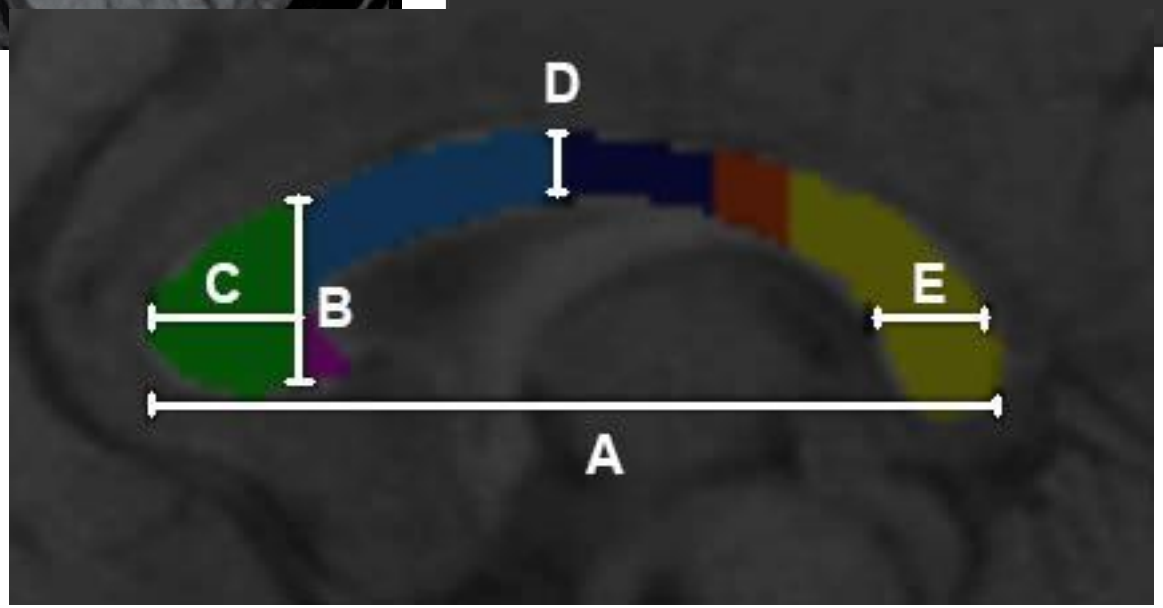
Quantitative Approach

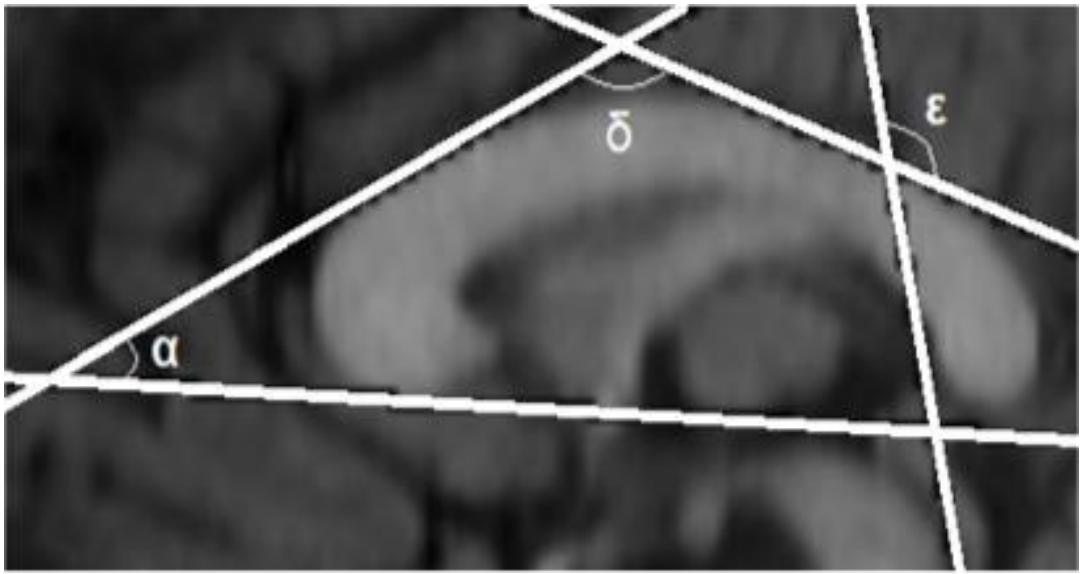






Qualitative Approach

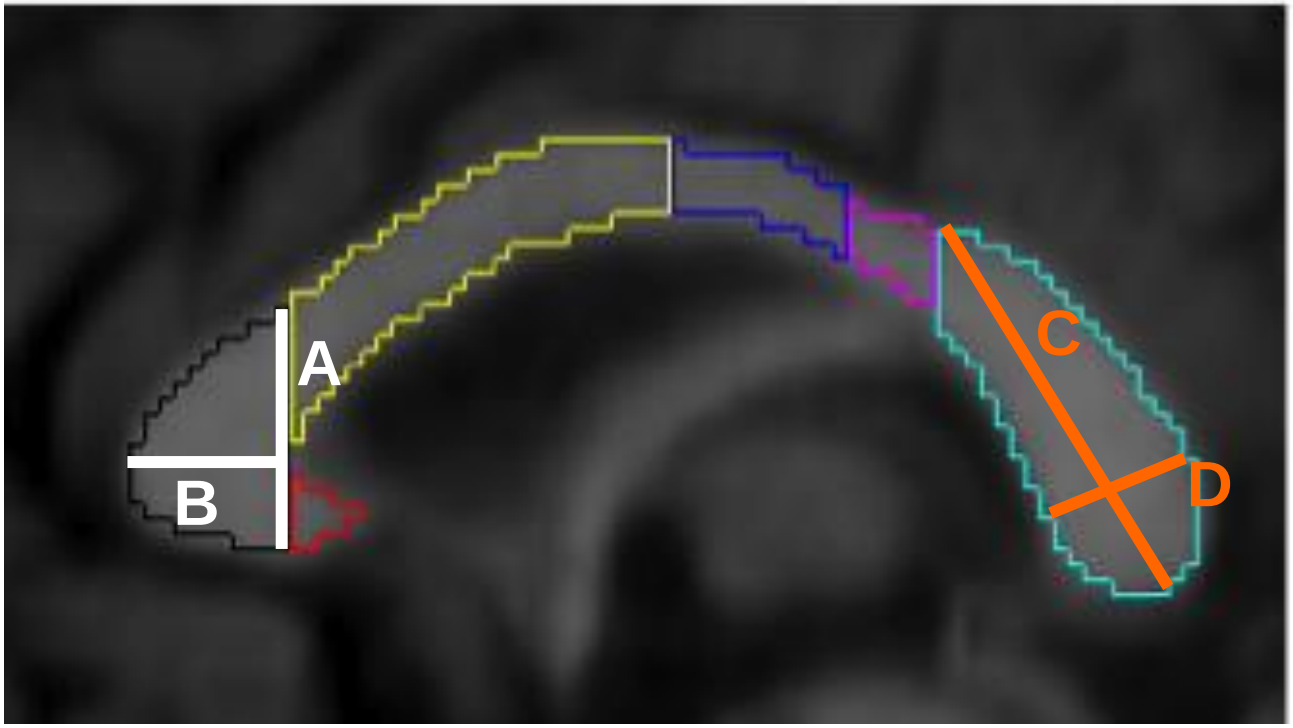
- Curvature (δ)
- Droop (ε)
- Peak (α)



Gabrielli O et al (1993) Neuroradiol 35:109-112

Qualitative Approach

- Shape ("bulbosity") of genu (A/B) and splenium (C/D)

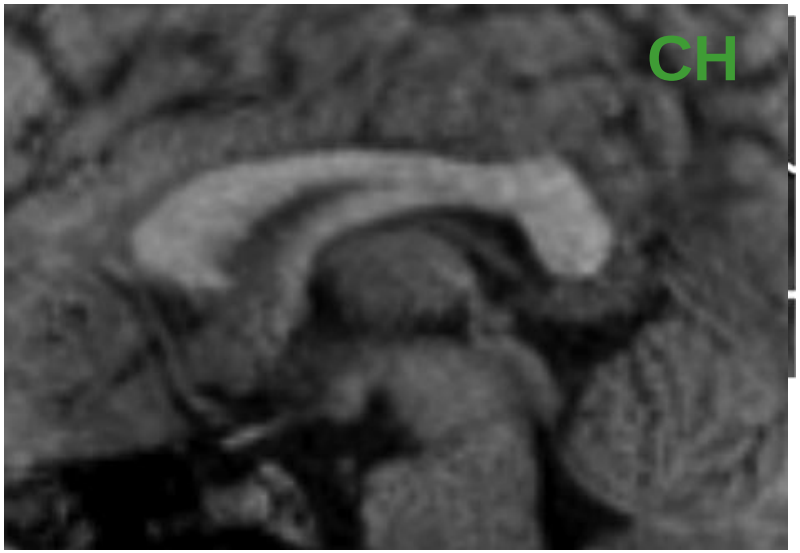


CH have smaller genus

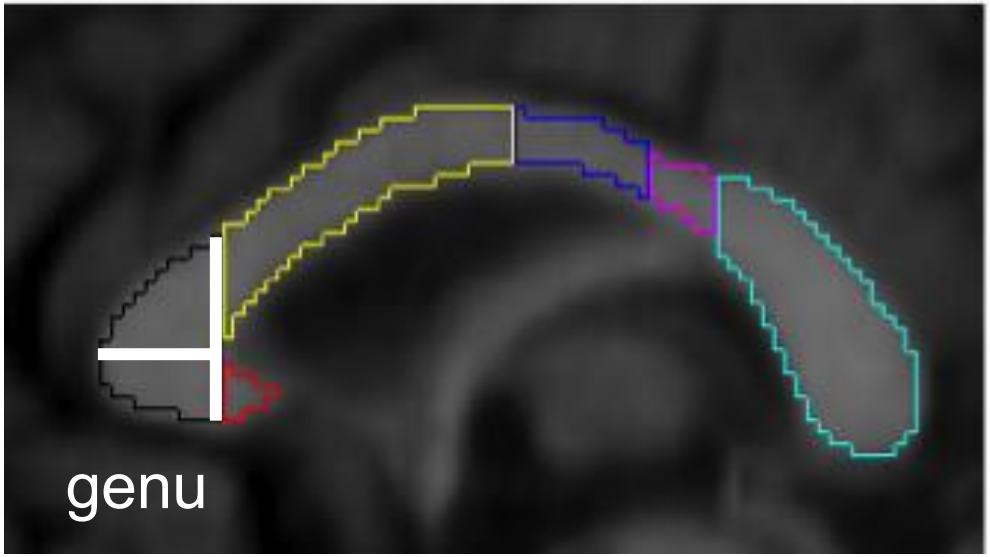
CH have narrower genus

CH show abnormal shape

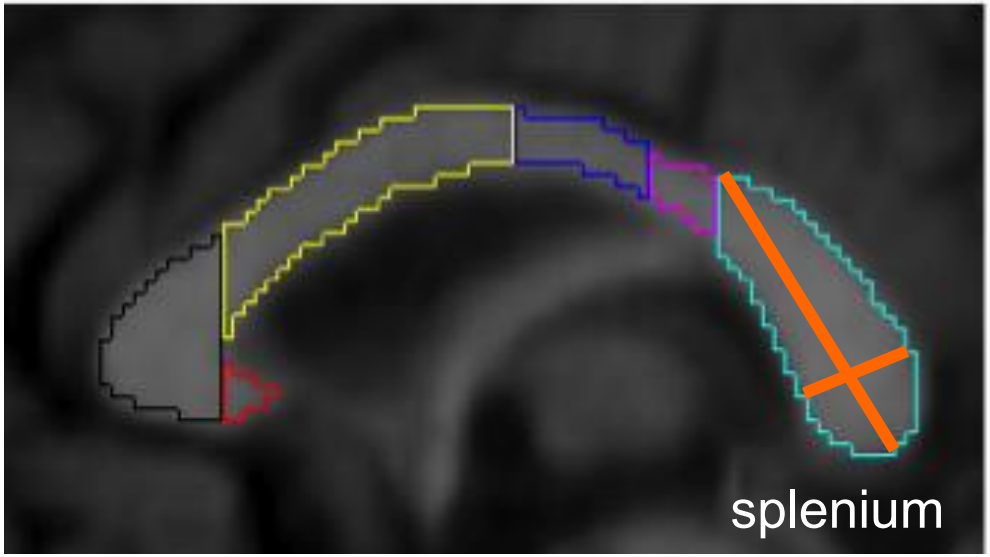
- Flatter corpus callosum, *p<0.001*
- Less droop in splenium, *p=0.017*
- No difference in peak of genu



CH show “more bulbous” genus



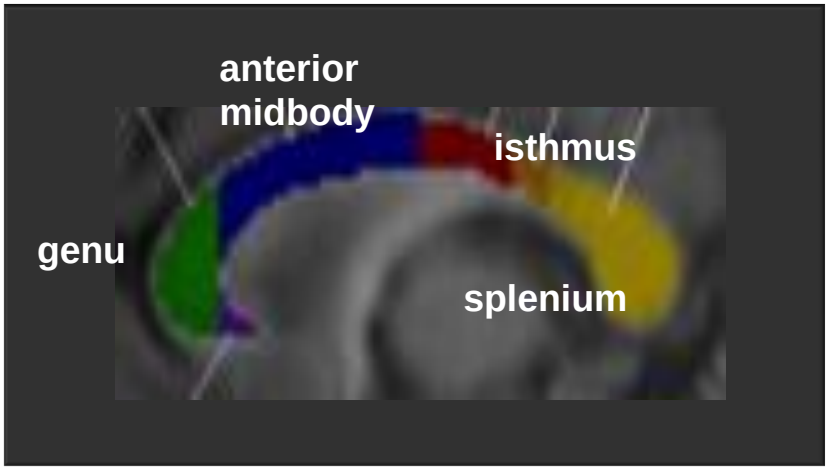
CH show normal spleniums



Question 2: Is CC Morphometry Associated with Early Disease Factors?

- No effect of TSH or T4 levels at diagnosis, age of treatment onset, starting dose LT4
- Genu smaller in athyrosis & dyshormonogenesis vs ectopic etiology

Question 3: Is CC size associated with specific abilities?



Genu & anterior midbody size highly correlated with IQ

In Summary

- Youth with CH show:
  - Reduced size and width of CC genu
  - Less curvature, abnormal orientation of splenium, more bulbous genu
- More severe CH at diagnosis associated with reduced size of genu
- Reduced size of certain CC regions predictive of specific cognitive weaknesses

Conclusion

- Despite the current optimal care of congenital hypothyroidism, persisting residual cognitive deficits may still arise from corpus callosum abnormalities associated with early thyroid hormone insufficiency

Farhana Islam

Thank You

CIHR IRSC