Children Born to Women with Hypothyroidism during Pregnancy Show Abnormal Corpus Callosum Development

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AMERICAN THYROID ASSOCIATION ANNUAL MEETING
SAN JUAN PUERTO RICO, OCTOBER 2013

Arash Samadi

Disclosure

I have nothing to disclose

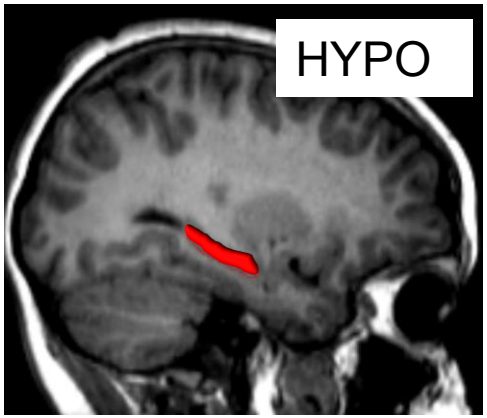
Maternal Thyroid Hormone Deficiency in Pregnancy

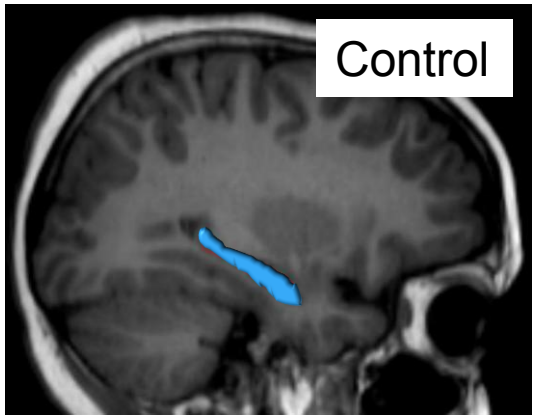
- Hypothyroxinemia (low T4)
- Subclinical hypothyroidism (high TSH)
- Clinical hypothyroidism (low T4/high TSH)
- Iodine deficiency

Maternal Thyroid Hormone Deficiency Effects on Offspring

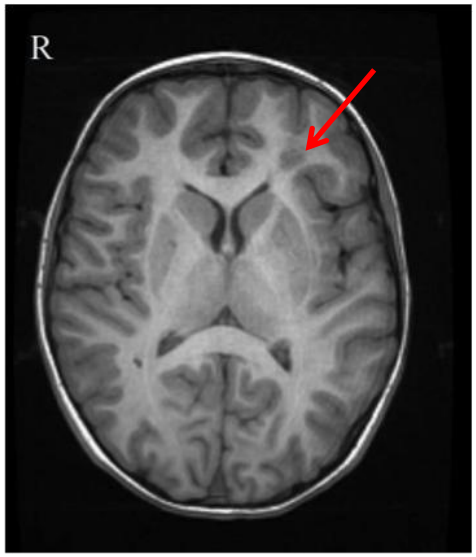
- Reduced IQ
- Attention problems
- Memory weaknesses
- Visual & visuomotor difficulties
- Poor language, auditory, & literacy skills
- Behavior problems

e.g., Haddow J et al 1999 NEJM; Henrichs et al 2010 JCEM; Ghassabian et al 2011 Pediatr Res; Ghassabian et al 2012, Thyroid; Hynes KL et al JCEM 2013; Mirabella G et al 2000 J Ped Endo Metab; Mirabella G et al 2005 Ped Res; Pharoah & Connelly 1990, Early Hum Develop; Pop V et al 1999 Clin Endo; Smit BJ et al 2000 Acta Paed; Roman G et al Ann Neurol, 2013: Vermiglio F et al 2004 JCEM; Willoughby K et al 2013 JINS

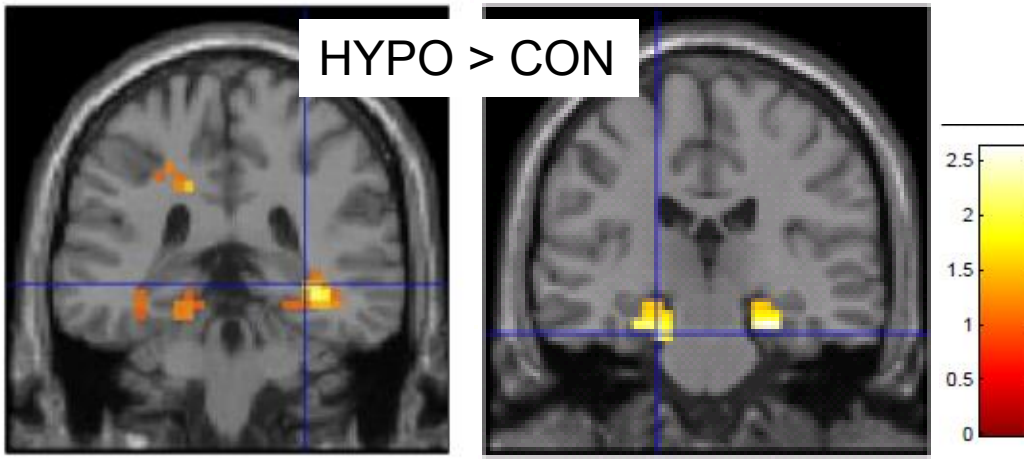




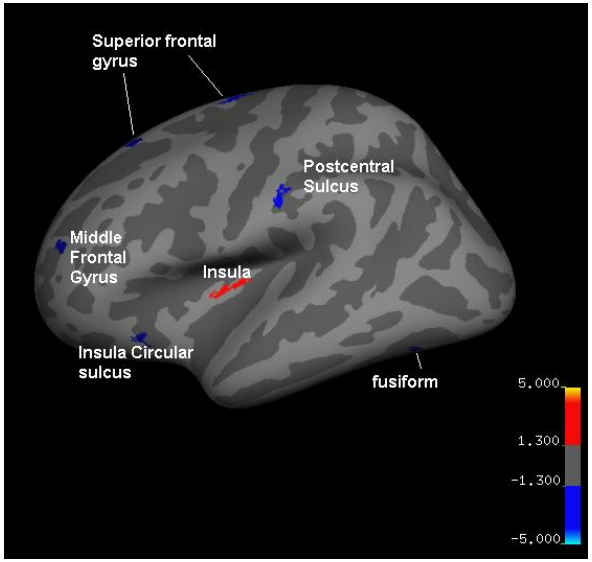
Willoughby K et al, 2013, Thyroid, in press



ITC 2011

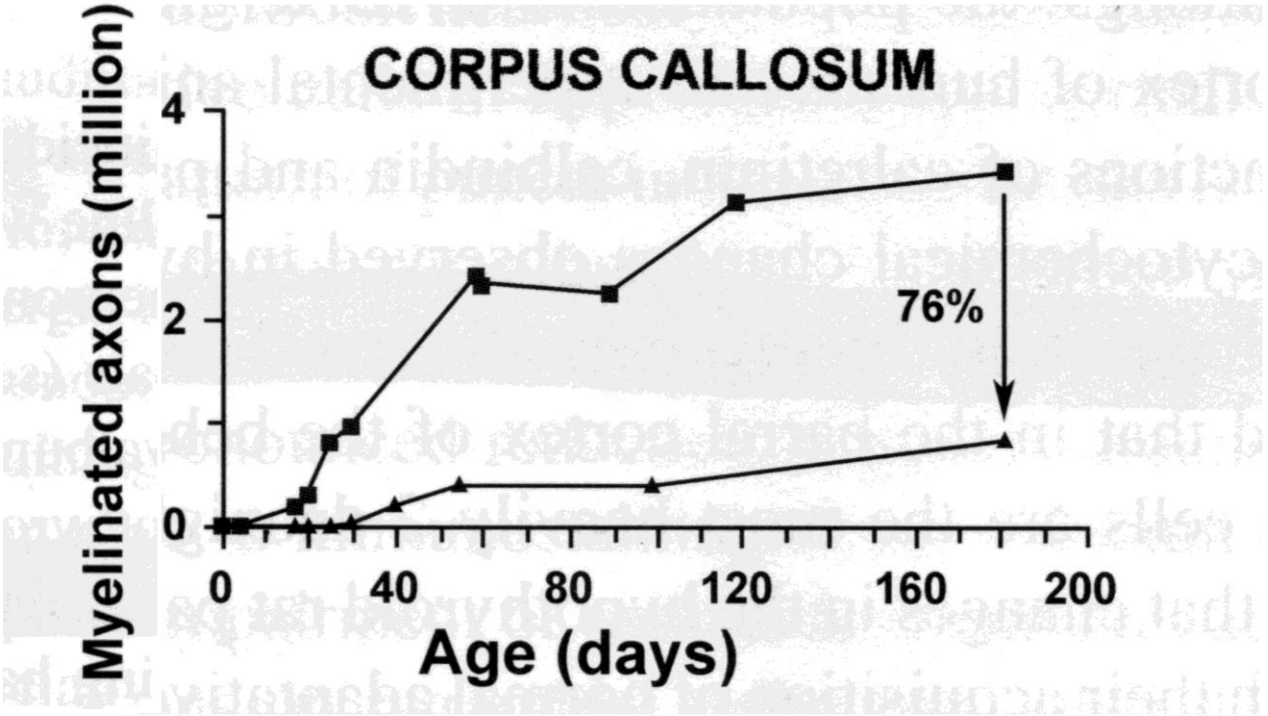


ATA 2011



ATA 2012

Thyroid hormone is essential for corpus callosum development



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

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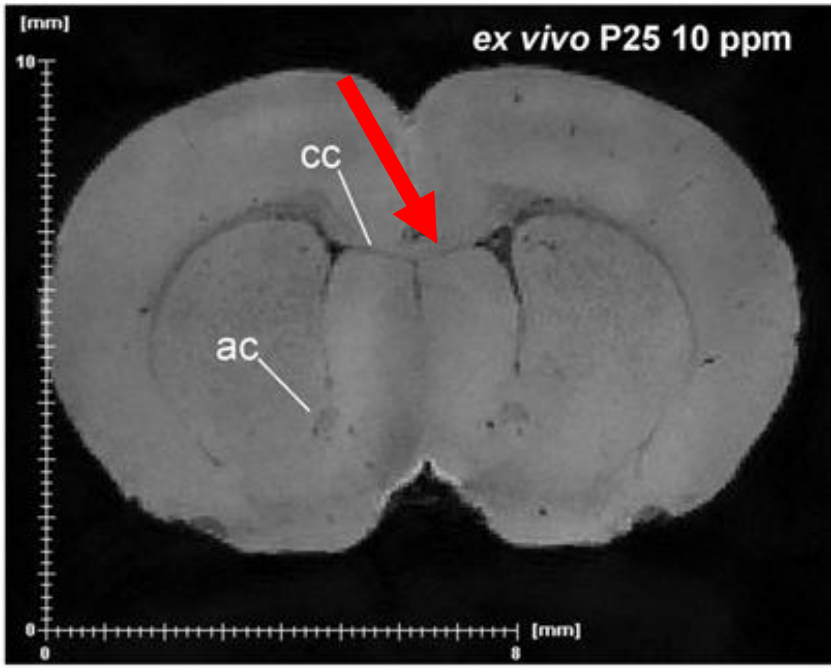

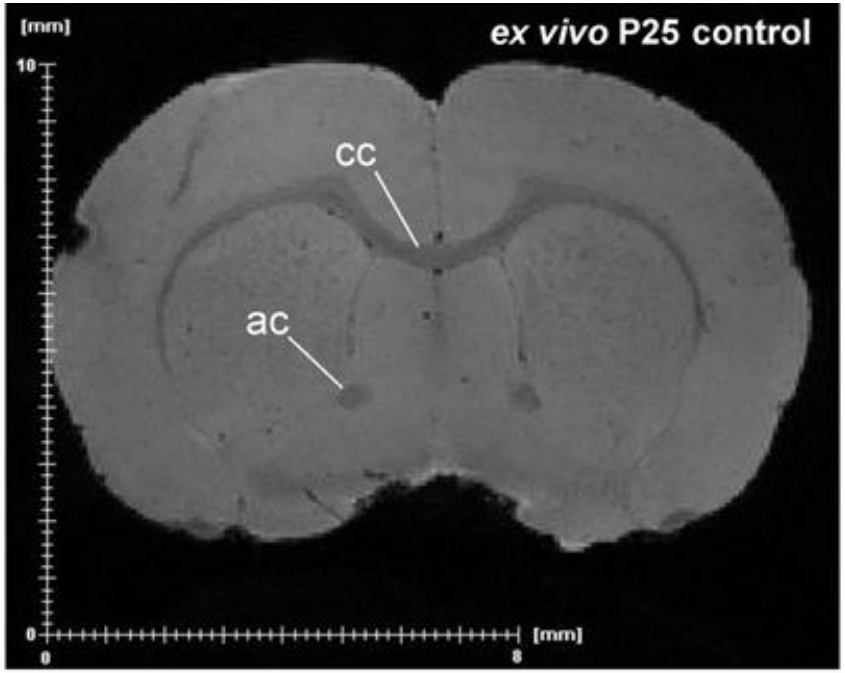

Powell M.H. et al (2012) Neurotoxicol 33: 1322-1329

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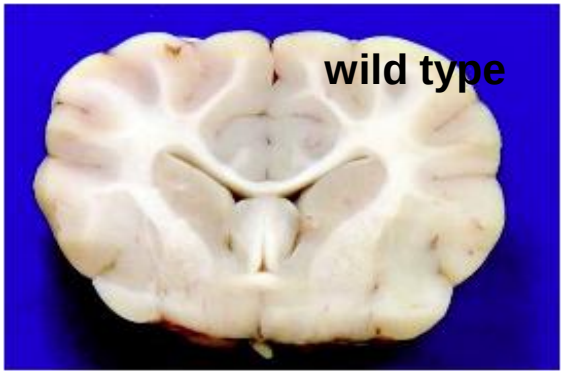
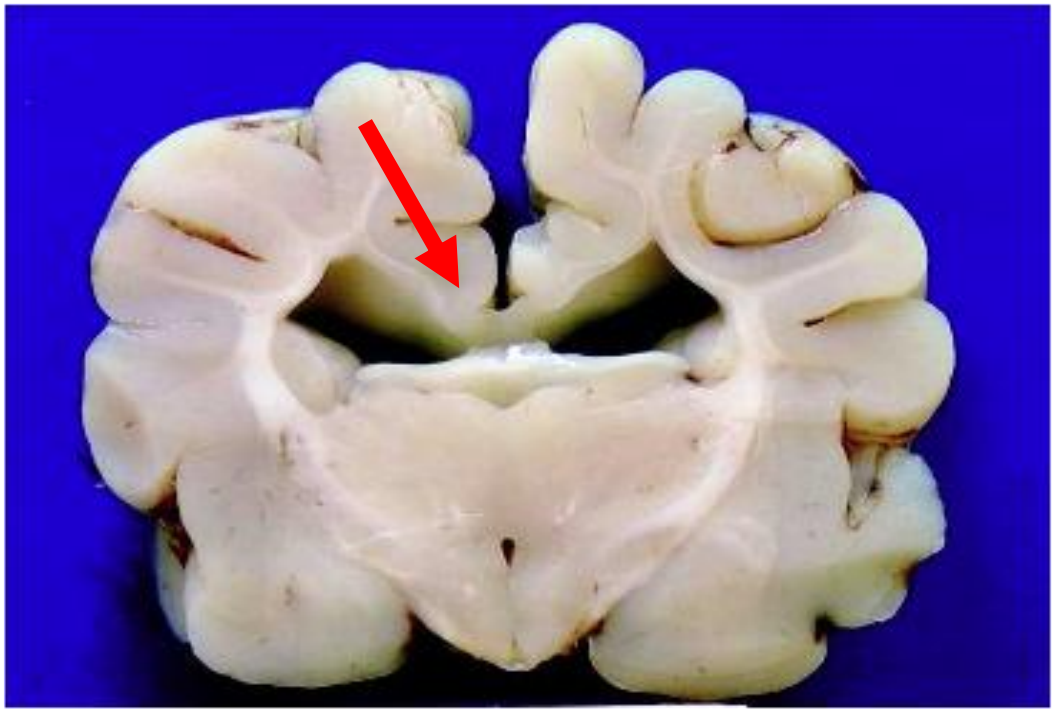
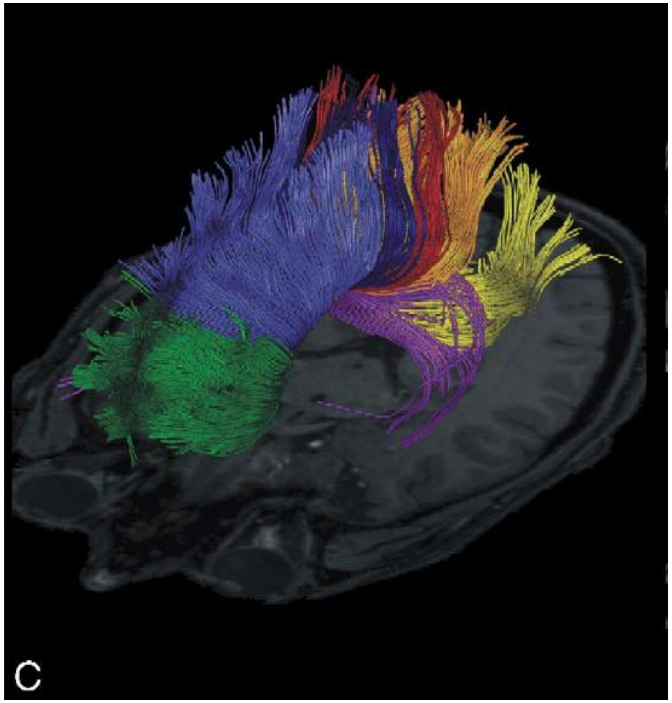




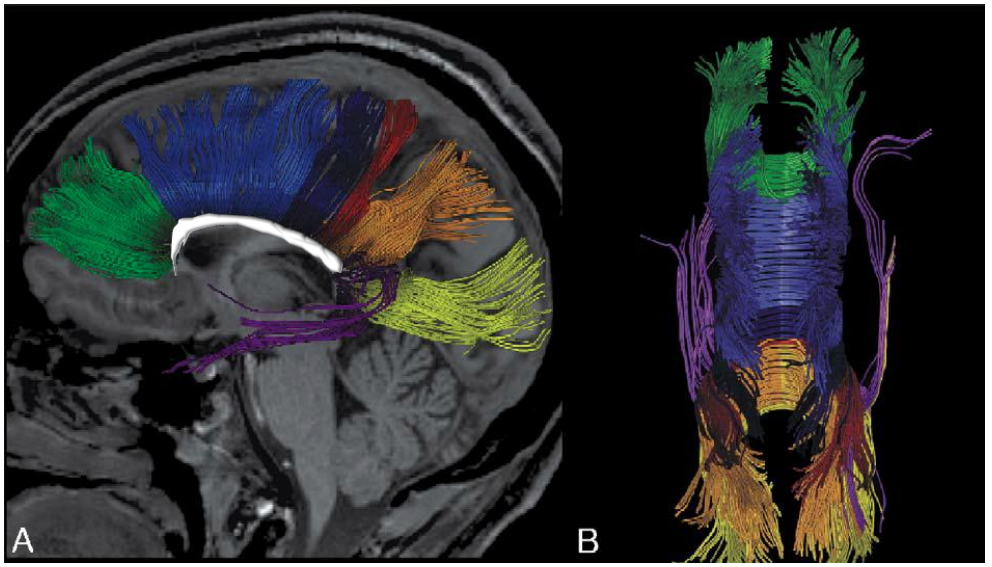
Pettigrew, R., et al (2007) Vet Pathol 44:50-56

Corpus Callosum

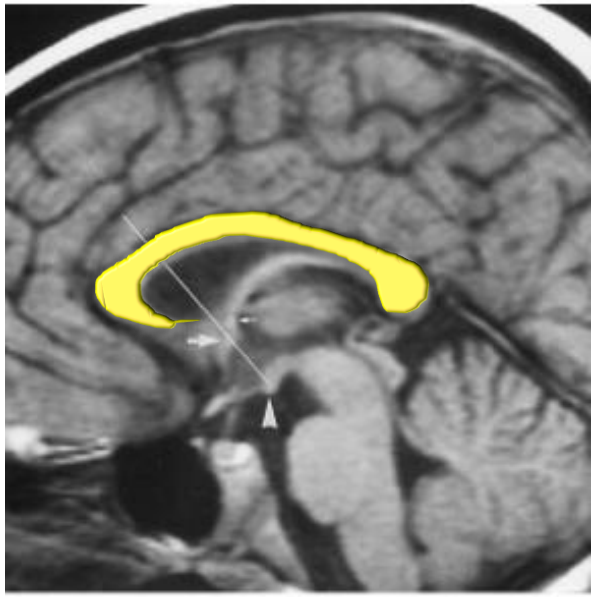


Hofer & Frahm (2006)
NeuroImage 32:989-994

- Largest white matter (WM) tract in brain
- Transfers information between hemispheres

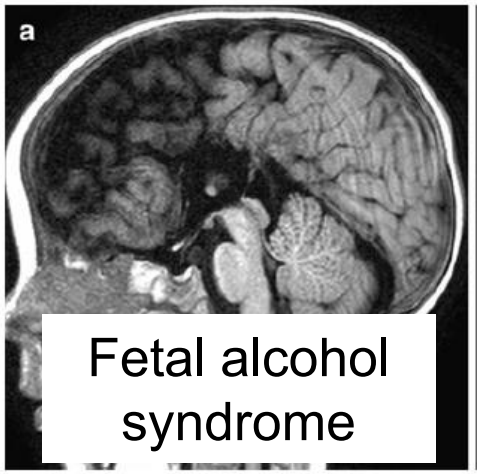


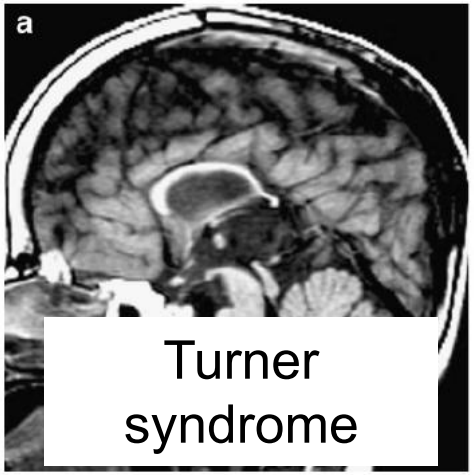
Corpus Callosum

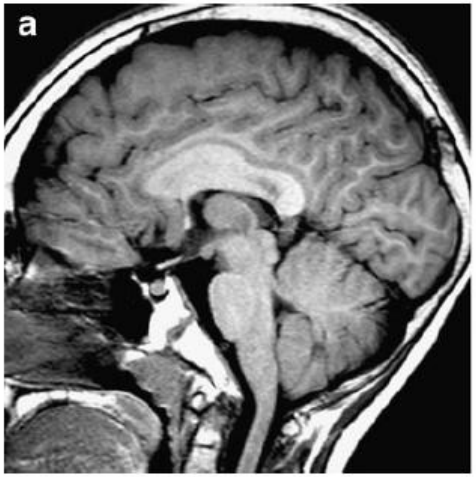


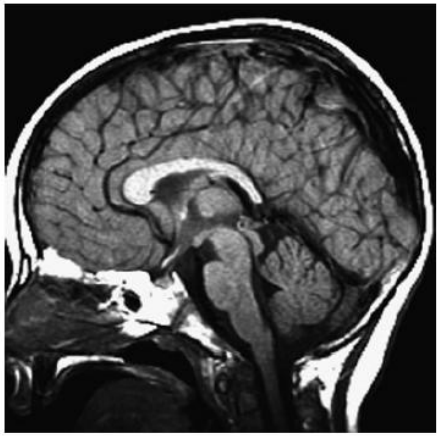
- Largest white matter (WM) tract in brain
- Transfers information between hemispheres
- Needed for many functions (e.g., bimanual coordination, social communication, complex reasoning)

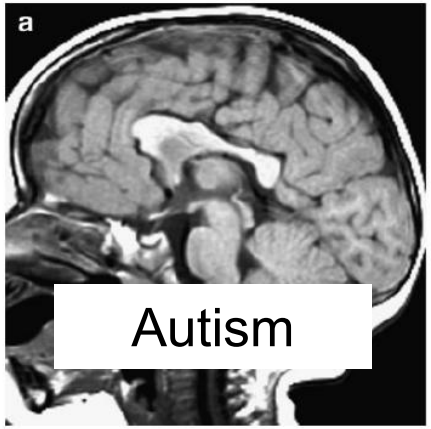
Corpus Callosum Abnormalities







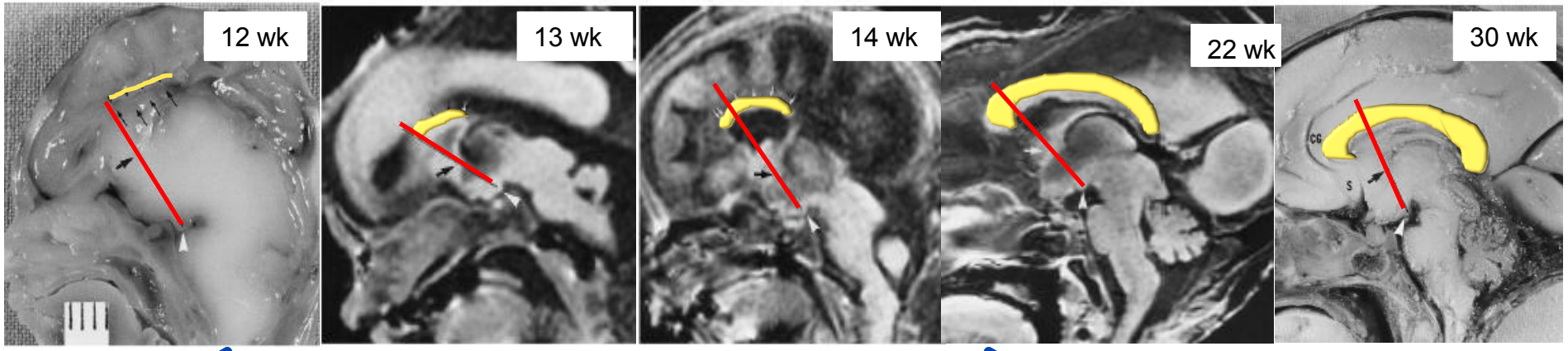




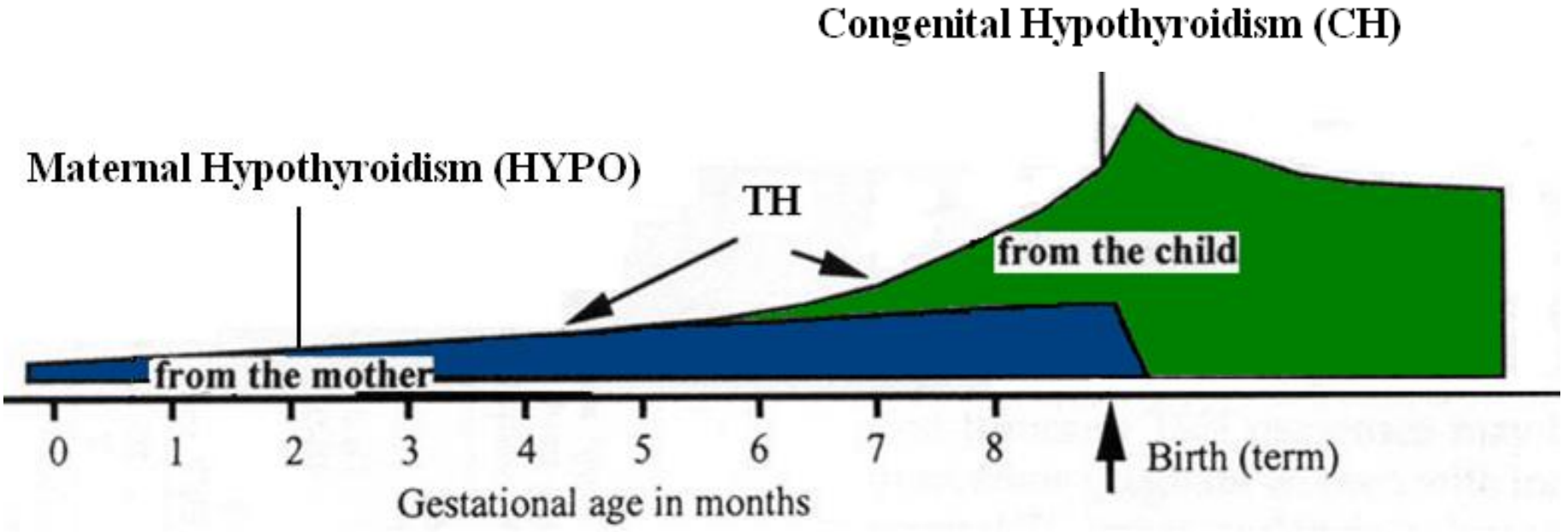
Raybaud, C. (2010) Neuroradiol 52:447-477

Corpus Callosum Development

- Exuberant axonal growth in first 2 trimesters
- Exuberant pruning in third trimester
- Myelination from birth to adulthood



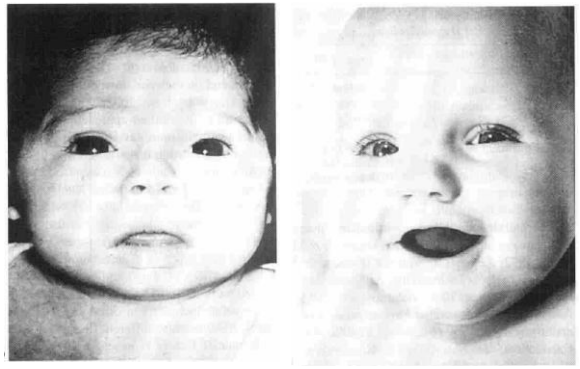
maternal thyroid hormones

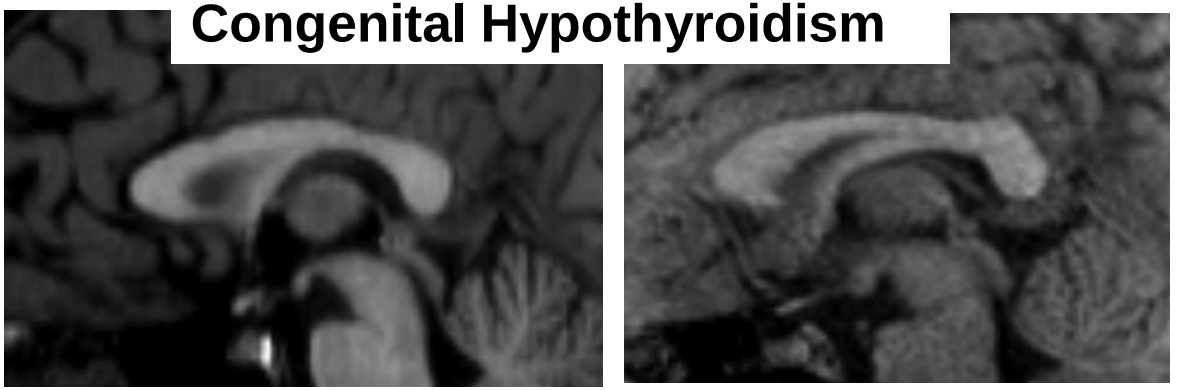


Morreale de Escobar G et al, 2000

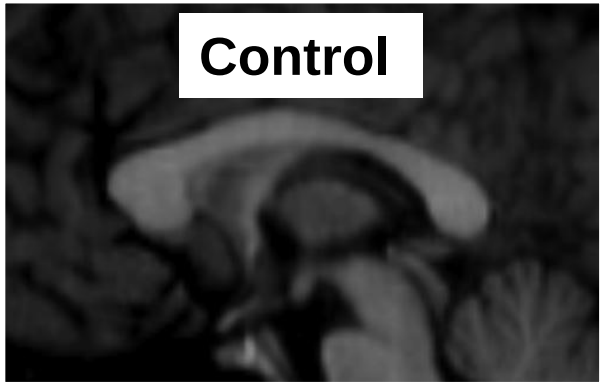
maternal thyroid hormones

Abnormal Corpus Callosum Morphology in Congenital Hypothyroidism

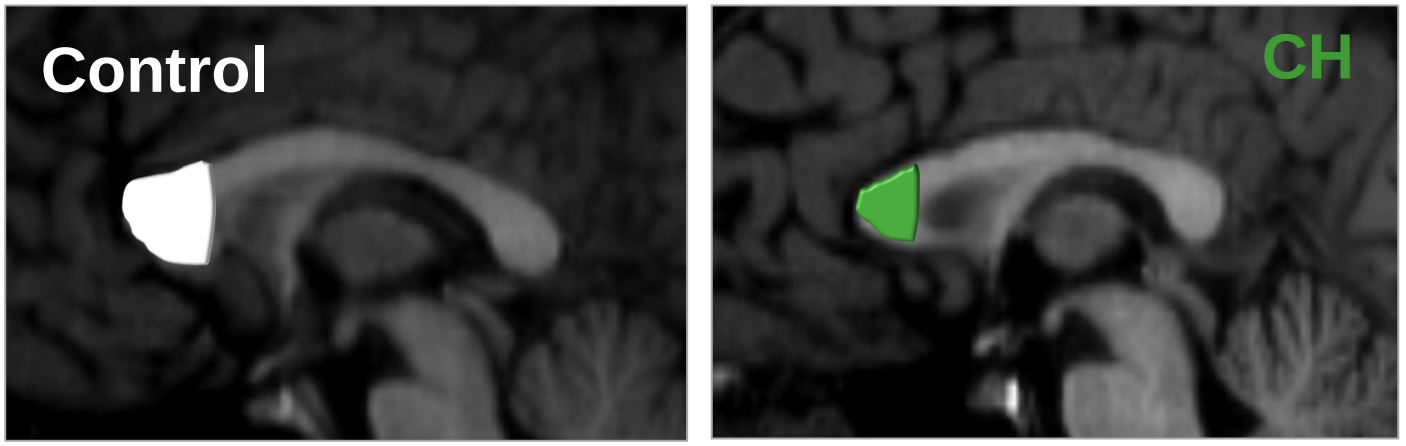


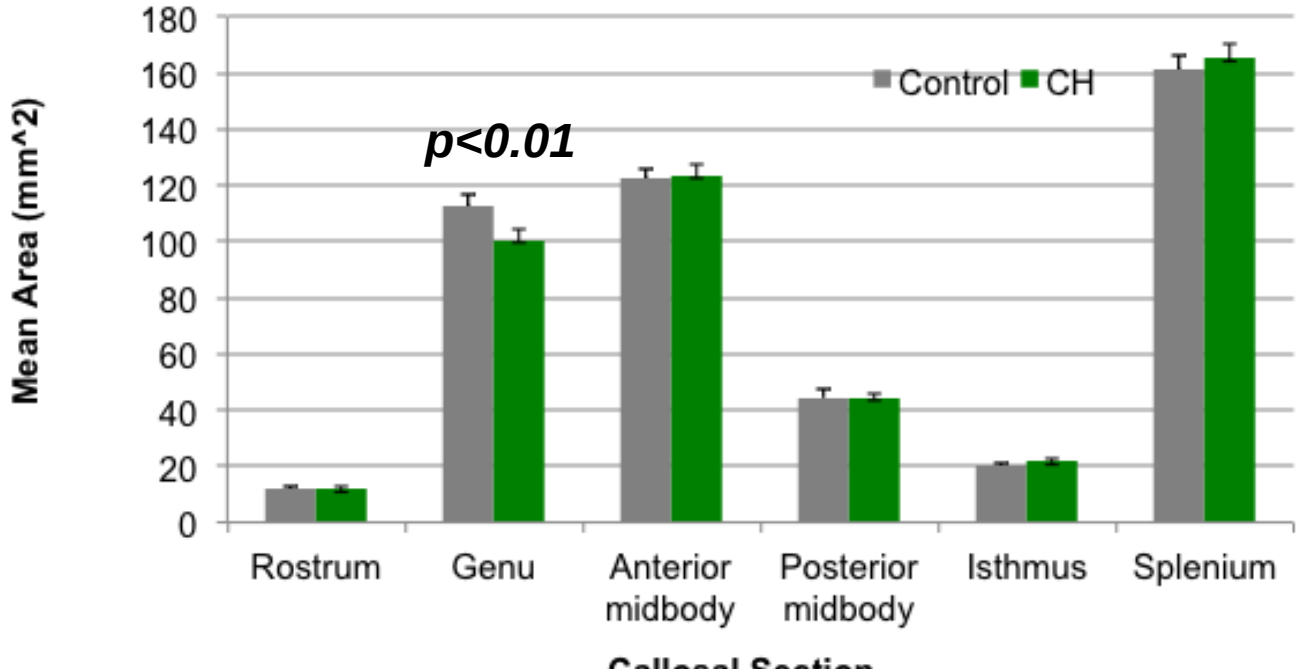


Ibrahim F et al, ATA 2013



CH have smaller genus





Is corpus callosum development abnormal in children born to women with thyroid hormone insufficiency during pregnancy?

Research Questions

1. Is the corpus callosum (CC) abnormal in size and/or shape in offspring of hypothyroid women (HYPO)?
2. Are CC abnormalities related to severity or duration of maternal hypothyroidism?
3. Do CC abnormalities predict outcome in HYPO?

Sample: HYPO

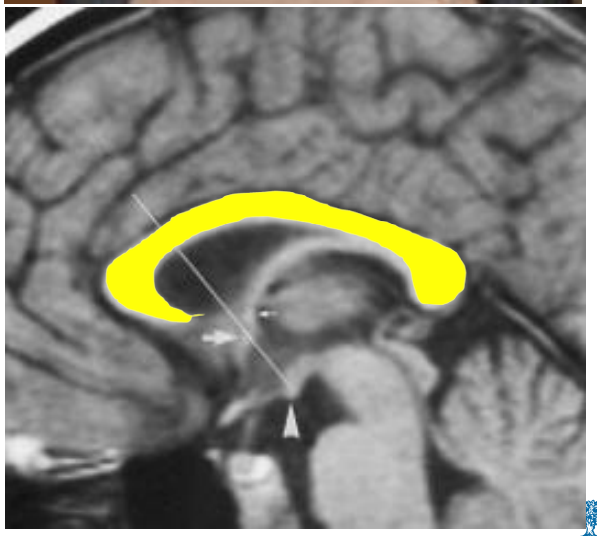
- N=20
- 9 to 12 yrs (mean=10.3 yrs)
- Born 1996-2001 to women with hypothyroidism diagnosed prior to (83%) or during pregnancy
- Inclusion criterion: mothers not given L-T4 dose increase in pregnancy
- Excluded if mothers had normal TSH levels in all trimesters

Sample: Controls

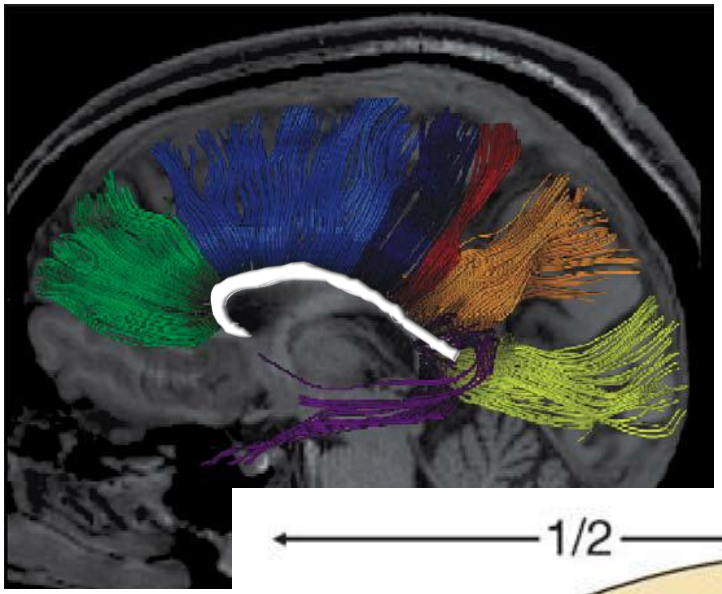
- 22 children, mostly from same birth cohort as HYPO
- Matched with HYPO for sex, age, socioeconomic status
- Mean age = 10.9 years
- All mothers *claimed* no hypothyroidism during pregnancy or since

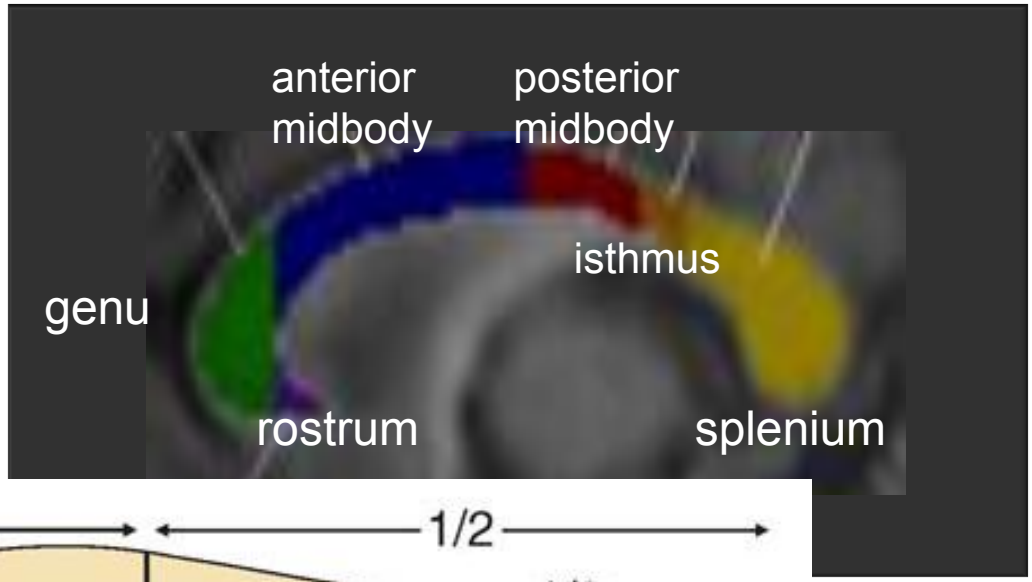
Procedures

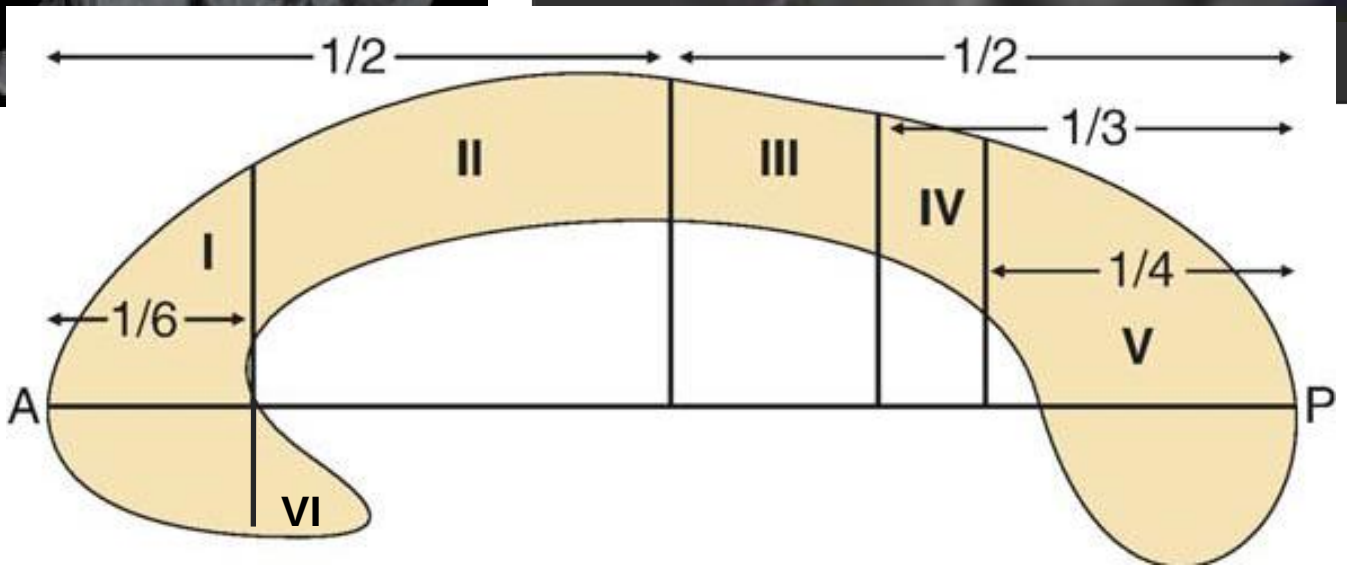
- Day 1: 4-hour neuropsychological evaluation
- Day 2: 1-hour MRI scan in 1.5 Tesla magnet
  - 7-min axial T1 FSPGR sequence (*TR/TE=10.3/4.2 ms, inversion time=400 ms, flip angle = 20^0, slice thickness = 1.5mm)*
- Corpus callosum manually traced and measured using Analyze 9.0



Quantitative Approach

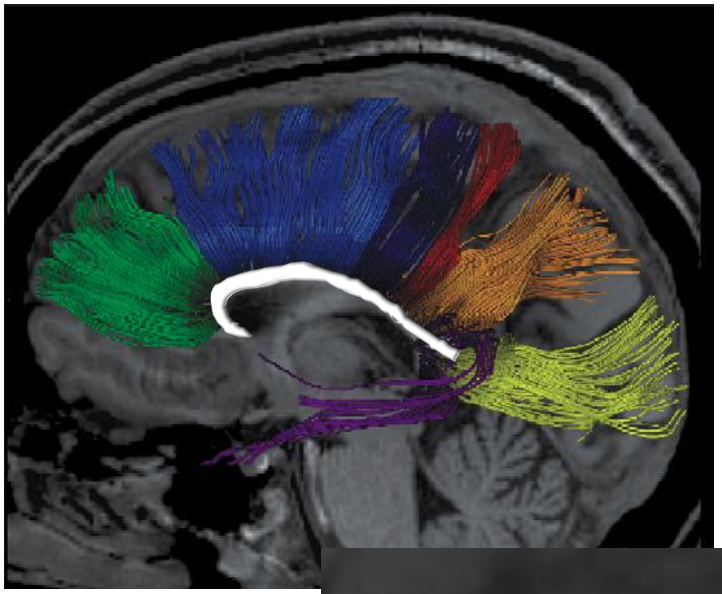


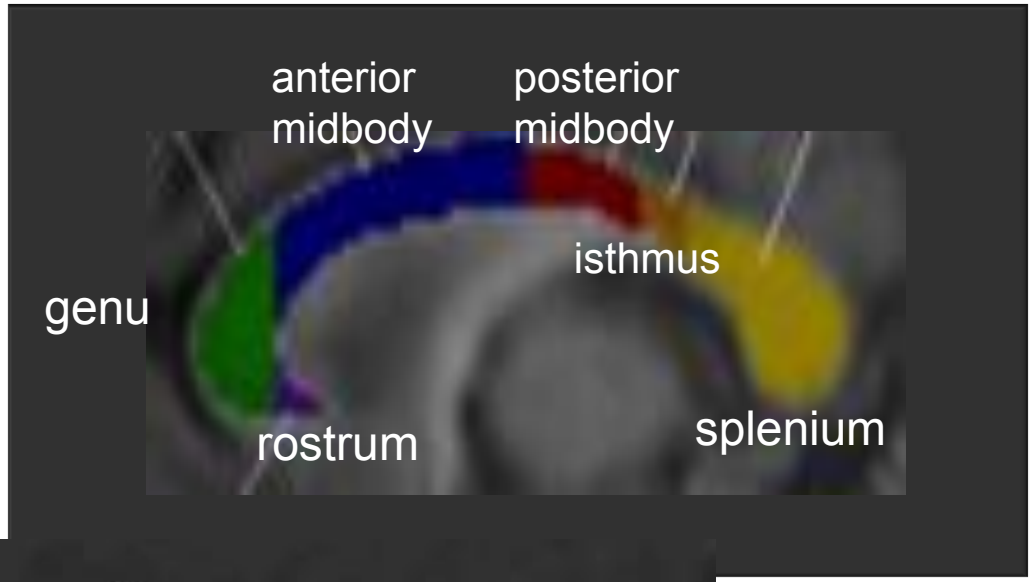


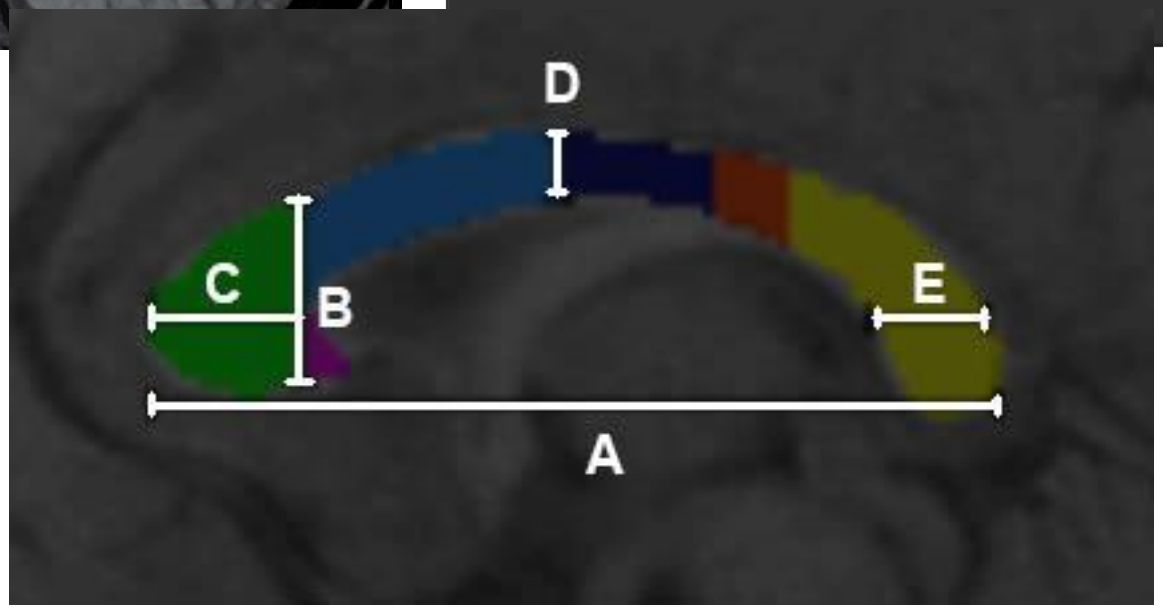


Hofer & Frahm (2006) NeuroImage 32:989-994

Quantitative Approach

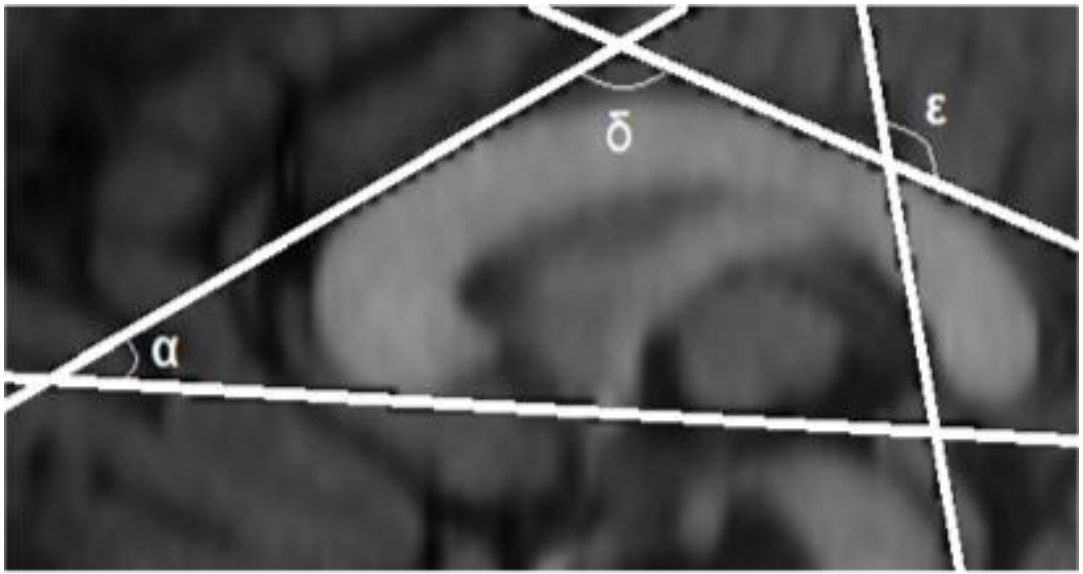






Qualitative Approach

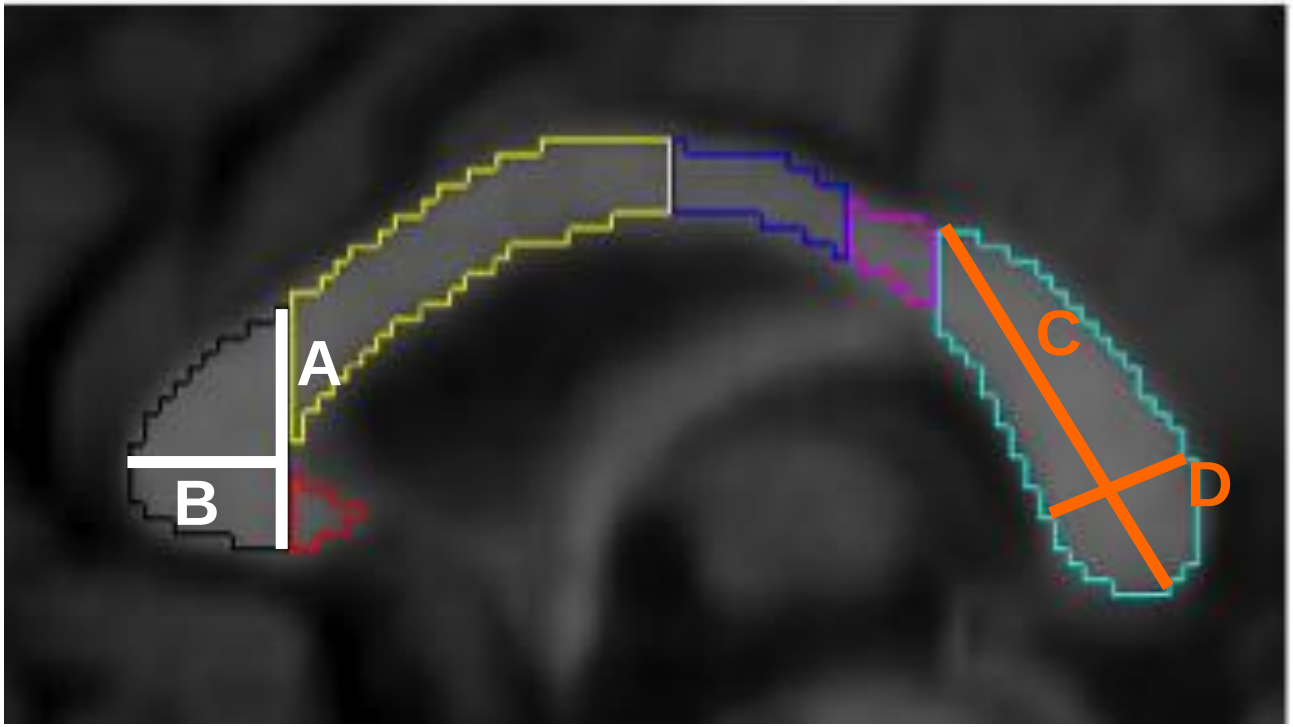
- Curvature (δ)
- Droop (ε)
- Peak (α)



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

Qualitative Approach

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



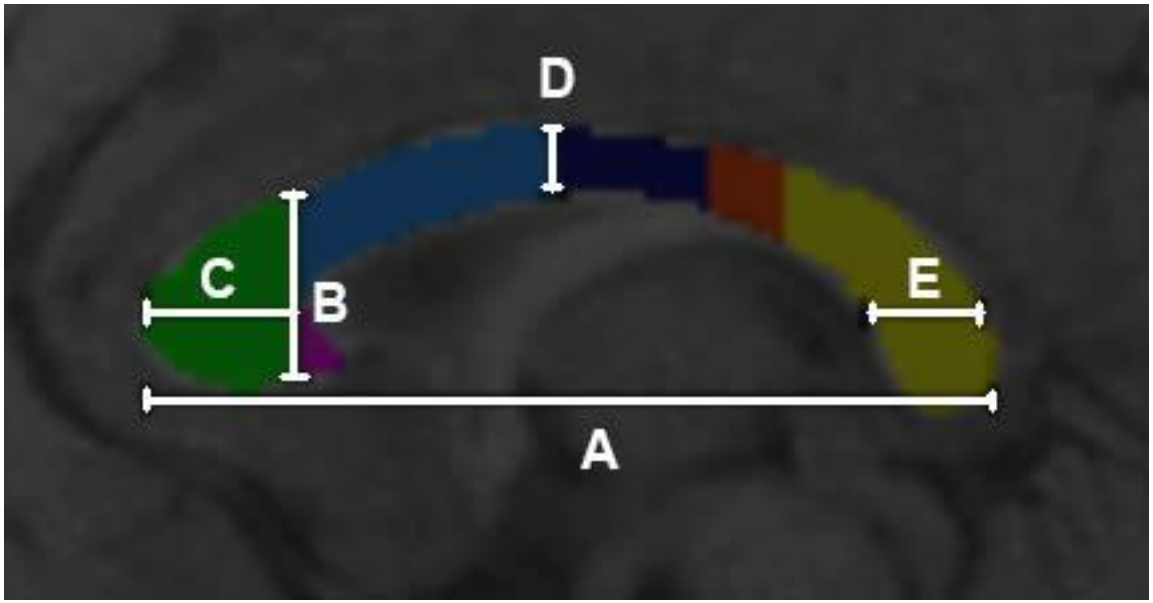
HYPO Have Smaller Genu/Larger Splenium

Group X Region Interactions

Raw areas: F=4.49, p=0.05

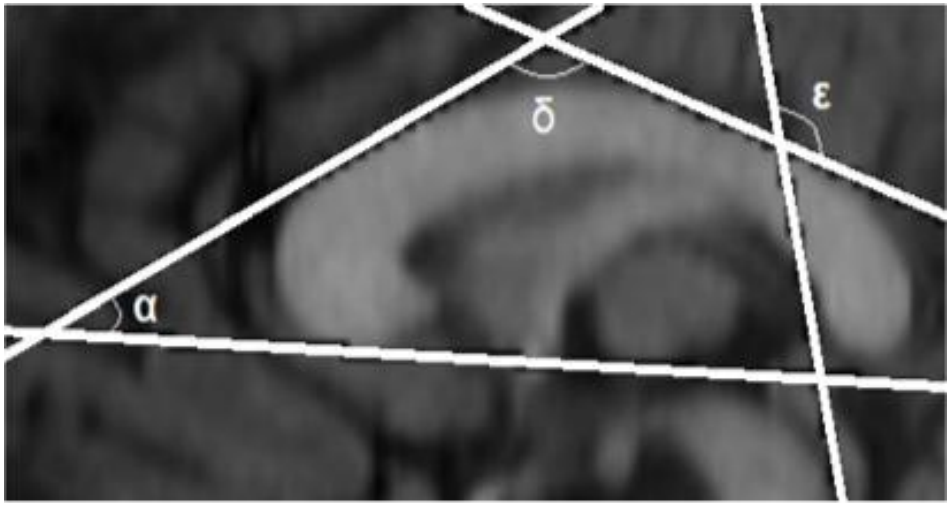
Proportions: F=5.15, p=0.02

Linear Measurements



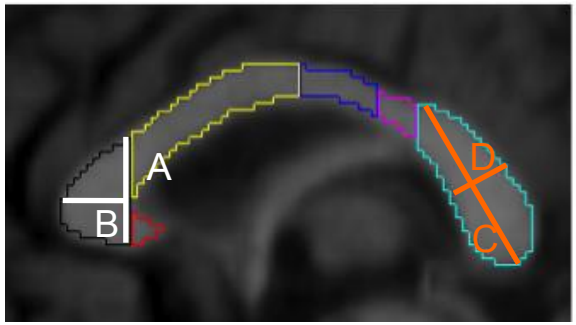
- No significant group differences in lengths or widths

Angles



- No significant group differences in curvature or orientation of genu or splenium

Shape of Genu & Splenium

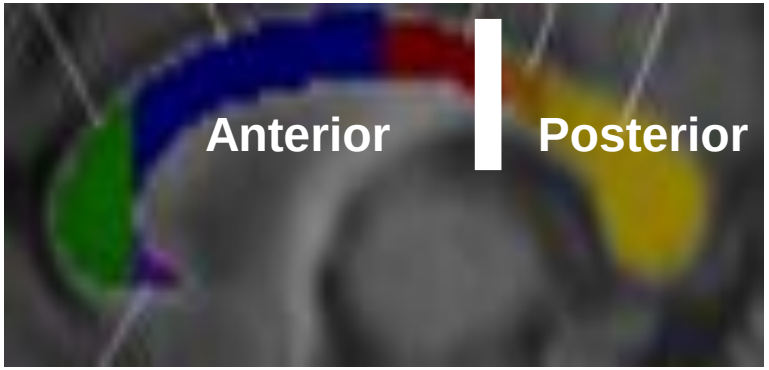


HYPO have shorter/wider genus than controls

HYPO have longer/narrow spleniums than controls

Correlations with Maternal Hypothyroidism

- Corpus callosum size/shape not correlated with any trimester maternal TSH/T4
- Size of anterior and posterior segments correlated with duration of maternal hypothyroidism in pregnancy



Structure/Function Correlations

- Larger anterior CC (posterior midbody) associated with better reading ability

- Larger genu with better cognitive flexibility

Structure/Function Correlations

- Smaller isthmus with better nonverbal memory

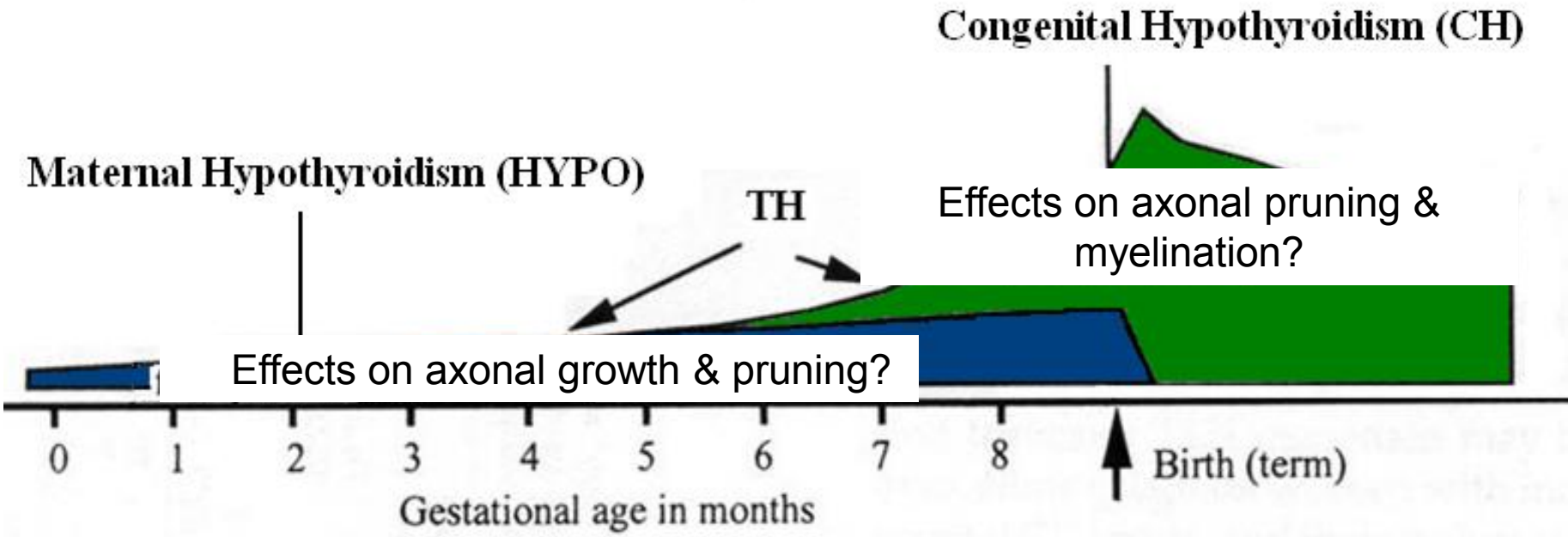
- Smaller splenium with better verbal ability

In Summary

- HYPO relative to controls show:
  - Reduced size of genu and increased size of splenium
  - Abnormal splenium and genu shapes
  - Normal lengths & thickness of CC
  - Normal CC shape

In Summary

- No effect of maternal hypothyroidism severity
- More severe effects reflect duration of hypothyroidism
- Size of specific CC regions associated performance in different cognitive abilities in HYPO



HYPO

- **Normal shaped CC**
- **Smaller & wider genu**
- **Larger (longer, skinnier) splenium**

CH

- **Flatter CC**
- **Smaller & narrower genu**
- **Abnormally oriented but normal size splenium**

Morreale de Escobar G et al, 2000

Conclusion

- Inadequately treated hypothyroidism in pregnancy disturbs corpus callosum development by disrupting the patterning of axonal growth and pruning
- These effects are associated with reduced cognitive abilities

Thank You

AMERICAN THYROID ASSOCIATION

FOUNDED 1923