

Neonatal pain management with glucose and thalamus and basal ganglia development: sex-specific effects

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Background

- Preterm infants undergo numerous invasive procedures.
- Glucose and sucrose commonly used for pain management in preterm neonates.
- Analgesia mediated through opioids receptors, dopaminergic and cholinergic pathways.
- **Hypothesis:** In the preterm population, subcortical grey matter structures represent vulnerable areas susceptible to disrupted maturation in relation to invasive procedures.

Objective

To determine the association of (i) pain and (ii) glucose exposure on thalamic and basal ganglia development in very preterm neonates.

Methods

Participants:

- 51 very preterm neonates (22 males, born gestational age (GA) 27.6 (26.6-28.6))
- 3 serial scans between birth and term-equivalent age (TEA) at median GA: i) 29.4 (27.9-30.1), ii) 31.8 (30.0-34.5) and iii) 41.0 (39.7-41.6)

Volume segmentation:

- Thalamus, basal ganglia and white matter tracts segmented in the T1-weighted images using MAGeT brain segmentation pipeline

Pain definition

- Pain operationalized as the total number of invasive procedures

Statistics:

- Log transformation of thalamic and basal ganglia volumes
- Generalized estimating equations for repeated measures to assess association between thalamic and basal ganglia volumes and pain and glucose exposure adjusting for factors related to prematurity (gestational age (GA) at birth and at MRI, number of days of mechanical ventilation, and exposure to morphine).

More invasive procedures predict smaller volumes in thalamus and basal ganglia: increasing effect over time

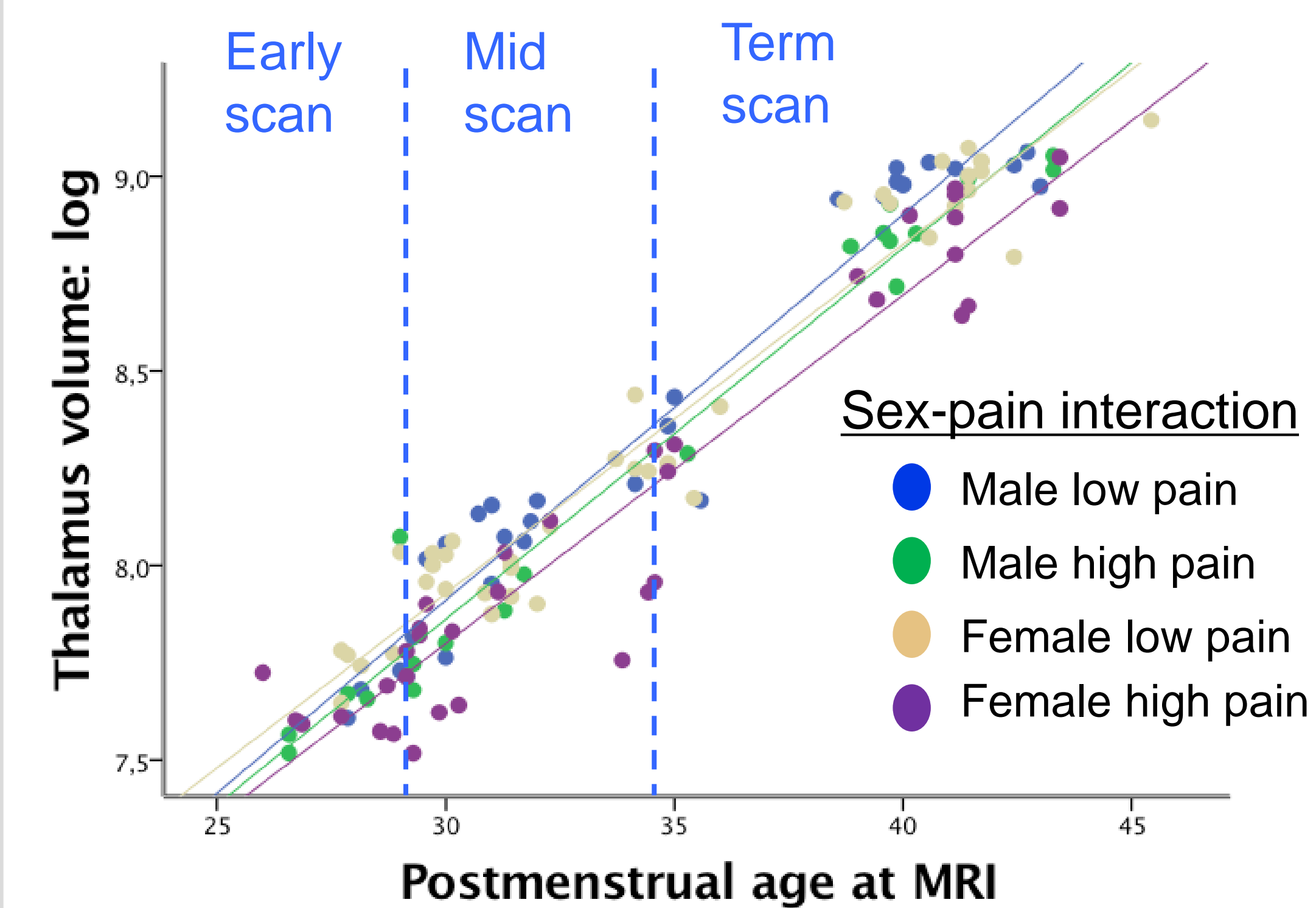
Thalamus volumes: log	Basic model – early period (scan 1 to scan 2)		Basic model – whole period (scan 1 to TEA scan)	
	β	p	β	p
GA at birth	0.017	0.246	-0.030	0.029
GA at MRI	0.063	<0.001	0.092	<0.001
Days of ventilation	0.007	0.317	0.006	0.230
Sex	0.056	0.259	0.093	0.008
Glucose	-0.006	0.118	-0.002	0.475
Invasive procedures	-0.001	0.023	-0.001	<0.001

Table 1: Generalized Estimated Equation Model for thalamus volumes with comparison of the early and the whole period.

For each invasive procedure, thalamic volume decreases per 0.1%. The association of invasive procedures and thalamic volumes is more apparent at term equivalent age.

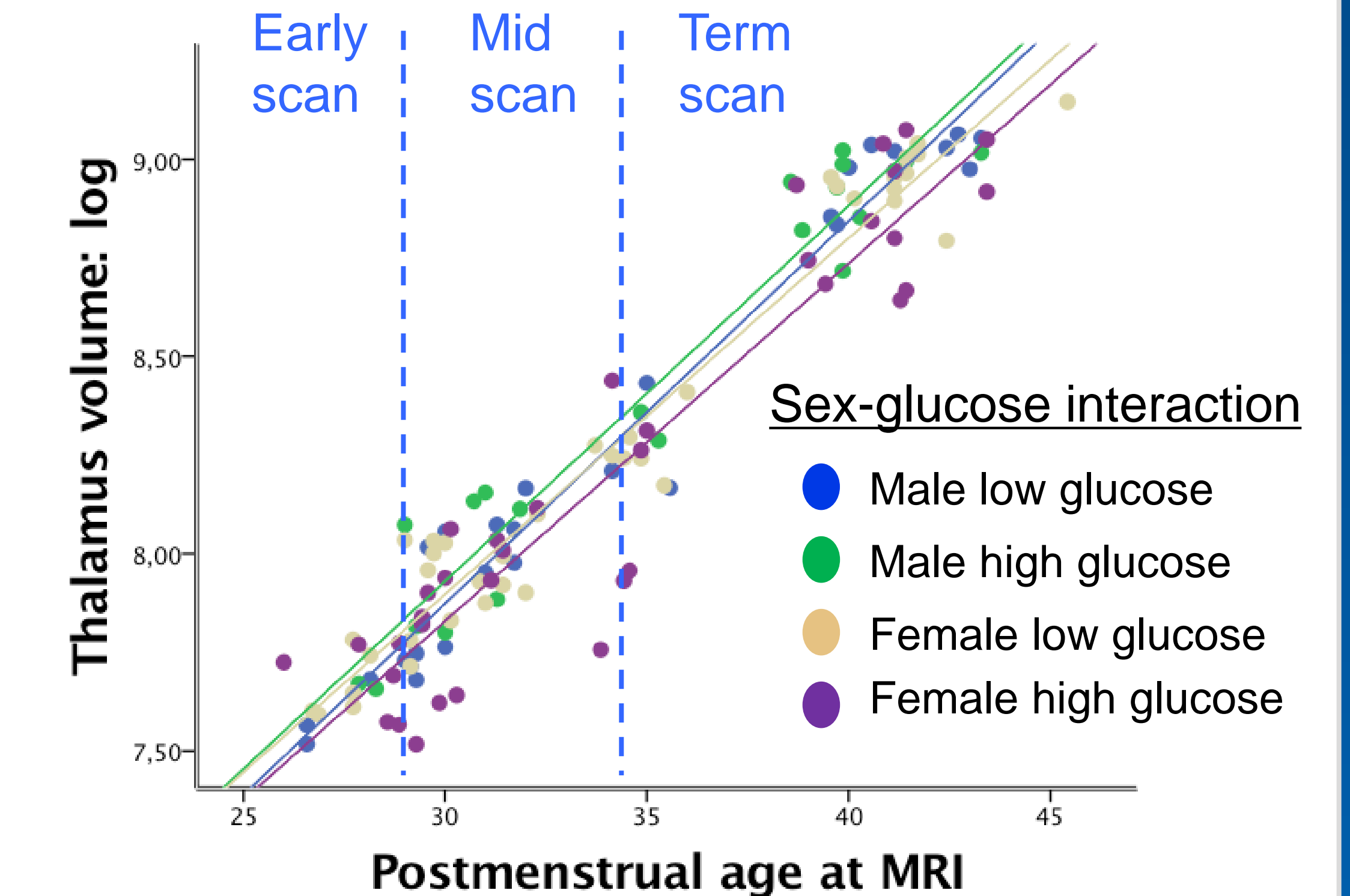
Results

More invasive procedures predict lower thalamus and basal ganglia volumes, especially in girls



Girls exposed to more procedures have the lowest volumes in thalamus ($\beta=-0.001$, $p<0.001$), and basal ganglia ($\beta=-0.001$, $p<0.001$), after accounting for factors related to prematurity.

More glucose exposure is associated with lower thalamus and basal ganglia volumes, only in girls



Growth of the thalamus is slower in infants receiving high amounts of pain and suggesting additive effects of glucose, which are more pronounced in girls ($\beta=-0.006$, $p=0.045$) than boys ($\beta=0.008$, $p=0.130$).

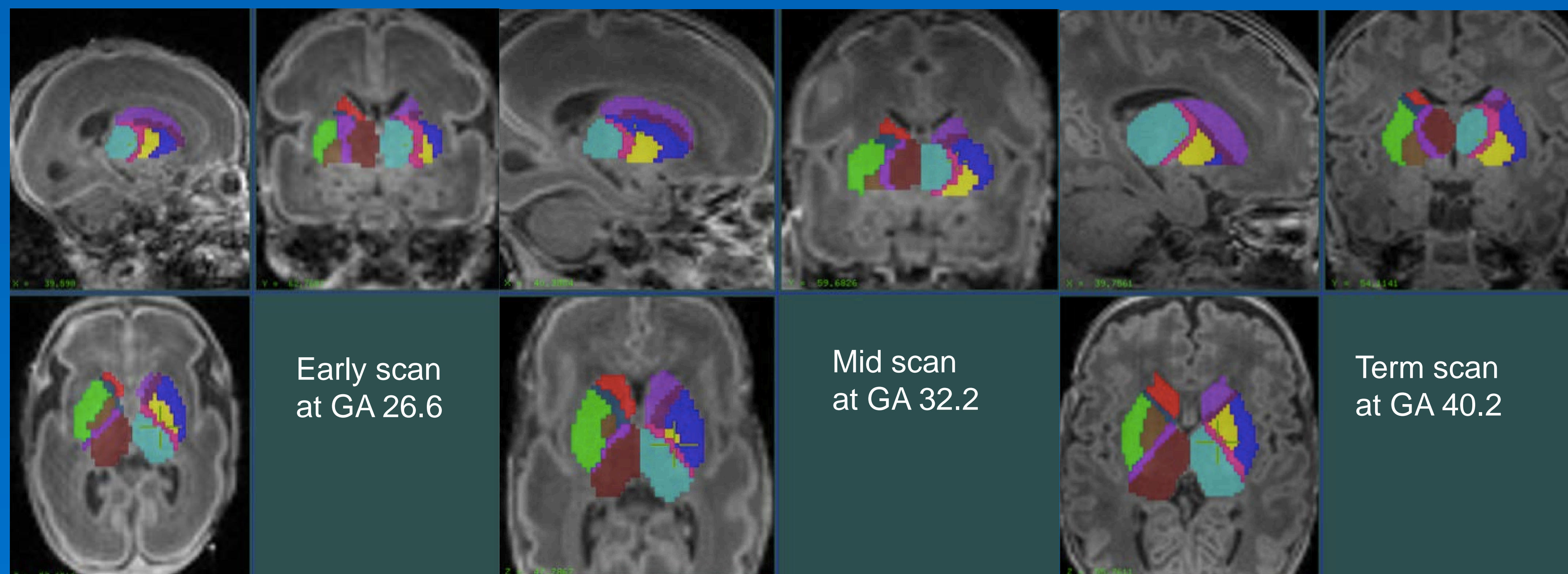


Figure 1: Segmentation templates on T1-weighted images from the same patient born at GA 27.3

Conclusions

- Subcortical grey matter structures appear to be vulnerable to repeated invasive procedures early in life.
- The adverse relationship of pain and glucose exposure with thalamic and basal ganglia development needs attention especially in girls in regards to long-term neurodevelopment.