A photograph of the main building of University College London, a grand neoclassical structure with a portico of tall columns and a large dome. People are seen sitting on the steps in front of the building. The sky is clear and blue.

FIAPAC 2024
RCOG update on fetal awareness

Maria Fitzgerald
University College London

Royal College of Obstetrics and Gynaecology Fetal Awareness Evidence Review, Dec 2022

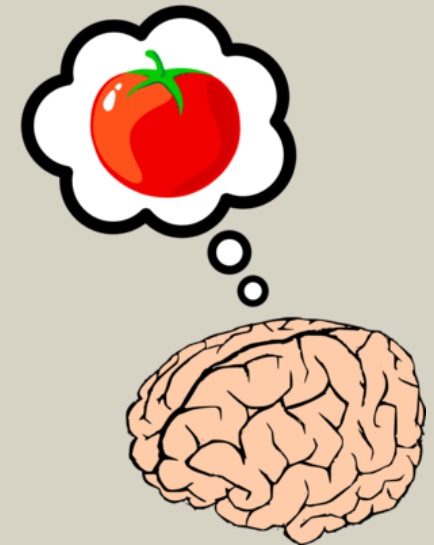


**Updated review of Research and Recommendations for Practice
from the Royal College of Obstetrics and Gynaecology**

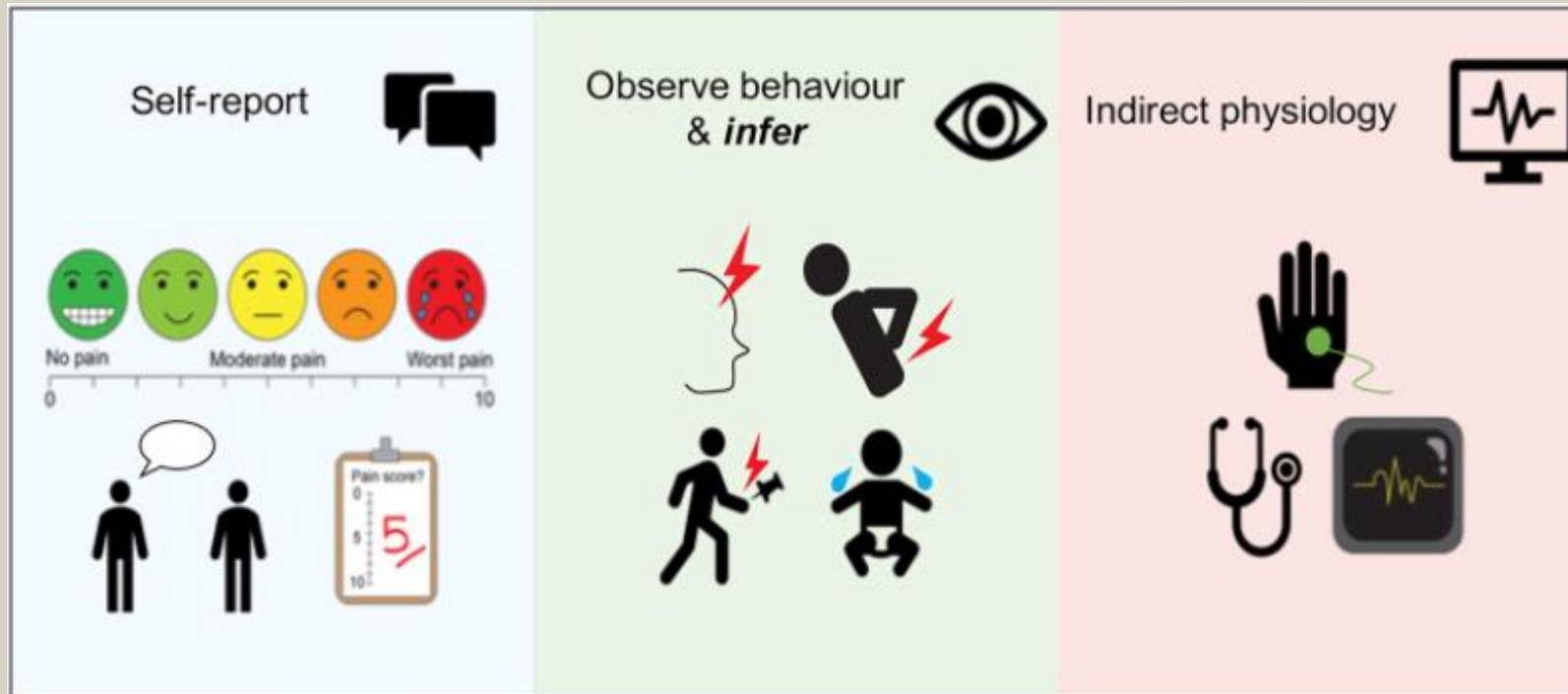
<https://www.rcog.org.uk/guidance/browse-all-guidance/other-guidelines-and-reports/fetal-awareness-updated-review-of-research-and-recommendations-for-practice/>

What is meant by 'awareness' of pain

- Pain is an alarm system, warning an organism of danger in the environment. This 'protective' pain triggers immediate attention, action, and adaptive learning (Tracey et al., 2019).
- But 'sensing' or 'detecting' a noxious event does not mean that it is necessarily 'perceived', in the form of a representation or image in the mind (Damasio, 2021).
- To experience pain requires consciousness. Phenomenal consciousness is the "what it is like" to be in pain. The report focussed upon when the most immediate and limited pain phenomenal experience might emerge in the fetus following tissue damage.



A challenge - measuring pain



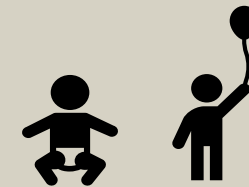
Reliability

Observer bias

Interpretation



Direct recordings & imaging in specific areas; single & multiple neurons, awake wildtype or mutant animals.

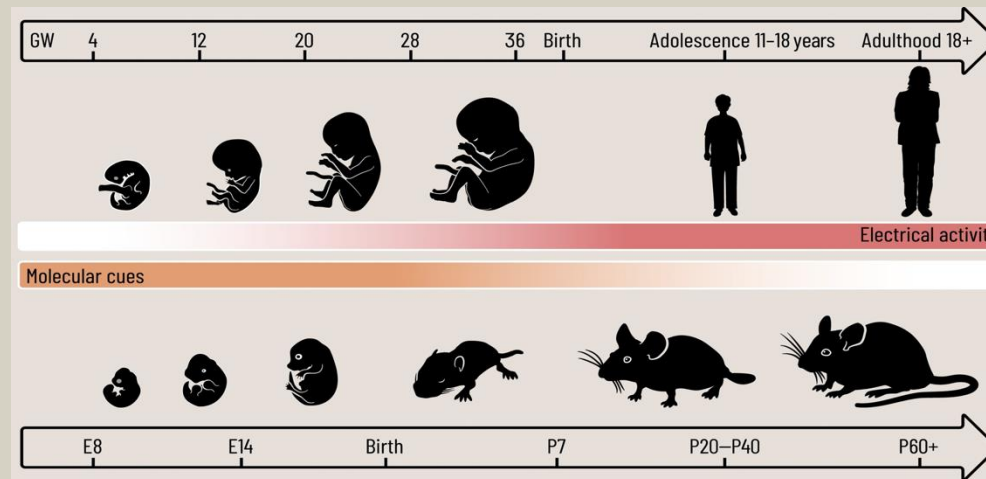


Pain reflexes & behaviour; whole or regional brain imaging & electrophysiology

Neuroscience can help us to understand the developing pain system



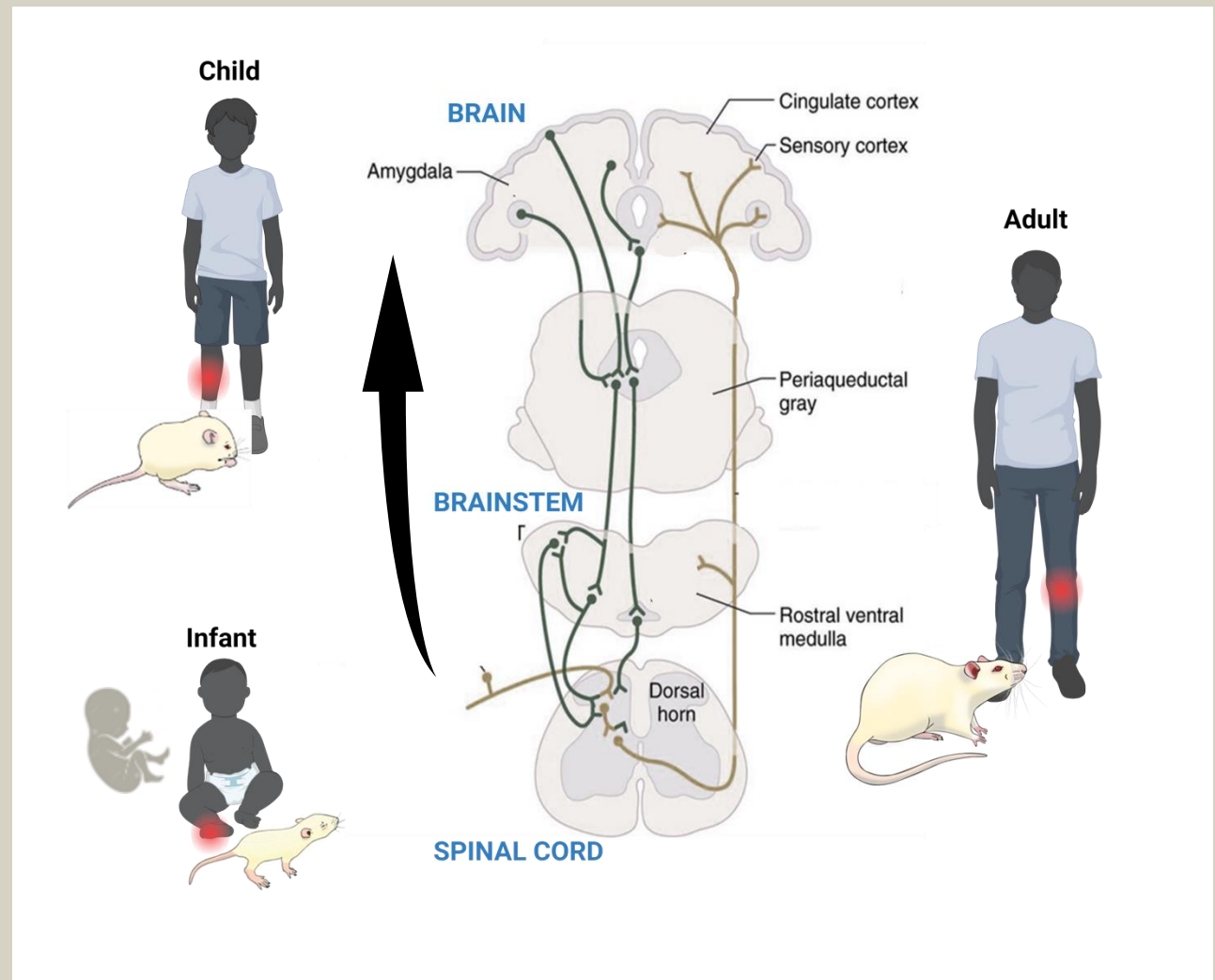
- Recording and interpreting fetal behaviour following noxious (tissue damaging) events.
- Mapping the anatomical and physiological development of nociceptive pathways in the central nervous system.
- Translating knowledge from animal models.



Pain is processed at multiple levels of the central nervous system

Maturation of nociceptive circuits proceeds bottom up:-

1. spinal cord & medulla
2. midbrain
3. cortex



What is the evidence for fetal sentience in the second trimester?



1. Study of fetal movements

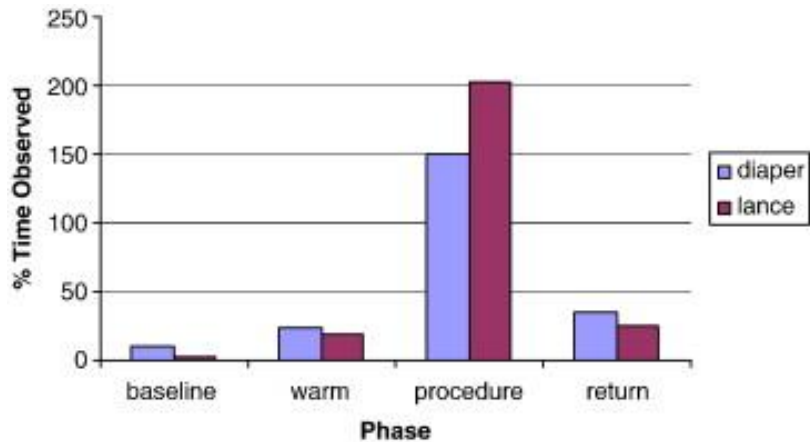
- Ultrasound recording, including 3D and dynamic magnetic resonance imaging (MRI) reveal fetal movements from 7.5 weeks gestation (Einspieler et al., 2021) .
- These early movements are spontaneously generated by neurons in the spinal cord and brainstem and do not require a sensory stimulus.
- However, they can be triggered by external stimulation. In the second trimester reflex withdrawal movements are observed following external sensory stimulation eg amniocentesis needle (Petrikovsky & Kaplan 1995)

Einspieler C, Prayer D, Marschik PB (2021) Fetal movements: the origin of human behaviour. *Dev Med Child Neurol* 63:1142.

Petrikovsky & Kaplan (1995) Fetal responses to inadvertent contact with the needle during amniocentesis. *Fetal Diagn Ther*;10:83

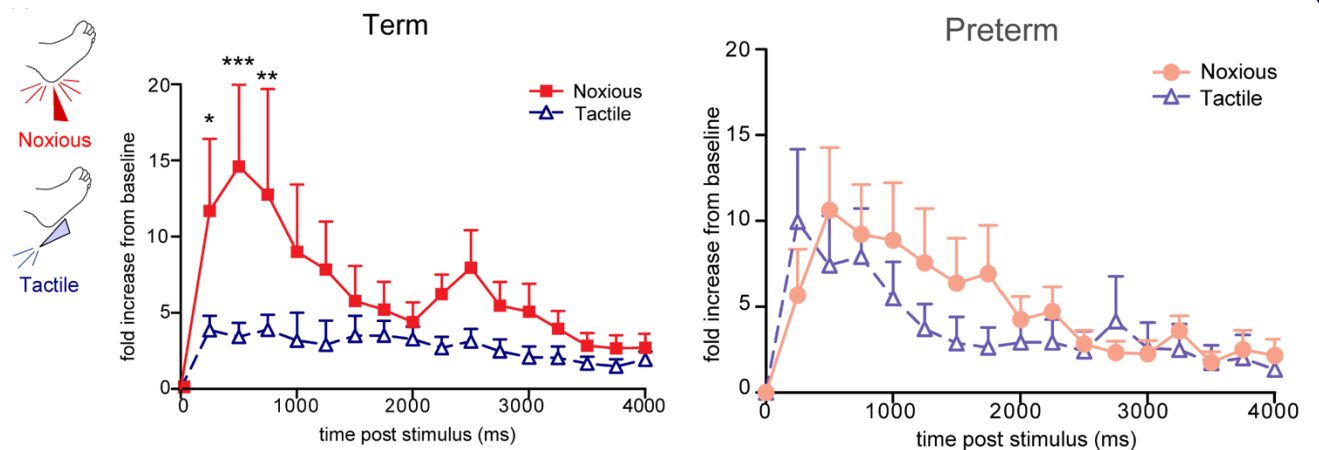
Does the fetus discriminate between pain and touch?

2. Comparison of preterm infant reflex movements to touch and heel lance



Preterm infants <28 weeks. Heel lance evoked no specific changes in movement. Effect of diaper change greater than heel lance.

Gibbins S, et al. (2008) Pain behaviours in extremely low gestational age infants. *Early Hum Dev* 84:45 1.



Preterm infants 28-36 weeks compared to term infants. Heel lance and touch evoke the same reflex EMG response, whereas at term there is a significant difference in response.

Cornelissen L, Fabrizi L, Patten D.....Fitzgerald M (2008) Postnatal temporal, spatial and modality tuning ...*PLoS One* 2013;8(10):e76470

Does the fetus discriminate between pain and touch?

3. Study of fetal grimacing



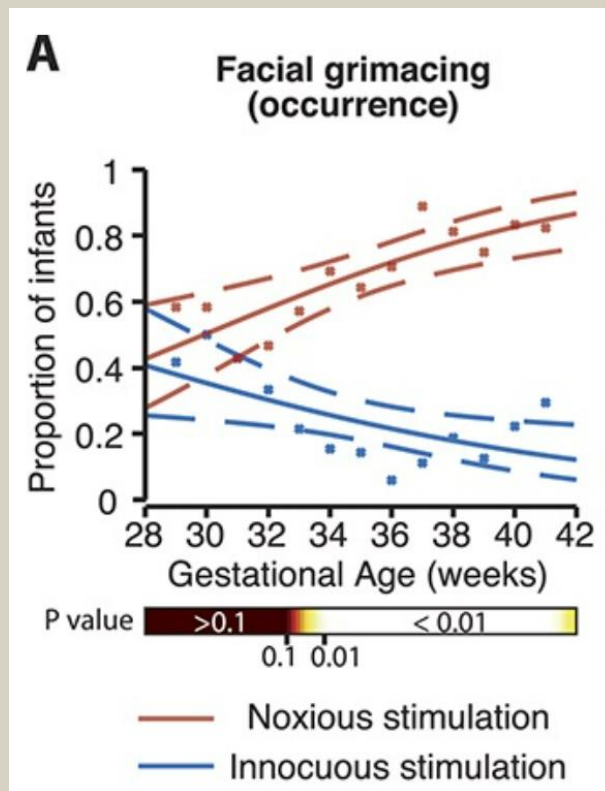
4D in utero image resting state 23 weeks



Injection of pacuronium & fentanyl i.m.
No innocuous sensory control. The same
grimacing occurs spontaneously

Does the fetus discriminate between pain and touch?

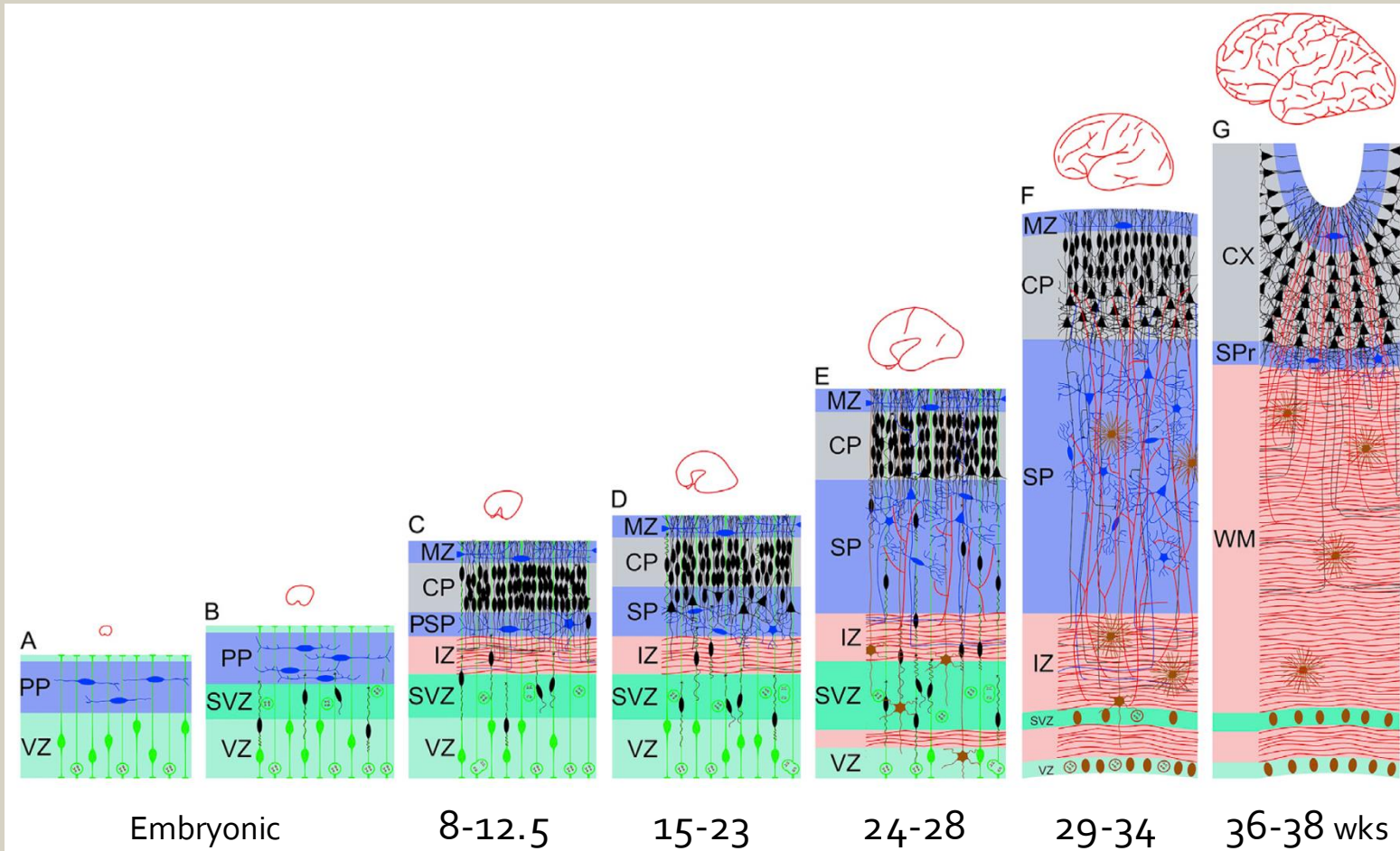
4. Comparison of preterm infant grimacing to touch and heel lance



Change of facial expression after noxious and innocuous stimulation is age-dependent.

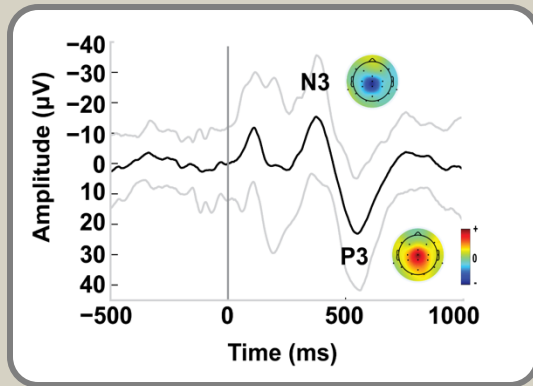
Facial grimacing that discriminate a noxious stimulus from an innocuous one emerge from approximately 33 weeks' gestation.

The perception and discrimination of pain requires the maturation of the brain

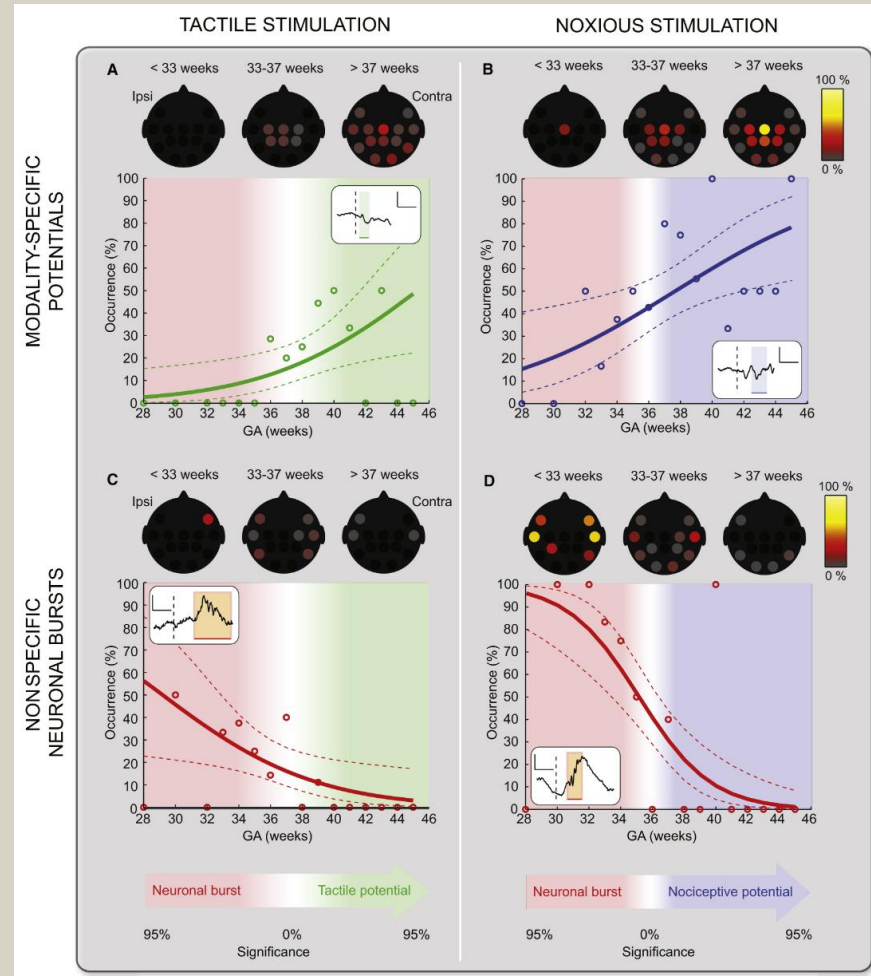


Growth of sensory thalamic fibres into the cortex occurs at 23-24 weeks. Early connections between with subplate neurons are instructional rather than sensory and generate the spontaneous activity required for healthy cortical development.

Fetal brain: 30-31 weeks a key stage – shift from endogenous activity to sensory driven cortical patterns



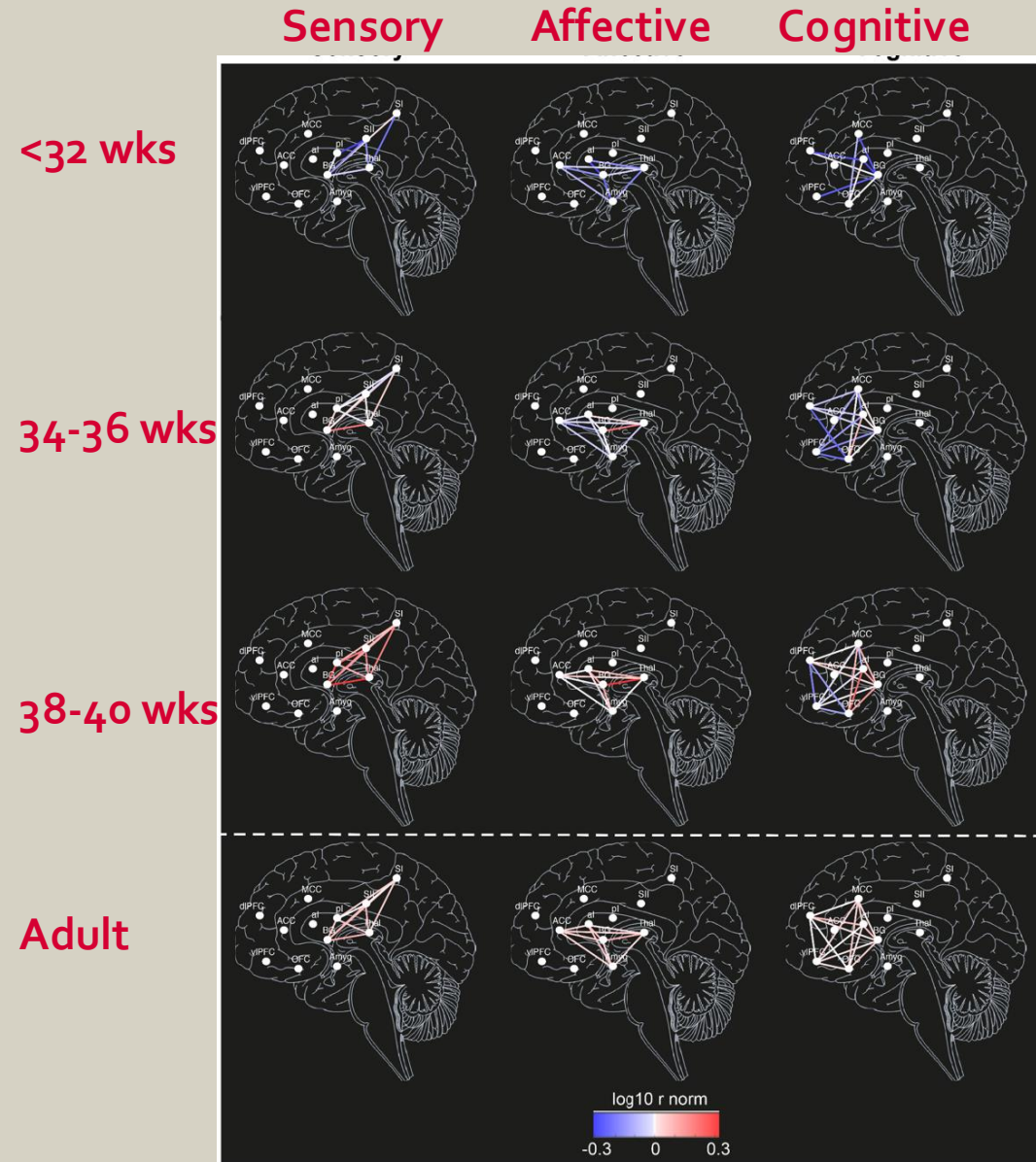
N₃/P₃, group average following heel prick (n=33)



Developmental trajectory of pain related brain connections

- Sensory/discriminative subnetwork matures first
- Affective/ motivational follows
- Cognitive/evaluative matures last

Jones L, Batalle D, Meek J, Edwards AD, Fitzgerald M, Arichi, T, Fabrizi, L under review



Strength of connections within the sensory, affective & cognitive subnetworks of the pain connectome

Summary

- The RCOG report focussed upon evidence indicating when the most immediate and limited pain phenomenal experience might emerge in the fetus following tissue damage.
- We have highlighted the problems in interpreting fetal movements and facial grimaces following noxious stimulation in utero, such as from surgical needles.
- Evidence from the study of preterm infants shows that before 33 weeks the movements and facial expressions evoked by a noxious (heel lance) are indistinguishable from those evoked by innocuous, light touch of the heel.
- From this, we conclude that fetal sentience in the second trimester consists of non-specific reactions to a body stimulus, rather than evidence of pain experience.
- Study of the preterm human infant brain supports the role of the cortex in the maturation of pain discrimination and experience, beginning at 33 weeks.
- The possibility of pain perception at earlier gestational ages is unlikely.