Imaging the developing brain in prenatal alcohol exposure

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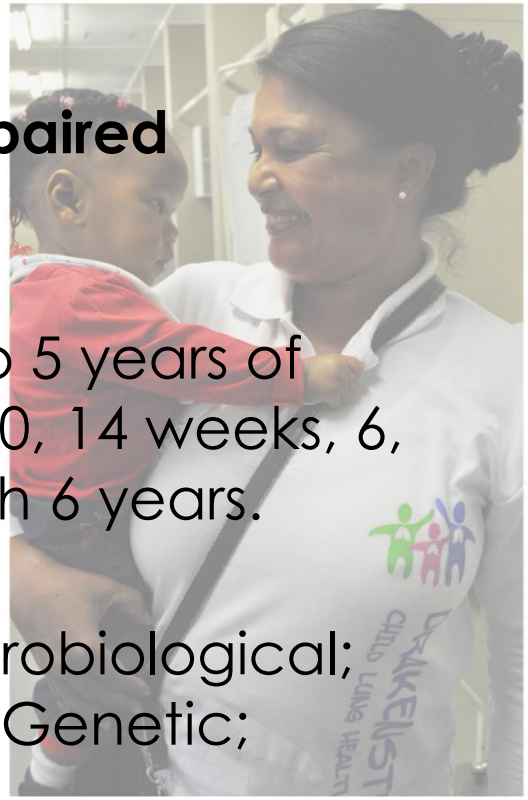
Outline

- **Background on study**
- Infant imaging
- Scan modalities and analysis
- What is next?

Drakenstein Child Health Study (DCHS)

- Multi-year birth cohort study following 1,200 mother-child dyads in the Drakenstein sub-district
- **OBJECTIVE:** Investigates risk factors for **impaired childhood health and development**
- Prospective follow up from 2nd trimester to 5 years of age. Intensive visits in first year of life - 6, 10, 14 weeks, 6, 9, 12 months; thereafter 6 monthly through 6 years.
- Risk factors in 7 areas: Environmental; Microbiological; Nutritional; Psychosocial; Immunological; Genetic;
- Maternal



Study Location

Paarl - semi-rural area, 60km from Cape Town

High levels of poverty, unemployment, illness

Good primary health care infrastructure, high vaccine coverage

Enrolment at 2 clinics:
TC Newman (mixed race),
Mbekweni (African population);
all births at Paarl hospital

- Stable population
- Excellent retention & follow-up, strong buy-in from community
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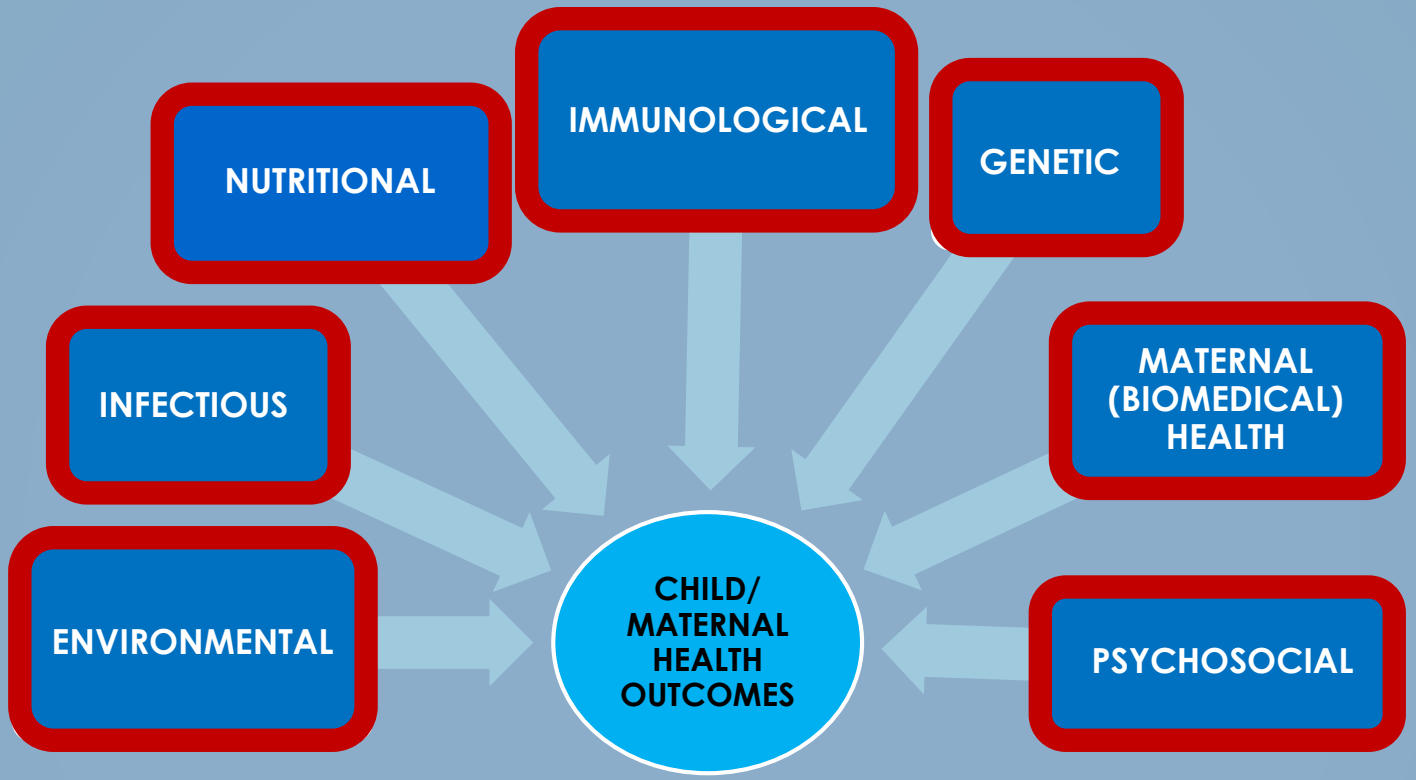
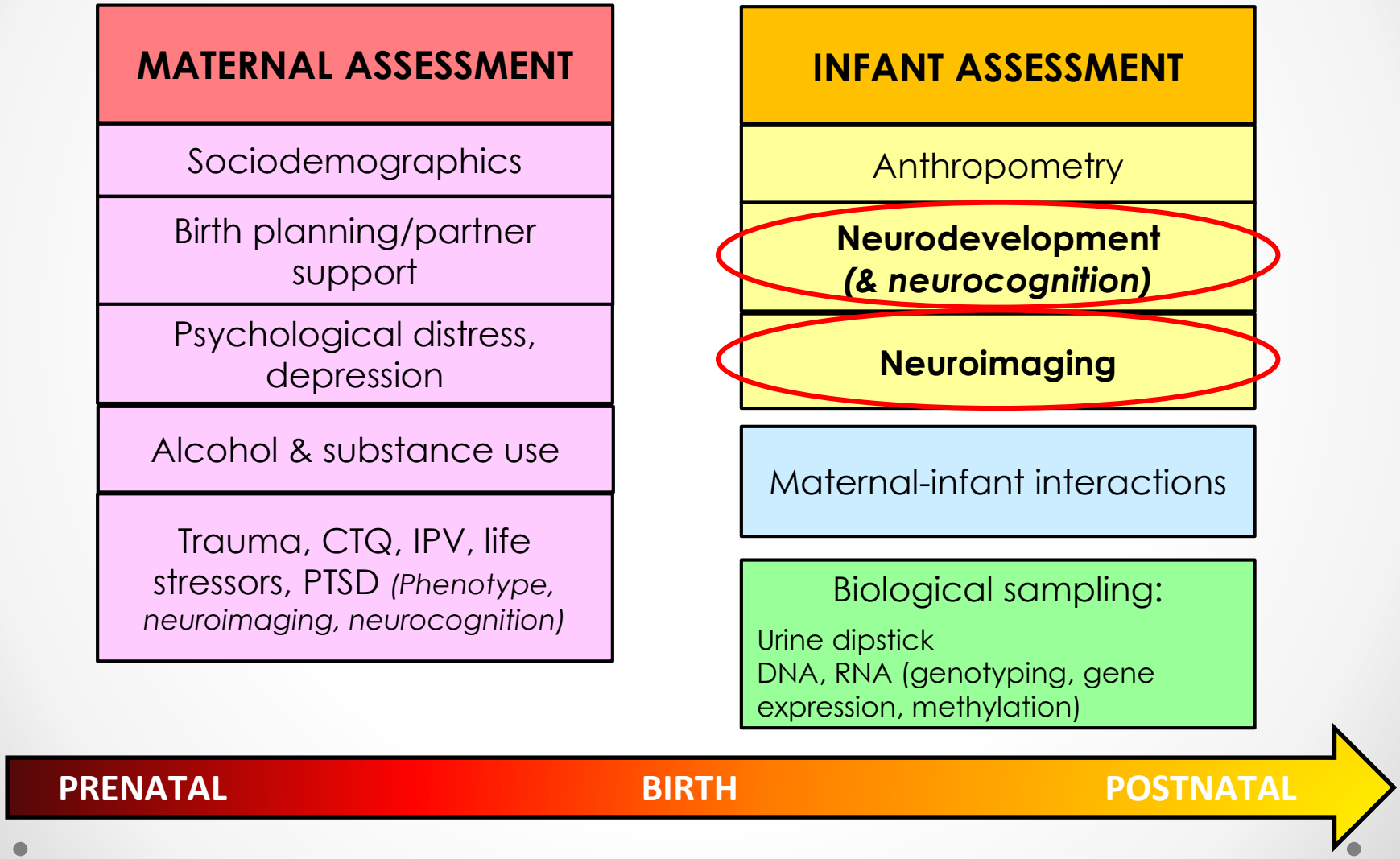
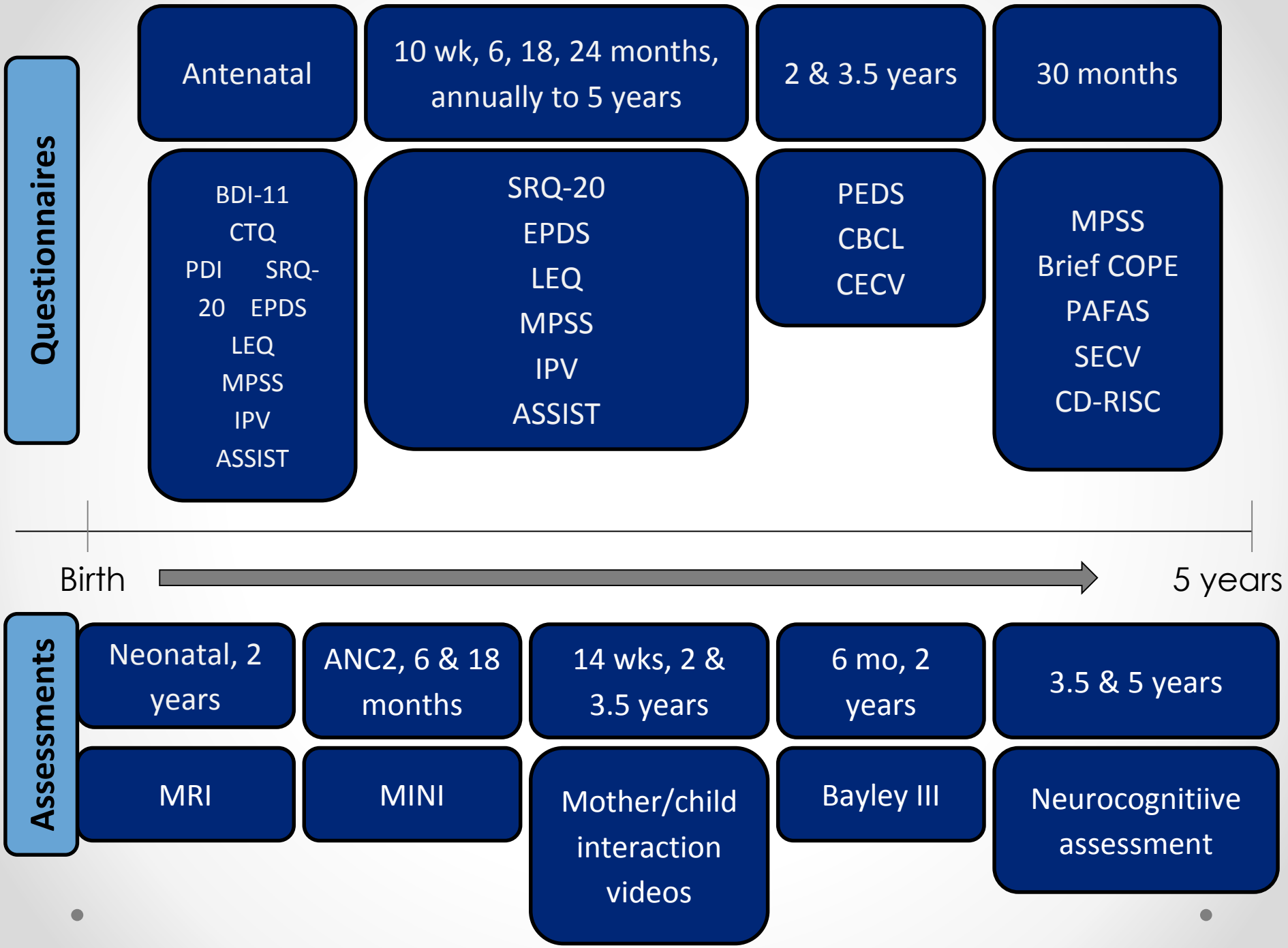


Drakenstein Child Health study - birth cohort following 1,200 mother child pairs in to investigate the epidemiology, aetiology and risk factors for **childhood illness and the impact on child health.**

Research activities




Questionnaires
Antenatal
10 wk, 6, 18, 24 months, annually to 5 years
2 & 3.5 years
30 months
BDI-11
CTQ
PDI SRQ-20 EPDS
LEQ
MPSS
IPV
ASSIST
SRQ-20
EPDS
LEQ
MPSS
IPV
ASSIST
PEDS
CBCL
CECV
MPSS
Brief COPE
PAFAS
SECV
CD-RISC
Birth
5 years
Assessments
Neonatal, 2 years
ANC2, 6 & 18 months
14 wks, 2 & 3.5 years
6 mo, 2 years
3.5 & 5 years
MRI
MINI
Mother/child interaction videos
Bayley III
Neurocognitiive assessment

Infant imaging

- Data acquired of 236 infants aged 2-4 weeks:
  - Alcohol exposed
  - *Healthy controls*
  - Clinical depression

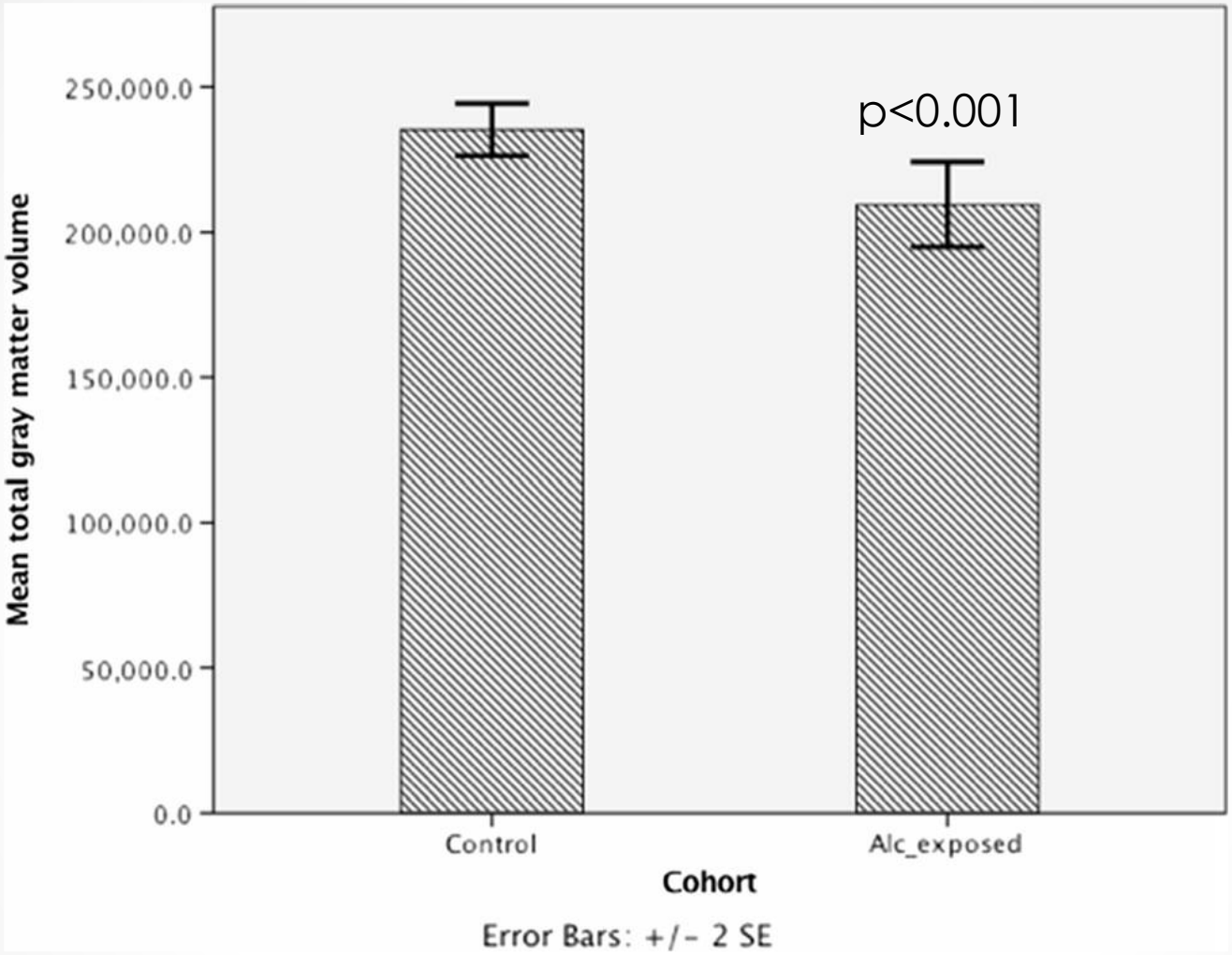
Scan modalities

1. **Structure:** T2 (and T1 initially)

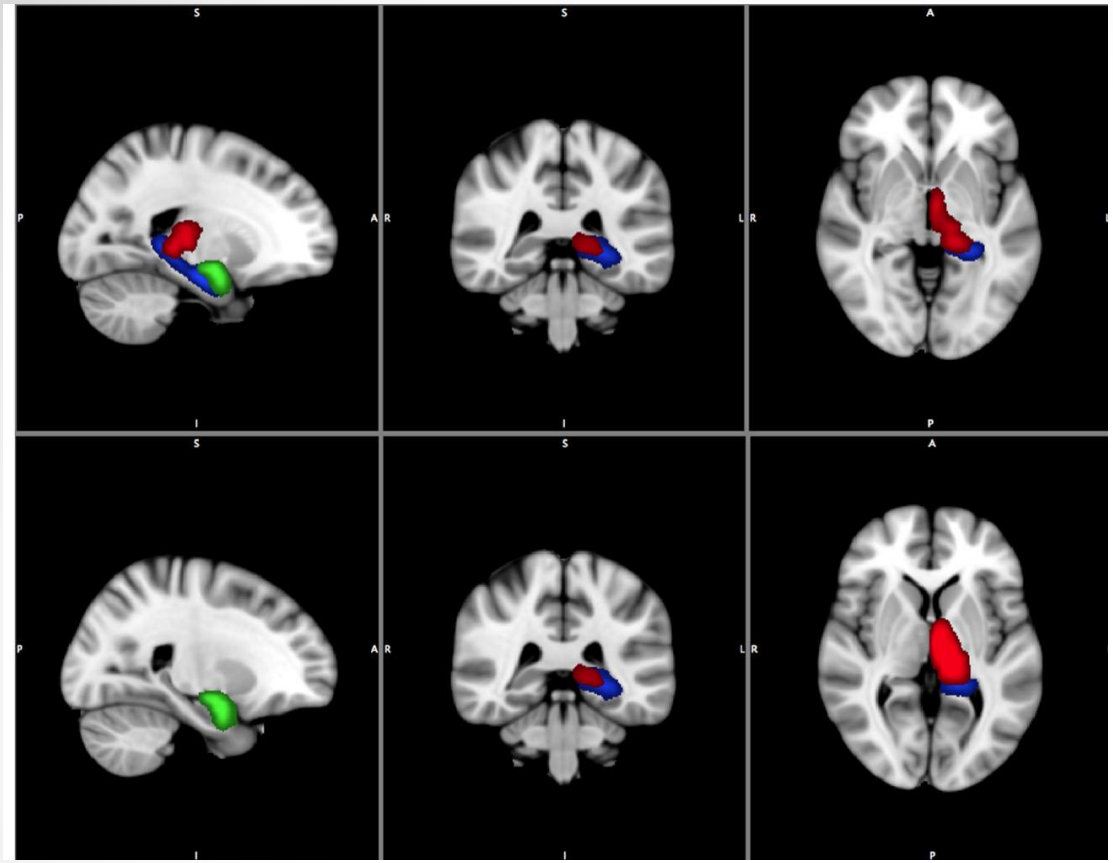
2. **Diffusion tensor imaging:** 45 volume, motion-corrected AP-PA encoding phases

3. **Magnetic Resonance Spectroscopy:** parietal white and gray matter

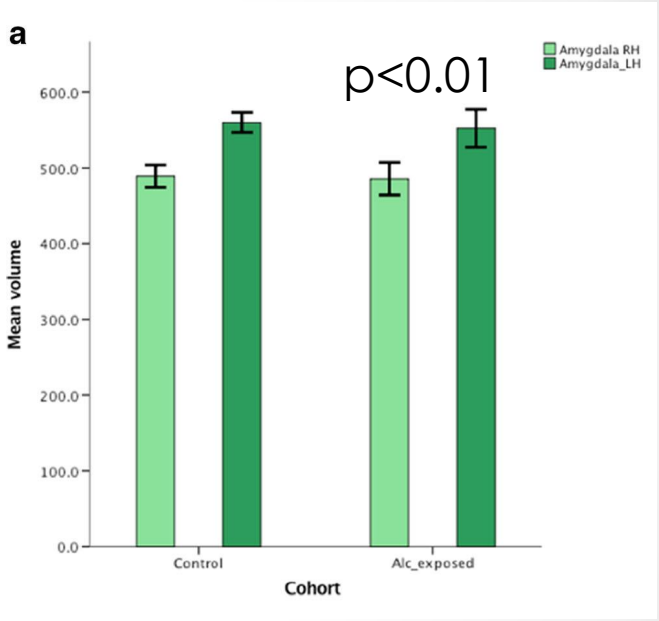
4. **Resting state functional connectivity**

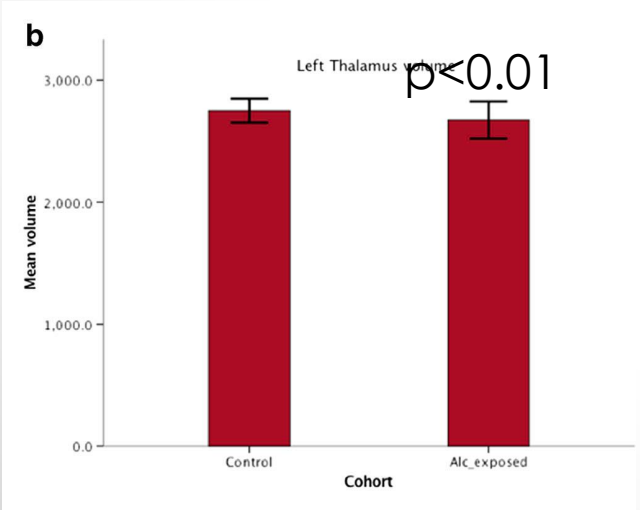


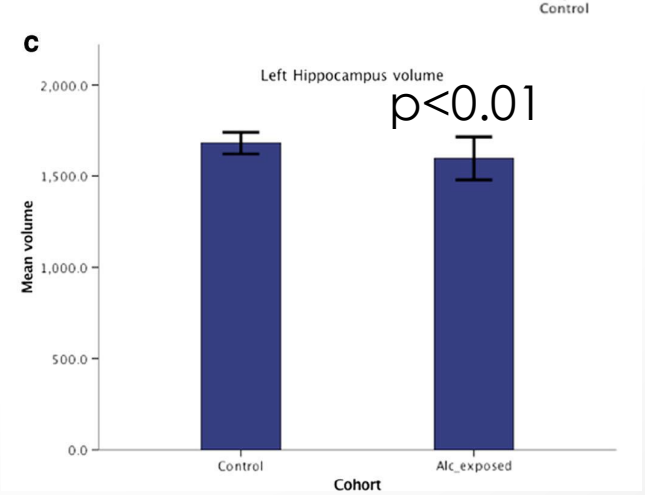
Decreased total gray matter volume in alcohol-exposed infants compared to controls.
[Donald et al 2016]



Gray matter volume decreases in
(a) amygdala (green),
(b) left thalamus (red)
(c) left hippocampus (blue)
[Donald et al 2016]







Neurological signs and behaviour

- **Dubowitz neurological scale:**
  - Neuromotor/-behavioural status at 2-4 weeks
  - tone, reflexes, spontaneous movement, behaviour, abnormal signs

- **Bayley Scales of Infant and Toddler Development III:**
  - neurobehavioral and developmental outcomes during year 1 and 2
  - cognitive, language, motor, socio-emotional and adaptive behaviour

Neurological signs and behaviour

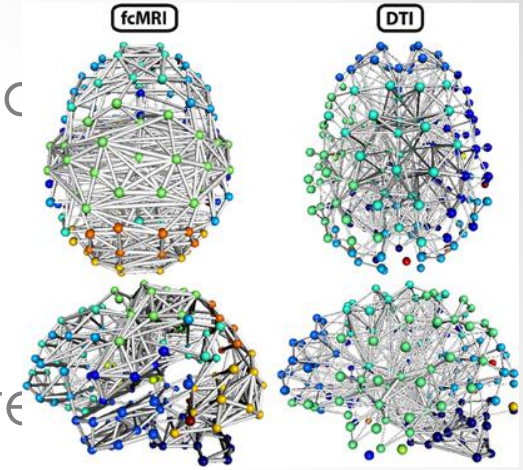
- **DTI:**
  - Abnormal neurobehaviour at 2-4 weeks associated with altered FA and MD in the right inferior cerebellar peduncles in alcohol-exposed infants

- **Structure:**
  - Adverse outcomes at 6 months across multiple domains associated with temporal and frontal volumes at 2-4 weeks in alcohol-exposed infants

Summary of Findings

Modality	Outcome in ALC
Structure	Altered **amygdala**, **thalamic** and **hippocampal** volume
DTI	Altered axial diffusivity in major tract linking frontal, **temporal** and **parietal** regions, pointing at early axonal damage; this parameter is not much changed later in life. [Also Taylor et al]
MRS	Altered glutamate in **parietal** matter suggesting delayed oligodendrocyte maturation.
Resting state	Higher intrinsic connectivity in sensorimotor networks including **thalamic**, **striatal** and **parietal** networks; suggesting delayed development of networks.

What is next?



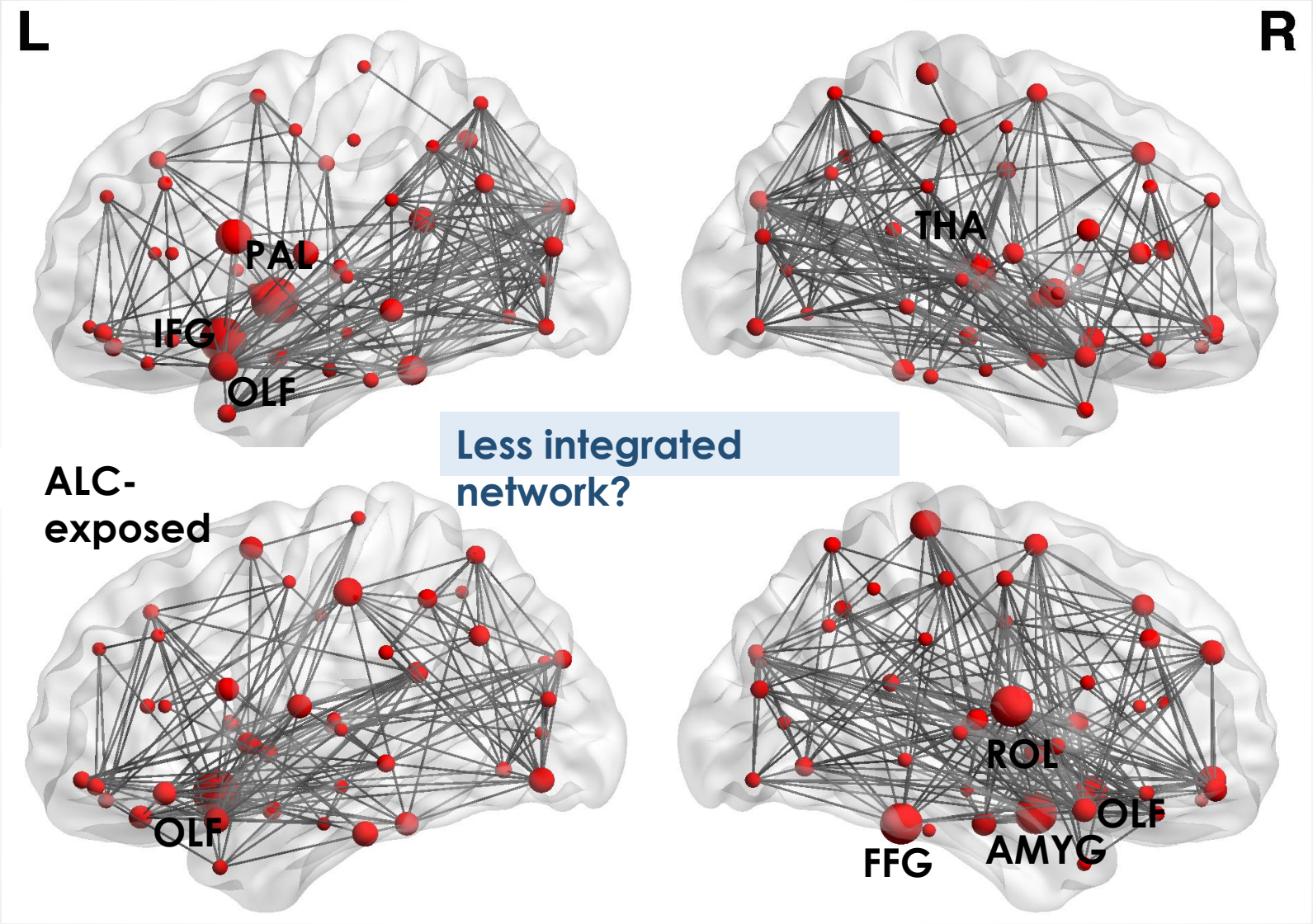
Comparative analysis of structural (diffusio tensor imaging) and functional (resting state) connectivity in alcohol-exposed infants.

The neonate brain has a primary integrate functional organisation of networks, that becomes well established by age 2 [Gao et al 2016].

Graph theoretical analysis (GAT) [Hosseini et al 2012]:

- brain organisation and connectivity on a regional and global level
- correlational networks are created that form a "small-world network" of connections

Control



Network hubs: The volume of the sphere corresponds to the betweenness centrality (bc) of the region. The labeled regions display significantly higher bc compared to other regions (2SD). Abbreviations: OLF – olfactory cortex; FFG – fusiform gyrus; ROL – rolandic operculum; AMYG – amygdala; PAL – pallidum; IFG – inferior frontal gyrus; THA – thalamus; L – left hemisphere; R – right hemisphere

Bottom-up development and integration of networks suboptimal **(Structure / RS)** in alcohol-exposed infants compared to controls and this may relate first to disrupted axon development **(DTI)** and myelination **(MRS)**

Too early though to say much about involvement of frontal lobe

Fig 1 Structural scans at 2 weeks

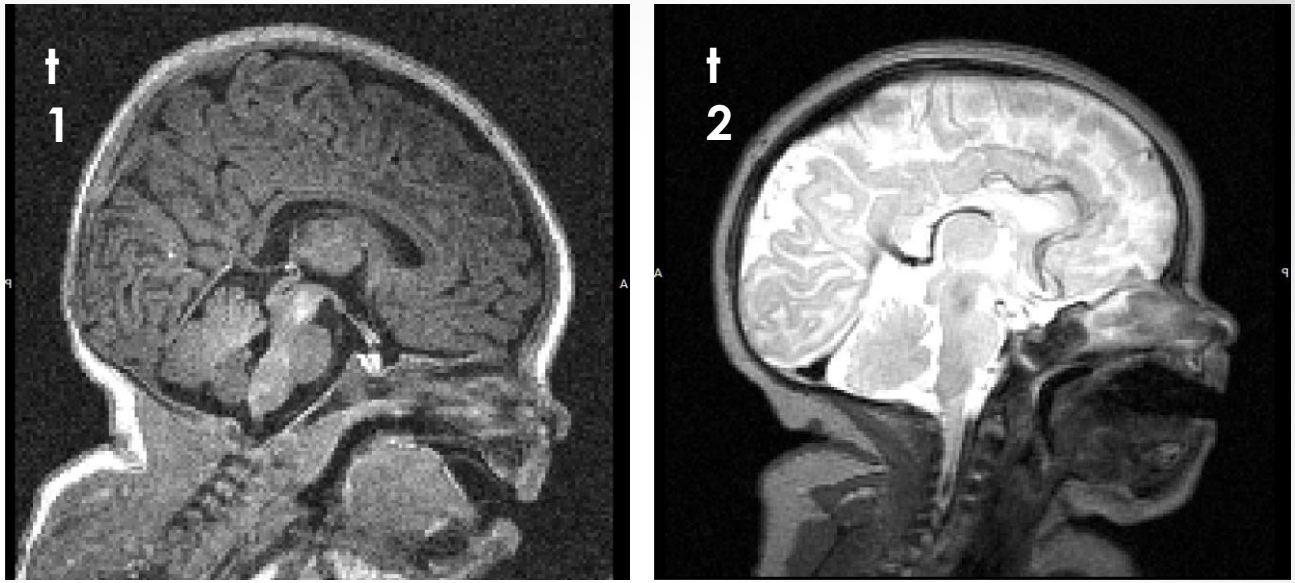
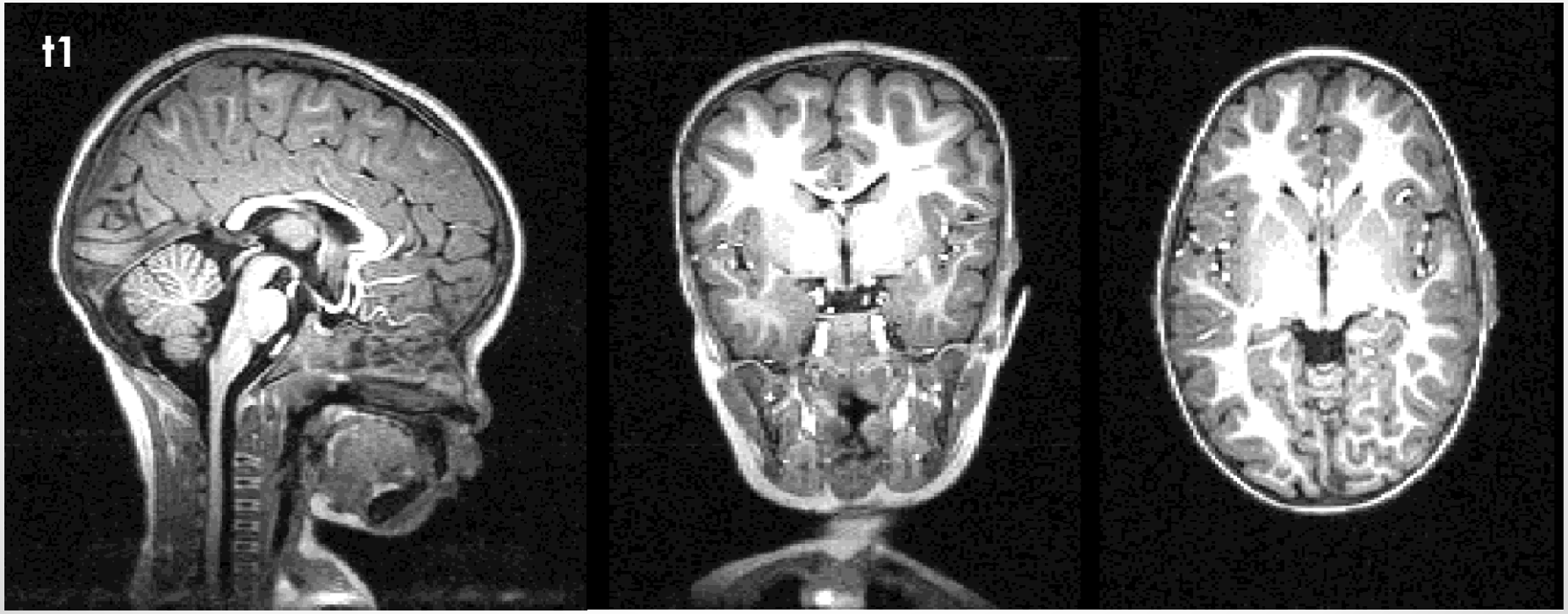


Fig 2 Structural scans at 2



Imaged 2 year olds

	ALC	CON	P-Value T-test and chi-square (Statistica)
N	34	35	
Age (months)	32,82	34,51	0,0003
Weight (Kg)	13,37	14,43	0,0328
HC (cm)	48,85	49,68	0,0527
Sex (Male/ Female)	14/20	26/9	0,0053
ALC exposed			
Trim 1 (Y/N)	26/8	0/35	<0.001
Trim 2 (Y/N)	14/19	0/35	<0.001
Trim 3 (Y/N)	11/22	0/35	0,0002
Smoke (Y/N)	15/19	5/30	0,0063

Genotyping:

- To date, we have genotyping for N = 150 infants (using the PsychChip), with a plan to genotype an additional N = 190 within the coming months (likely using the Global Screening Array)

Methylation:

- We have usable (ie. uncontaminated, QC'd data) from N = 286 offspring.

Gene expression:

- We have N = approx 168 offspring with gene expression data

What will this add?

- early development
- environmental and other

Why is it important?

- early identification
- mechanisms and trajectory
- interventions
- outcomes
- risk and resilience

Why CIFASD?

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