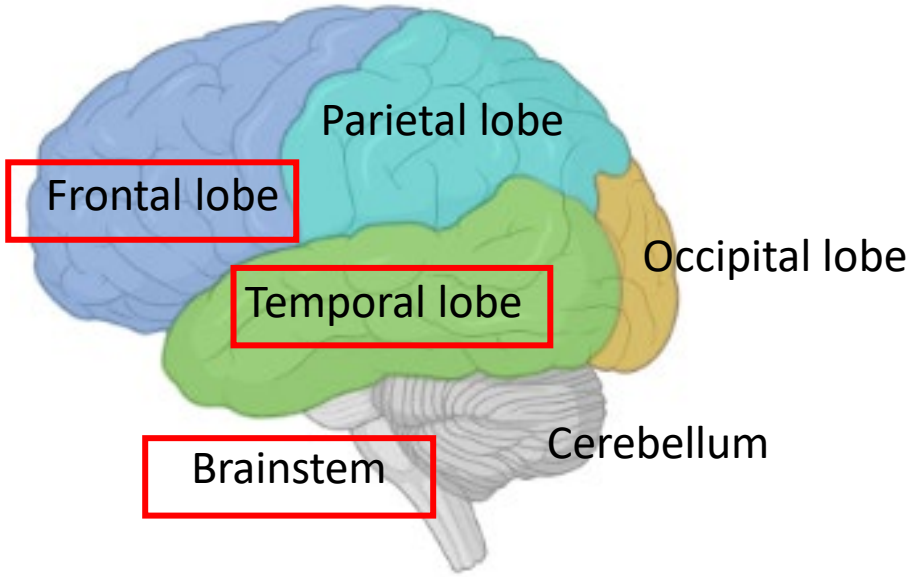
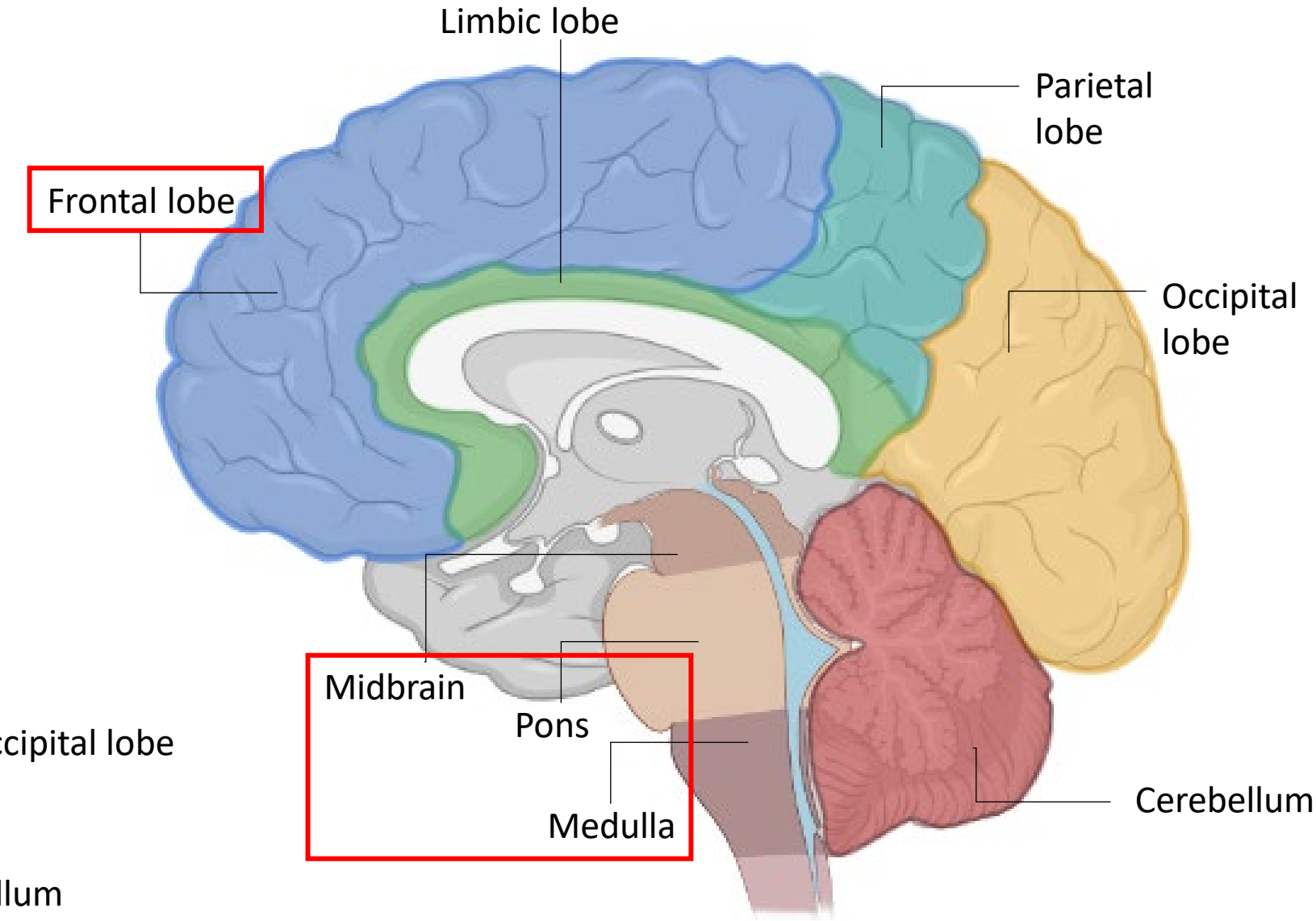
The impact of low-level CO on the brain

Dr Mari Herigstad
Sheffield Hallam University

The brain: regions

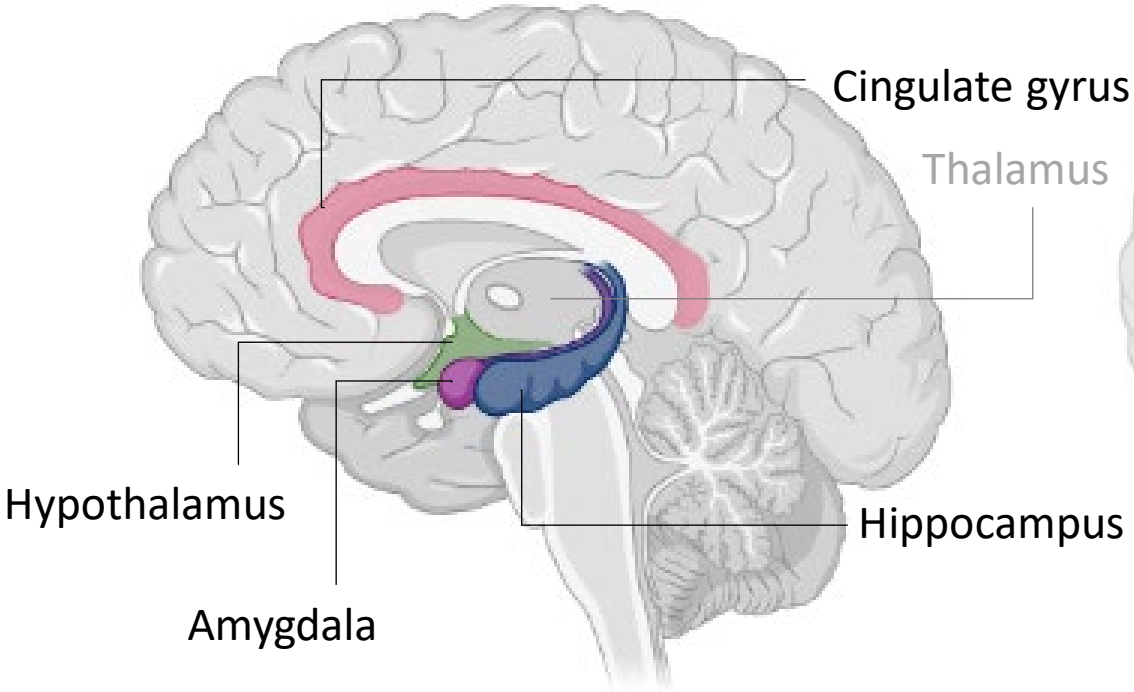
- Complex
- Distinct regions
- Cognitive/non-cognitive
- Susceptibility varies





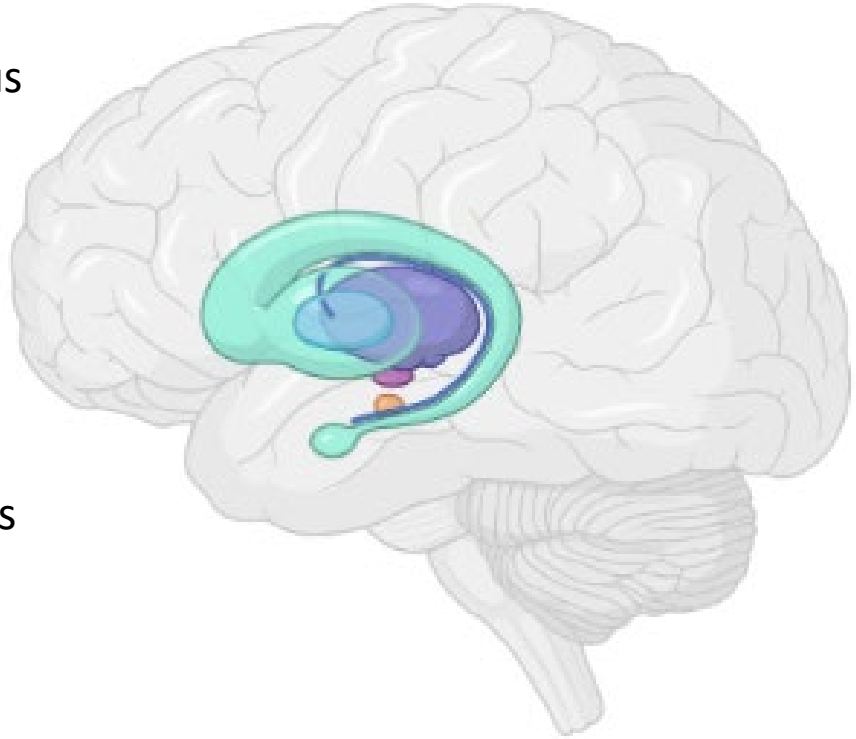
The Brain: systems

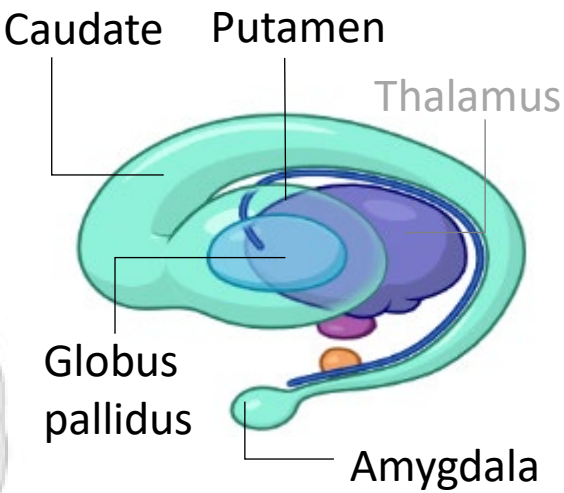
The limbic system



- Emotion
- Behaviour
- Learning
- Long-term memory
- Autonomic processes

Basal ganglia

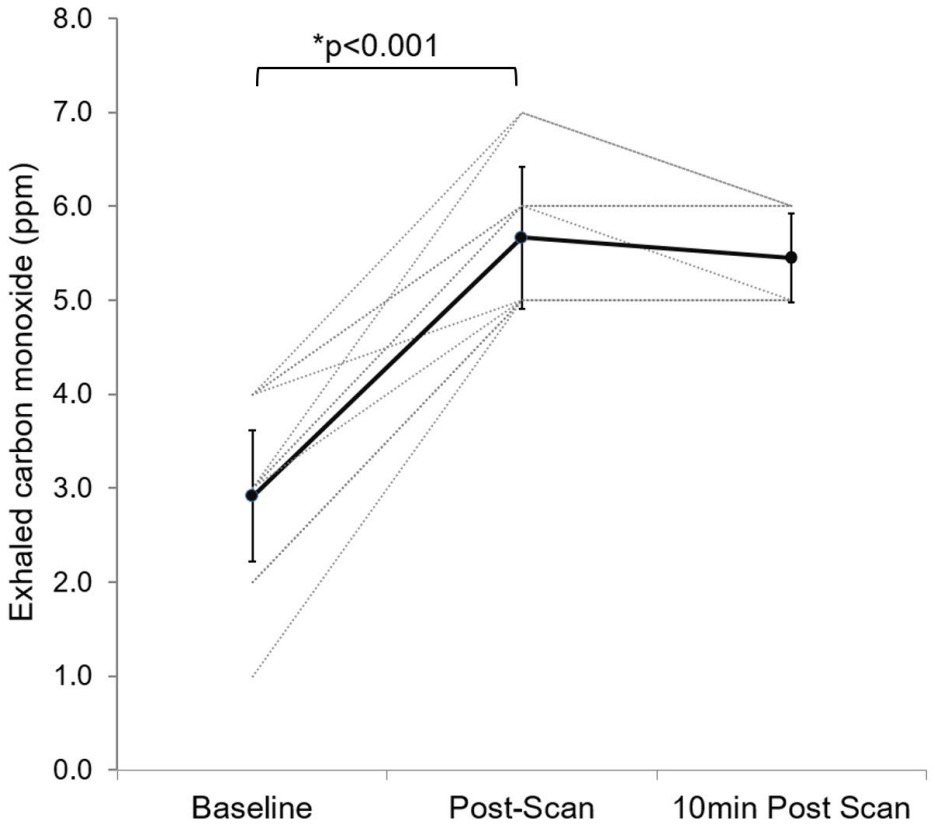




- Cognition/emotion
- Movement
- Procedural/habitual/conditional learning

Neurological function: Breathing/motor tasks

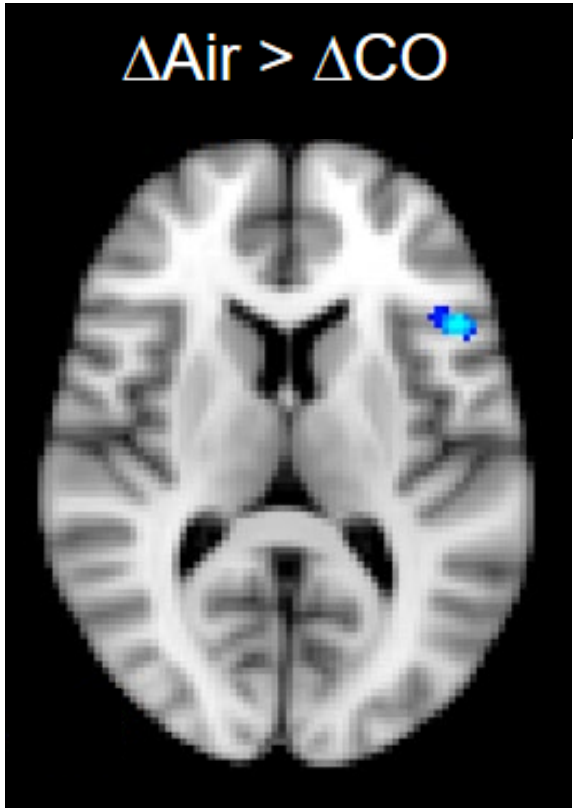
A



B

	preliminary visit	MRI visit (CO)	MRI visit (Air)
Sex (F/M)	8/4	8/4	8/4
Age (years)	25.3 (4.3)	25.3 (4.3)	25.3 (4.3)
BMI (kg/m^2)	23.6 (3.0)	23.6 (3.0)	23.6 (3.0)
Trait anxiety score	35.4 (7.2) [23-47]	N/A	N/A
State anxiety score	31.1 (8.6) [21-55]	27.0 (4.3) [21-35]	28.2 (4.4) [23-37]

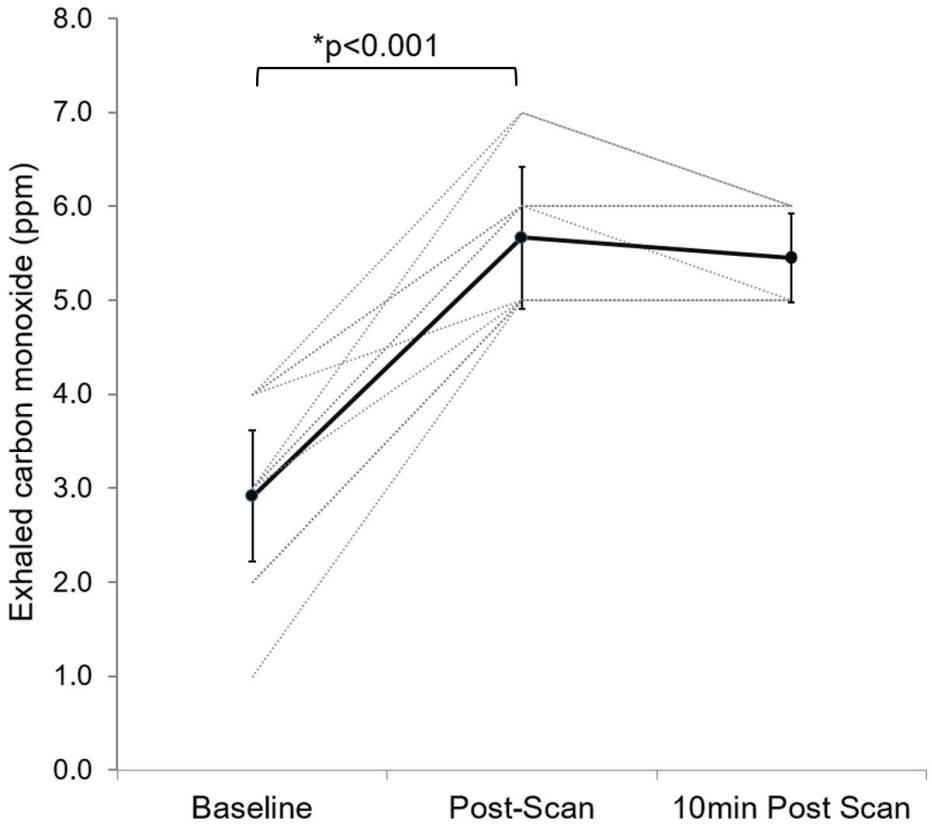
C



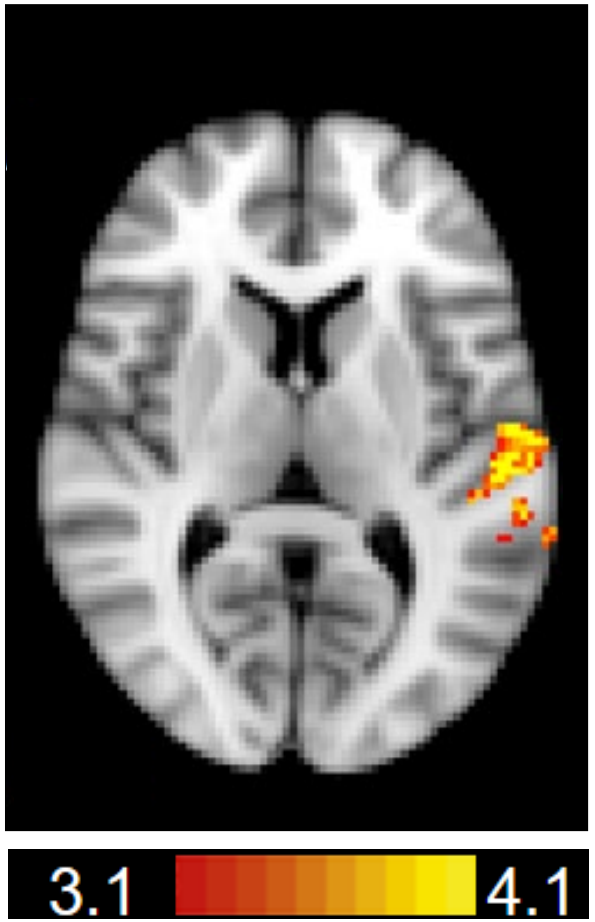
D

(A) Exhaled CO levels and **(B)** demographic data for a fMRI study, showing reduced activation during a **(C)** breathing task (insula), and **(D)** visual activation task (visual cortex), from Bendell, Moosavi & Herigstad, J Cereb Blood Flow Metab, 2020;40(11), 2215-2224.

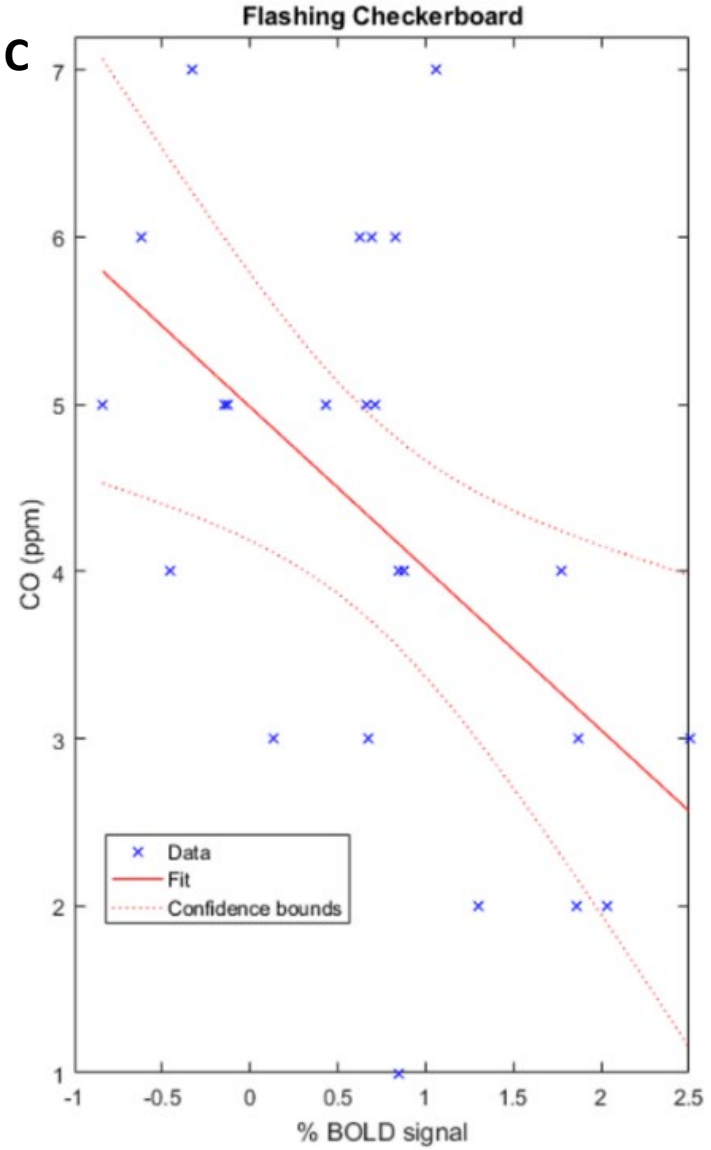
Neurological function: Breathing/motor tasks



B



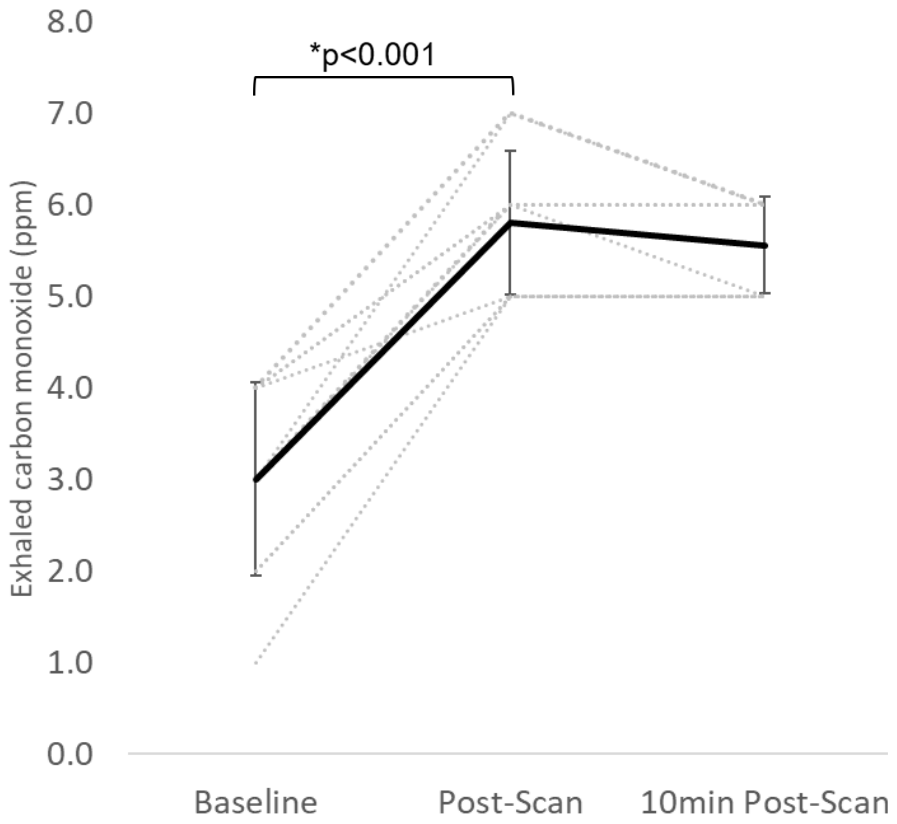
C



(A) Exhaled CO levels and **(B)** areas where change in BOLD fMRI signal correlates with individual CO level. **(C)** %BOLD fMRI signal is negatively correlated with exhaled CO (visual activation). R2=0.264, R2(adj)=0.231, p=0.010. From Bendell, Moosavi & Herigstad, J Cereb Blood Flow Metab, 2020;40(11),2215-2224.

Neurological function: Cognitive task

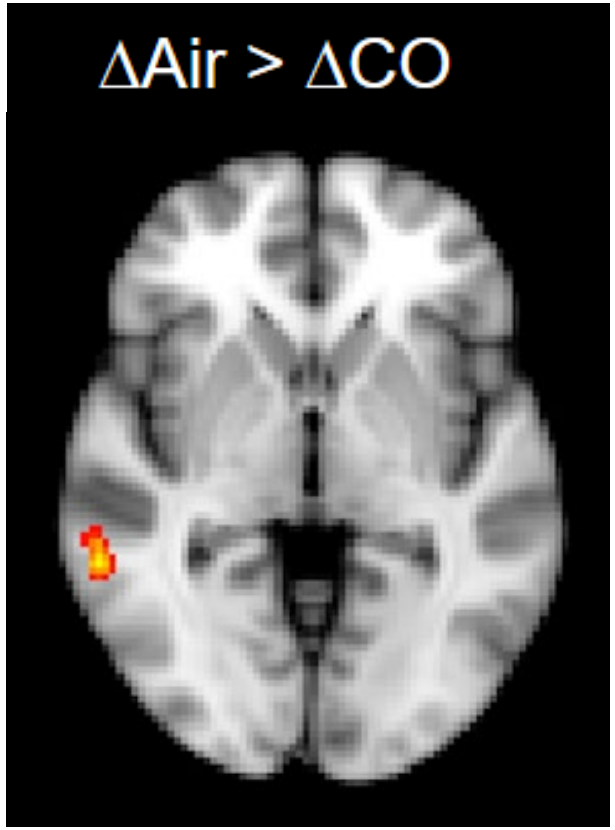
A



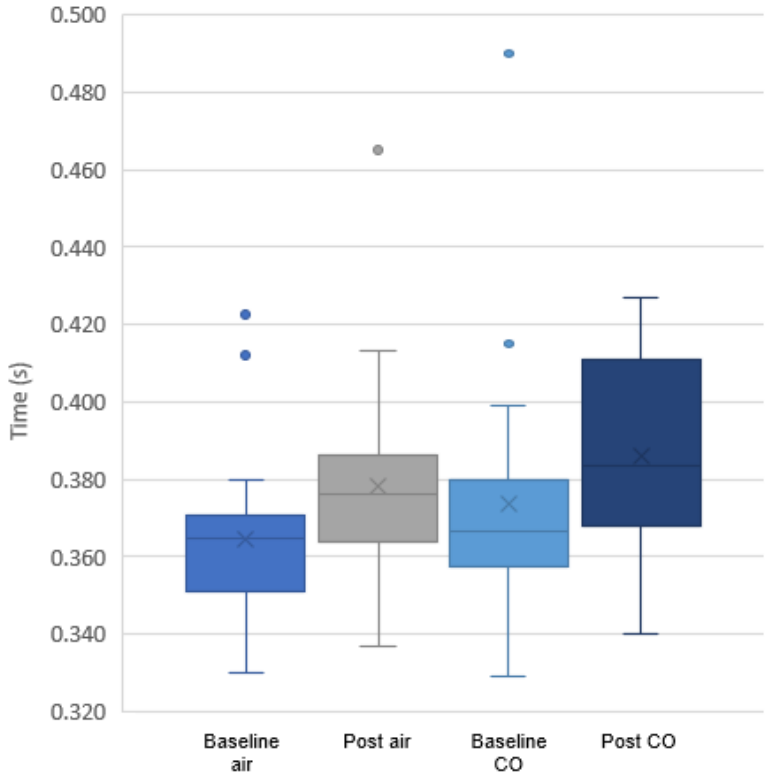
B

	preliminary visit	MRI visit (CO)	MRI visit (Air)
Sex (F/M)	6/4	6/4	6/4
Age (years)	25.3 +/-4.8	25.3 +/-4.8	25.3 +/-4.8
BMI (kg/m2)	24.0 +/- 3.2	24.0 +/- 3.2	24.0 +/- 3.2
RT change (post>pre, s)	N/A	+9.2	+13.9

C



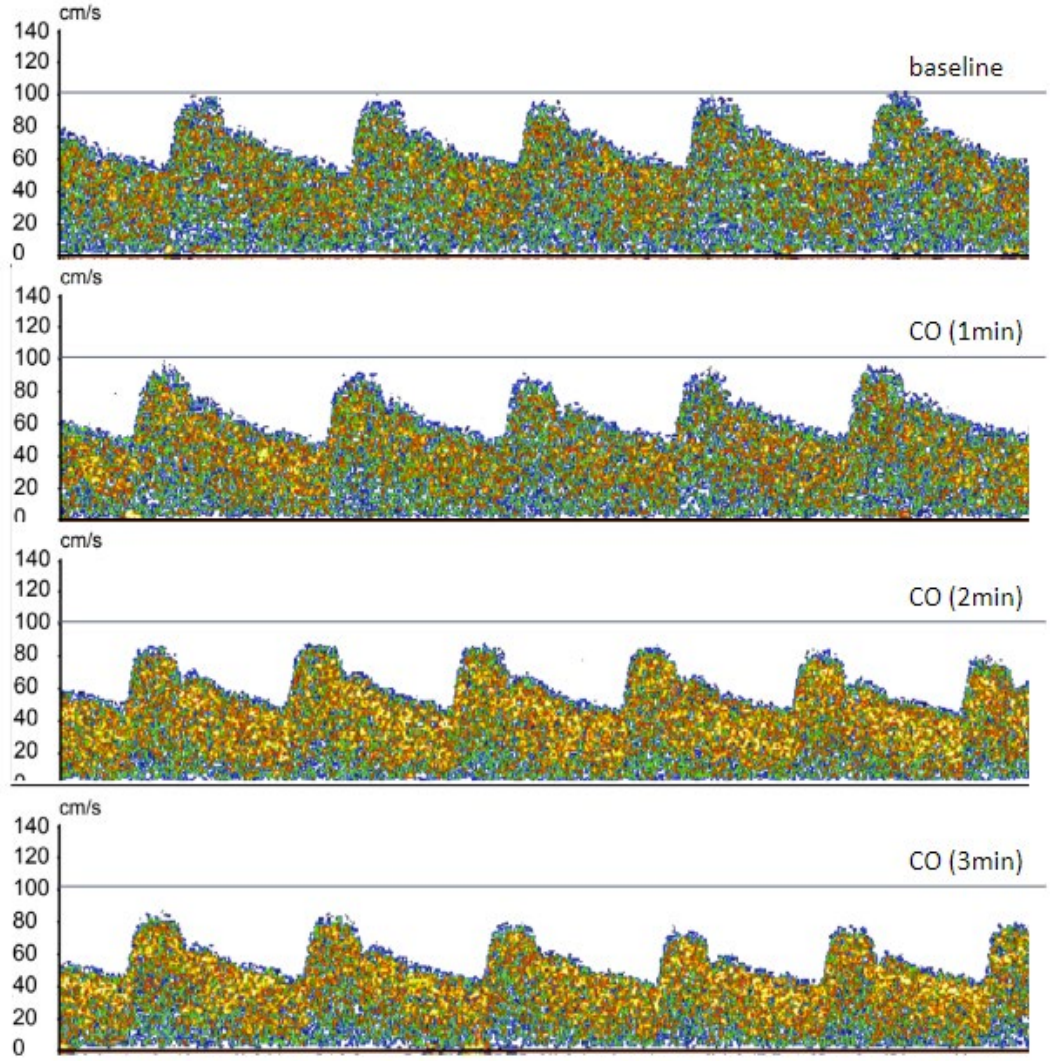
D



(A) Exhaled CO levels and **(B)** demographic data for a fMRI study, showing **(C)** reduced activation during a reaction time (RT) task (temporal lobe). D. RT data, air and CO protocol, from Wilson & Herigstad, Biorxiv, 2022, doi: 10.1101/2023.01.17.524443.

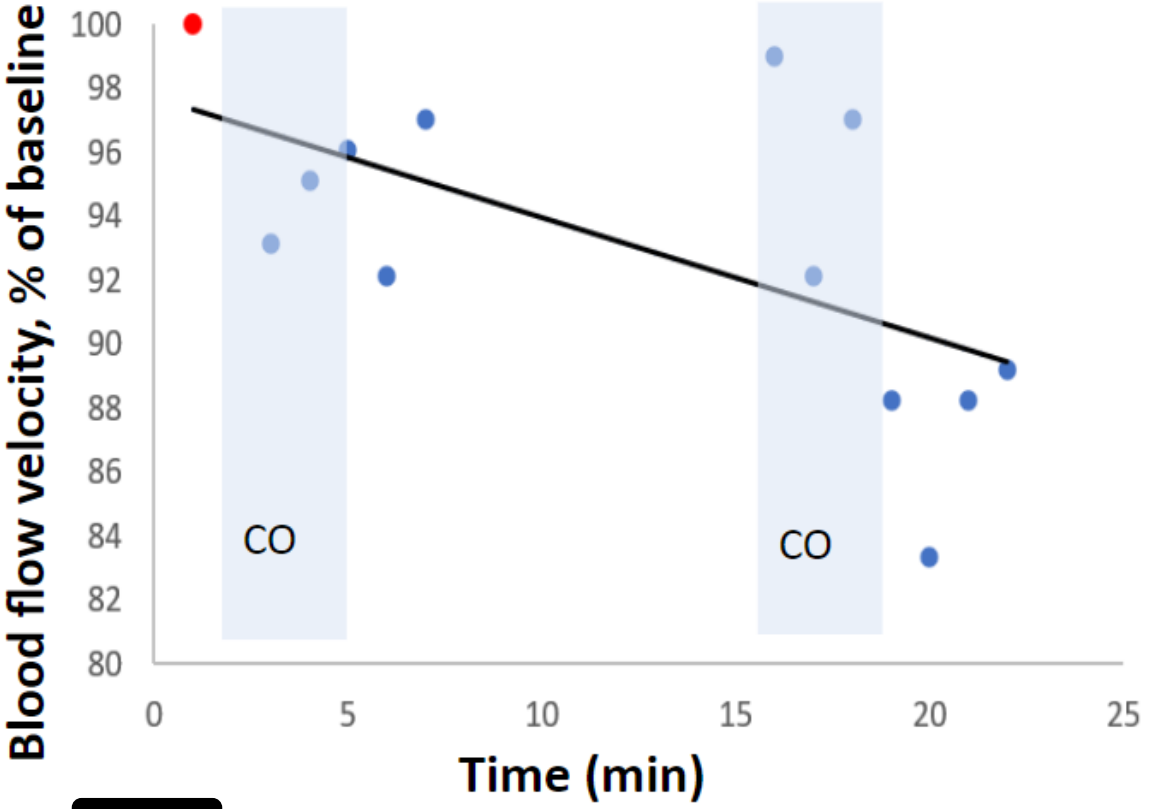
Cerebrovascular function

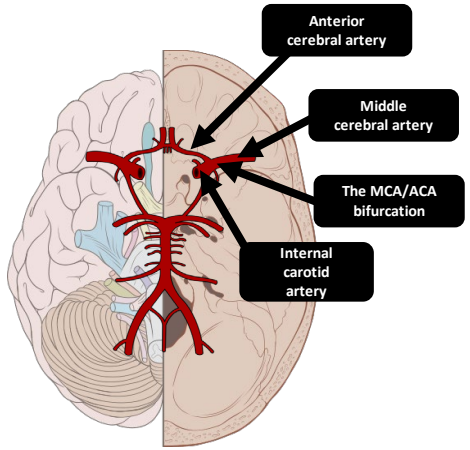
A



(A) Preliminary data: velocity profiles from the MCA at set timepoints following CO inhalation (3ppm increase in exhaled CO), measured by TCD. Horisontal bar indicates baseline values (approx. 100 cm/s)

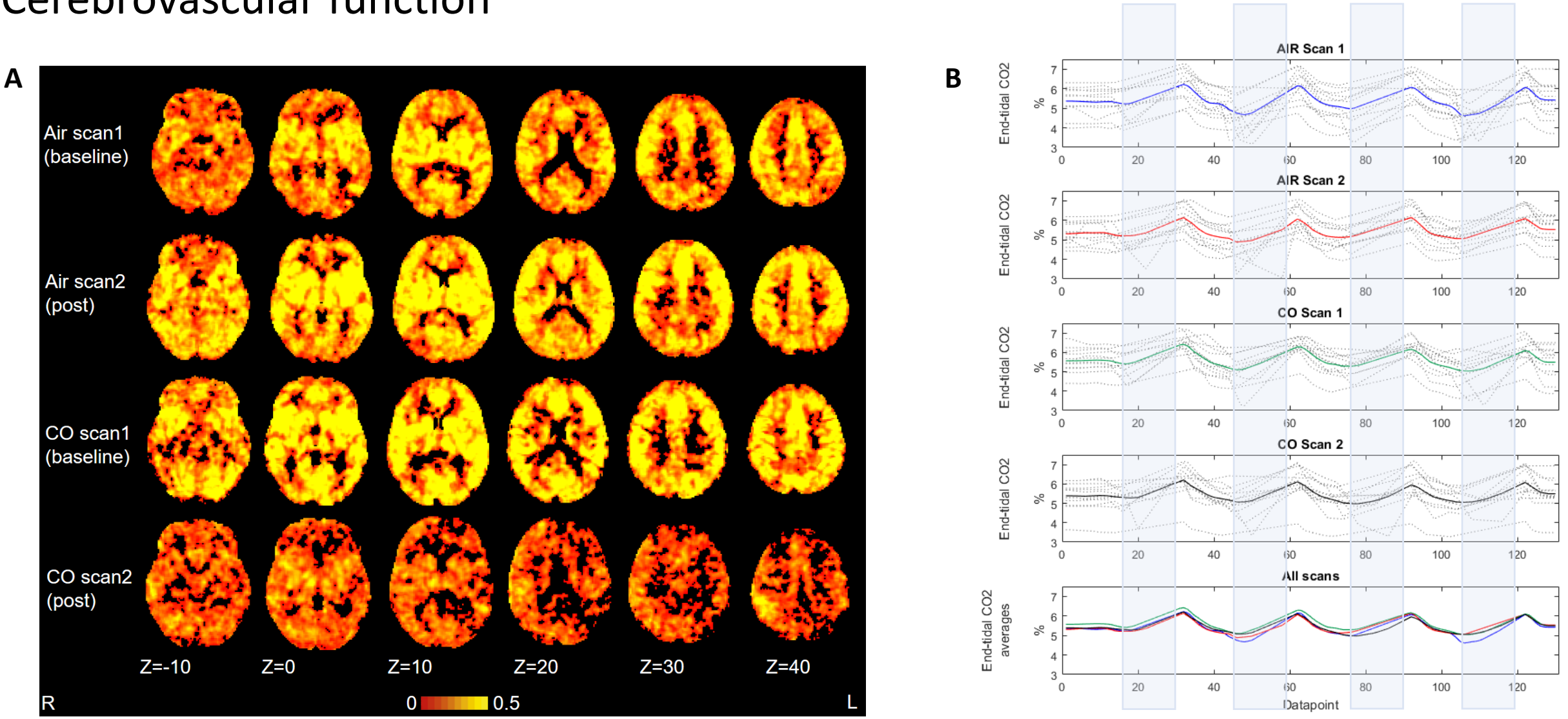
B





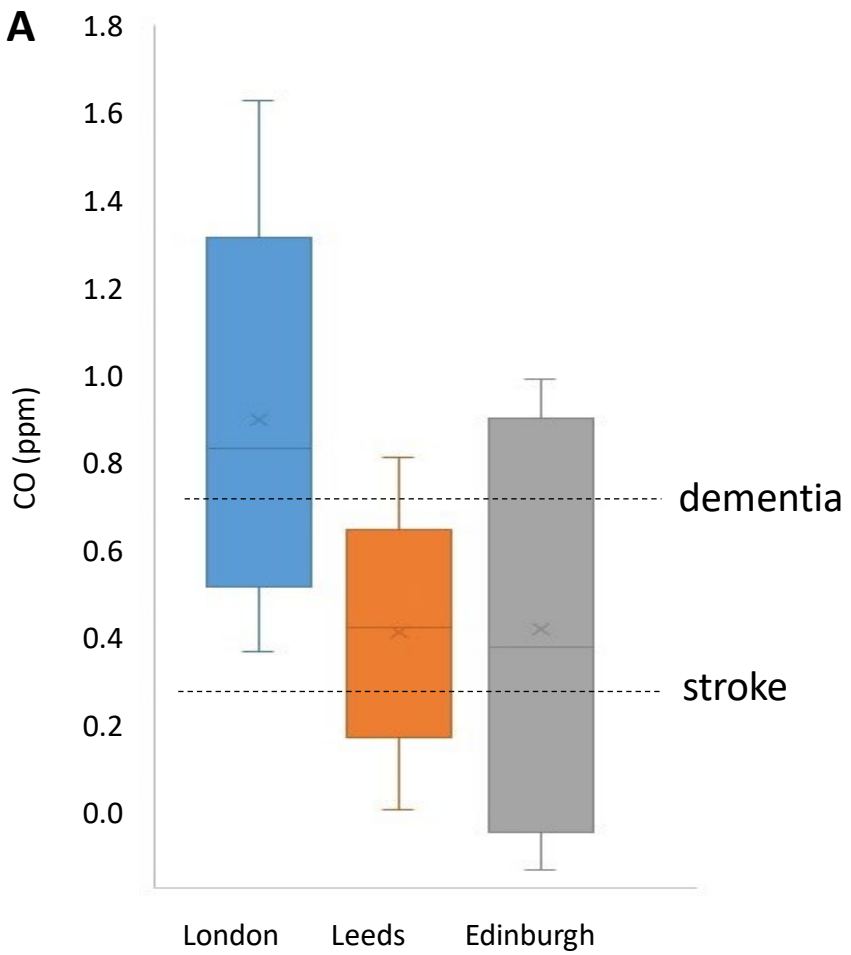
(B) Preliminary data: blood flow velocity at the MCA (shown as % of baseline, red dot) dropping with CO inhalation (3ppm increase in exhaled CO, undertaken in two bolus inhalations), as measured by TCD. Individual data points and trendline.

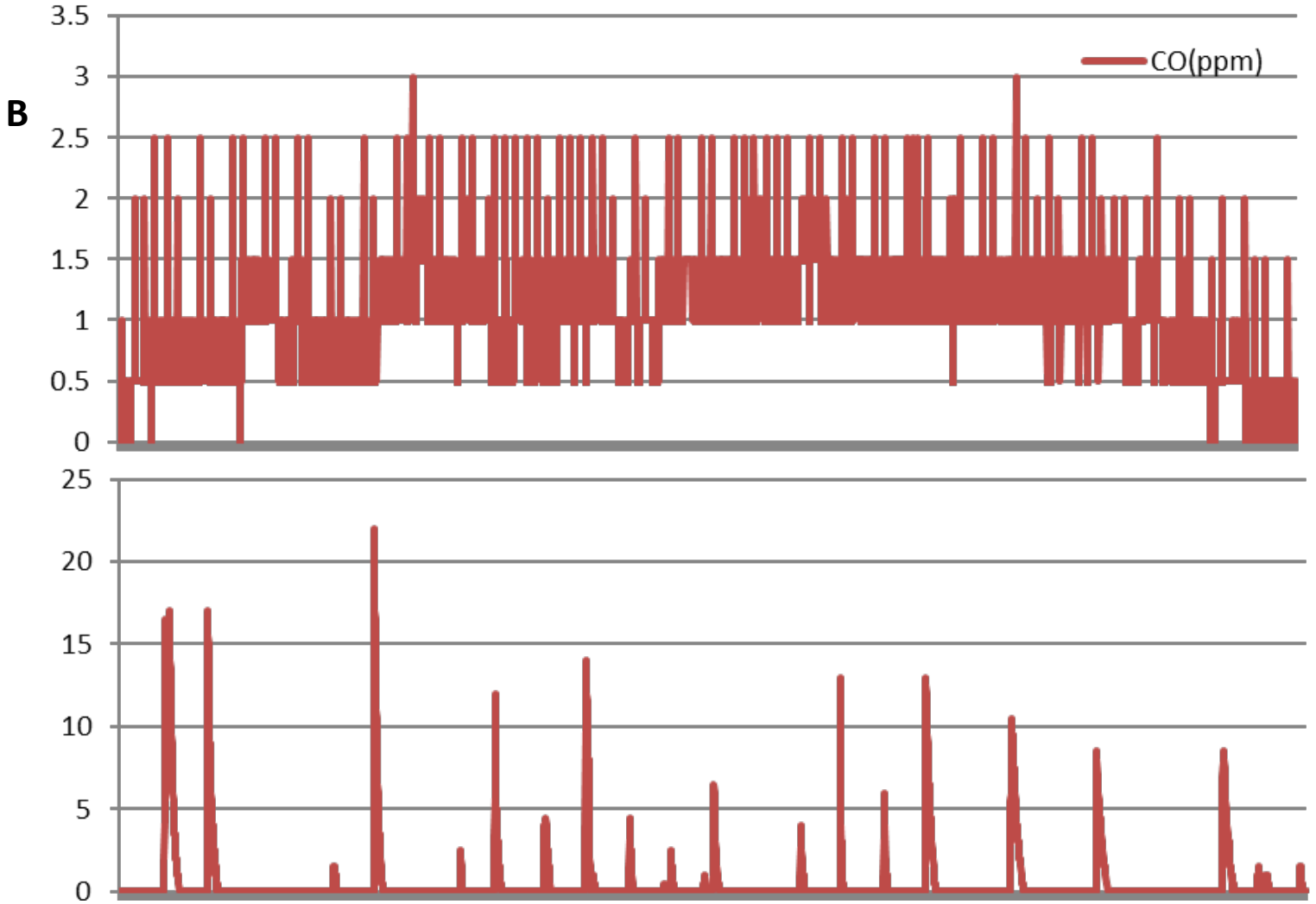
Cerebrovascular function



(A) Cerebrovascular Reactivity (CVR) after air and CO inhalation. Red indicates lower and yellow higher CVR. MRI data. **(B)** Individual CO2 traces for the CVR task (four consecutive breath holds) for all protocols. Average end-tidal values presented (solid line). Blue=Air pre-intervention scan; Red=Air post-intervention scan; Green=CO pre-intervention scan; Black=CO post-intervention scan. From Bendell, Moosavi & Herigstad, J Cereb Blood Flow Metab, 2020;40(11),2215-2224.

Impact?



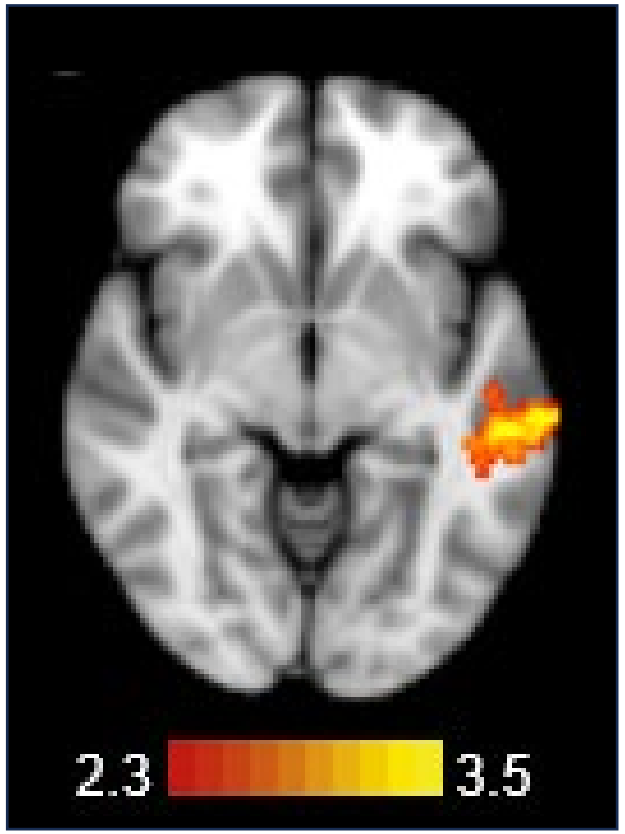


(A) Department for Environment, Food & Rural Affairs, Jan-March 2019: ambient CO in major UK cities (street-level, averaged). Dotted lines are levels of CO linked to disease risk (epidemiological data): dementia (Chang et al., PLoS One 2014;9:e103078), stroke (Maheswaran et al., Stroke 2005;36:239-43).

(B) Example data (**courtesy of Dr Beth Cheshire, University of Lancashire**) showing continuous CO measurements in the home of elderly individuals over a full month. In her work, 60% of homes had some CO readings in this period, with CO peak of 29ppm. Cognitive performance decreased with greater CO exposure, including reduced processing speed, auditory working memory, selective attention.

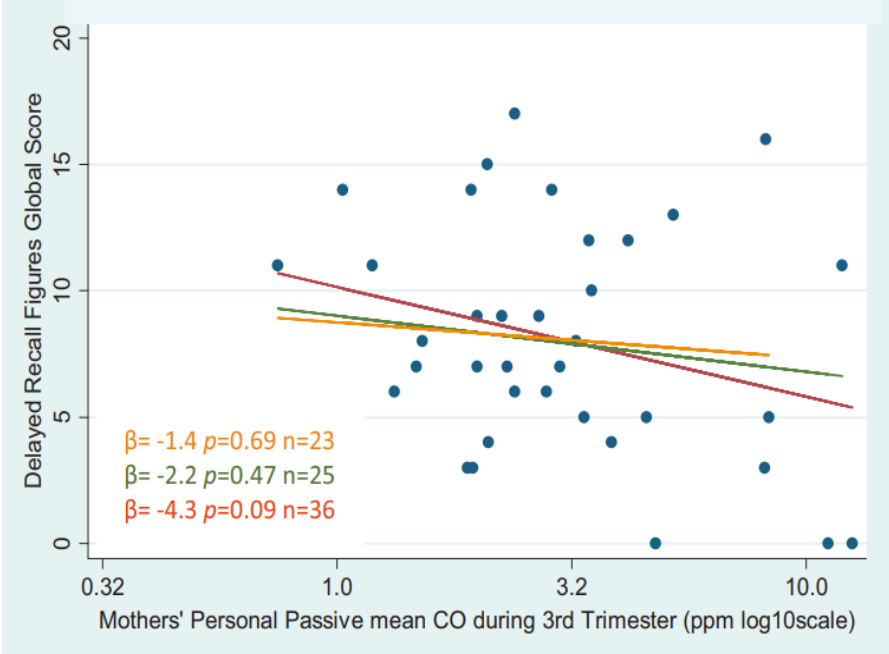
Impact?

A

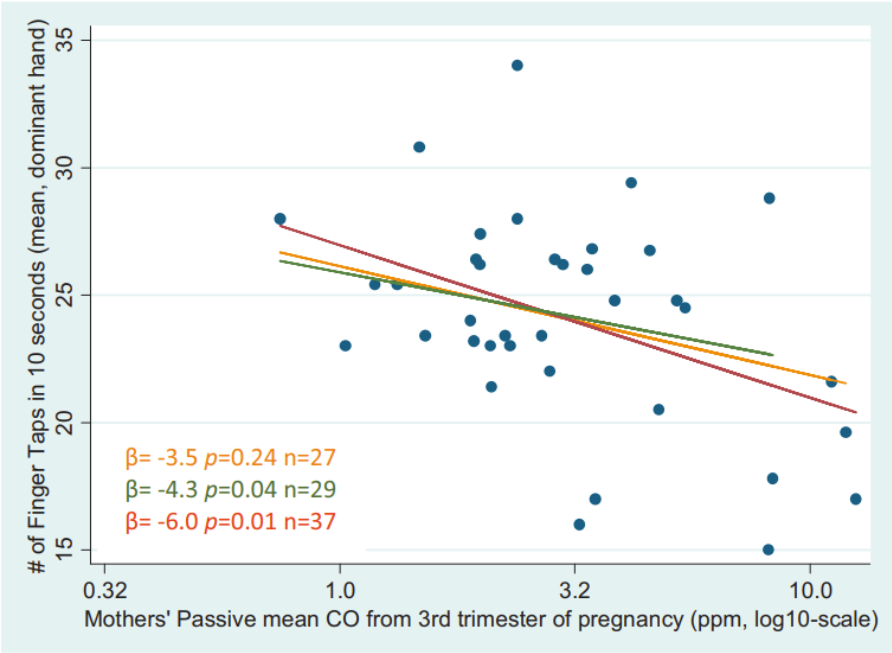


(A) Delayed fMRI activation in healthy ex-smokers compared to never-smokers, demonstrating persisting functional impact of cigarette smoking. Data from Herigstad et al., ERJ, 2017;50(3):1701029 13.

B



C



(B) Data from children (6-7yo), showing neurodevelopmental performance (memory recall) and **(C)** motor skills correlating with maternal CO exposure. From Dix-Cooper et al., Neurotoxicology, 2012;33(2):246-54.

Air pollution	Impaired memory/learning	De Salvia et al., Psychopharmacology (Berl). 1995;122:66–71 Giustino et al., Brain Res. 1999;844:201–5
	Autism spectrum disorder risk	Jung et al., PLoS One. 2013;e75510
Second-hand smoke	Impaired motor ability	Hernandez-Martinez et al., Early Hum Dev. 2012;88(6):403-8
	Neurodevelopmental delay	Lee et al., Environ Res. 2011,111(4):539-544
Wood smoke	Memory recall	Dix-Cooper et al., Neurotoxicology, 2012;33(2):246-54
	Visuo-spatial integration	Dix-Cooper et al., Neurotoxicology, 2012;33(2):246-54
	Motor performance	Dix-Cooper et al., Neurotoxicology, 2012;33(2):246-54

Thank you

Carbon Monoxide Safety Coalition
by NCOAA

Ms Lucy Anne Wilson (Sheffield Hallam University)
Dr Beth Cheshire (University of Lancashire)
Prof Marysia Placzek (University of Sheffield)
Dr Celine Souilhol (Sheffield Hallam University)

CO Research Trust
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Knowledge Applied

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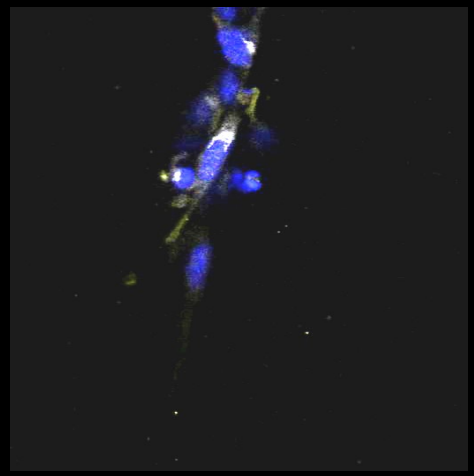
CO & the Developing Heart



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Sheffield Hallam University

Does low dose carbon monoxide exposure effect cardiac development...?

- **Endogenously produced molecule - vital role in normal physiology**
- **Exogenous exposure to high levels (>100ppm) of CO is known to be detrimental to cardiac health (OHb -> COHb)**
- **Impact of low-level exposure (<25ppm), akin to air pollution in urban areas, remains largely ill-defined**
- **Embryonic brain and CV systems are particularly vulnerable to CO**
- **Enhanced understanding of CO impact on developing embryo will help inform public health policy to define 'safe' exposure levels**

Joshua Durans accepting his award from Baroness Finlay and Ian McCluskey

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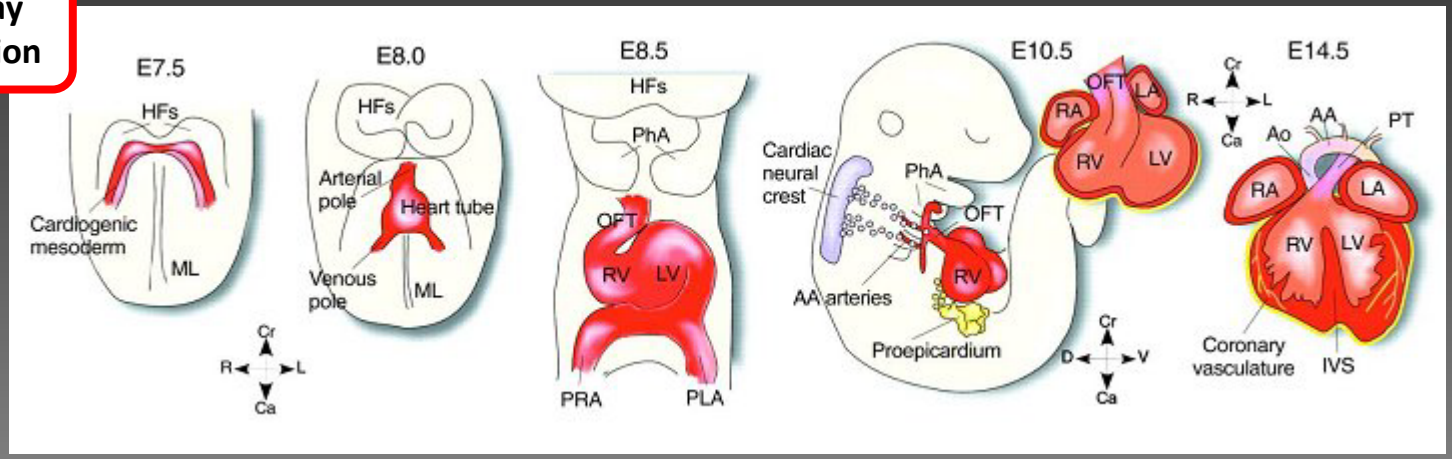
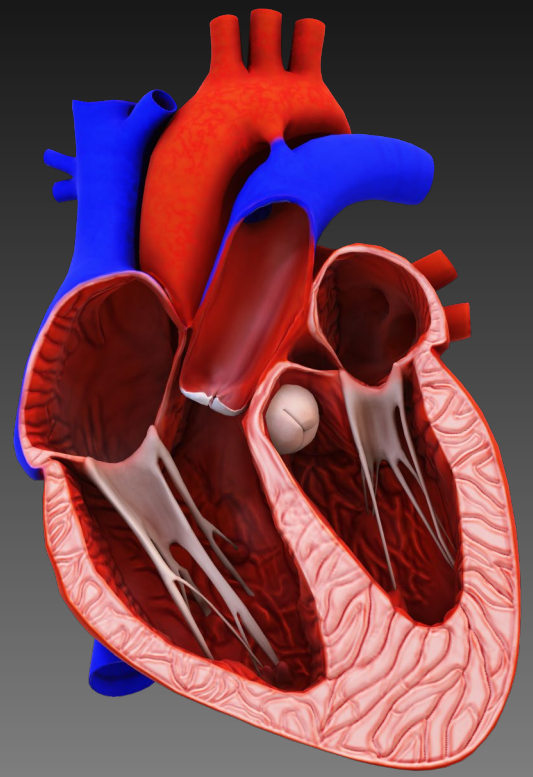
Background to cardiogenesis...

Cardiac development requires spatial-temporal contributions from multiple progenitor cell populations

21-day gestation





It is important to understand the biological mechanisms that regulate cardiac progenitor cells:

- **Disruption of cardiogenesis (environmental or genetic) can result in anatomical and/or physiological abnormalities, collectively termed congenital heart defects (CHDs)**
- **Research that furthers our understanding of CHD aetiology may provide the 'blueprints' upon which to base clinical therapies for patients with cardiovascular disease (congenital and acquired)**

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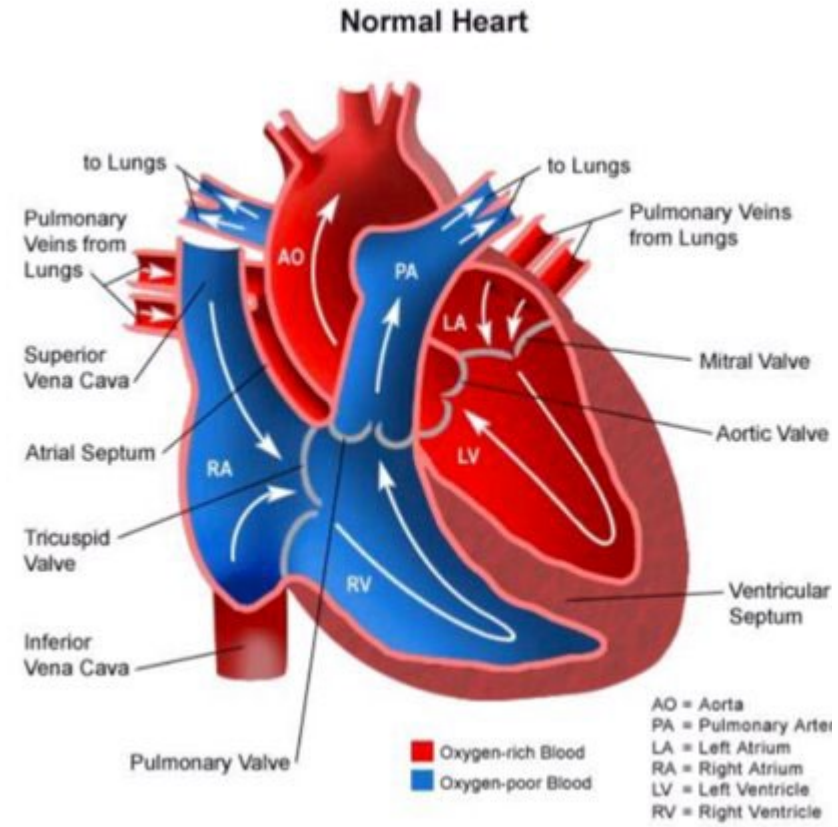
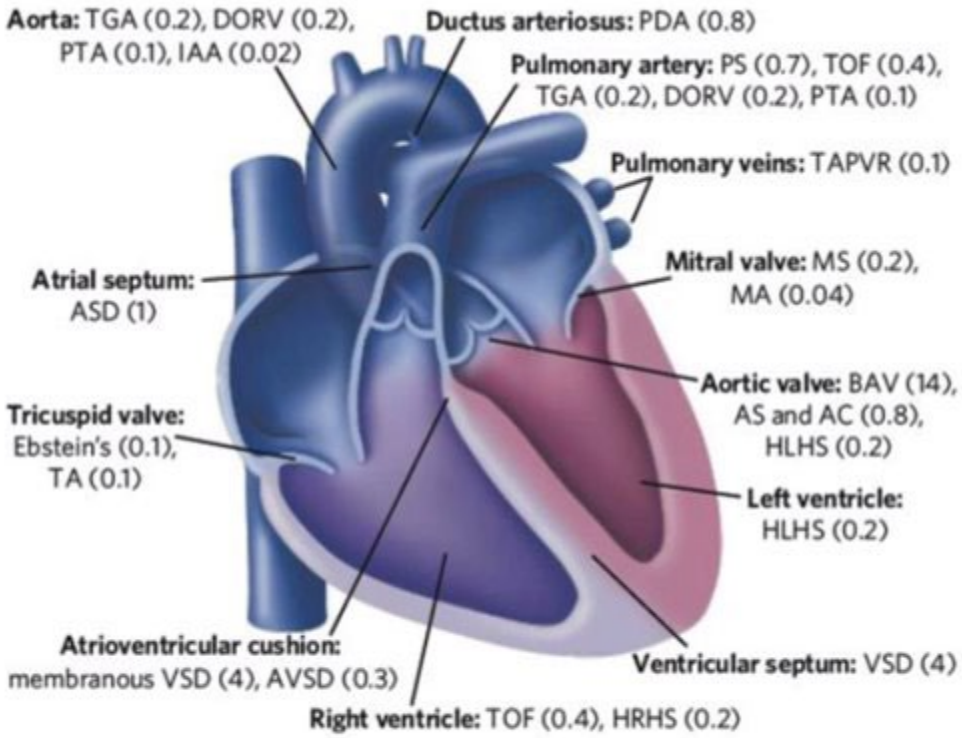
Congenital heart defects...





(x): incidence per 1000 live births, Bruneau BG, Nature, 2008

Increasing prevalence >8-10/1000 live births world-wide (Lui et al., 2019)
Epidemiological evidence of CO-association (Dadvand et al., 2011; Zhang et al., 2016)

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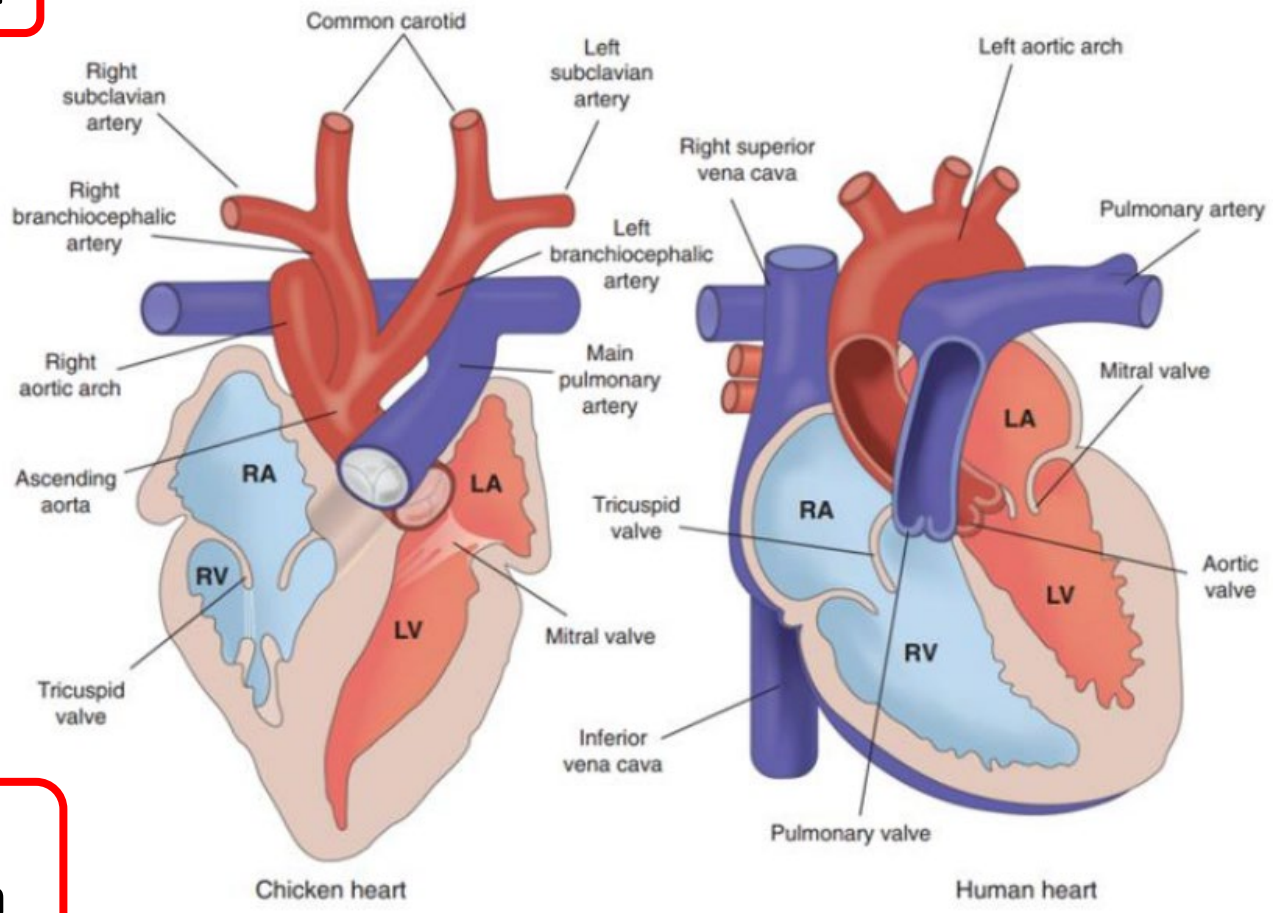
We use model organisms to study CHD aetiology...

chick heart



21-day gestation

Wittig and Munsterberg (2020)

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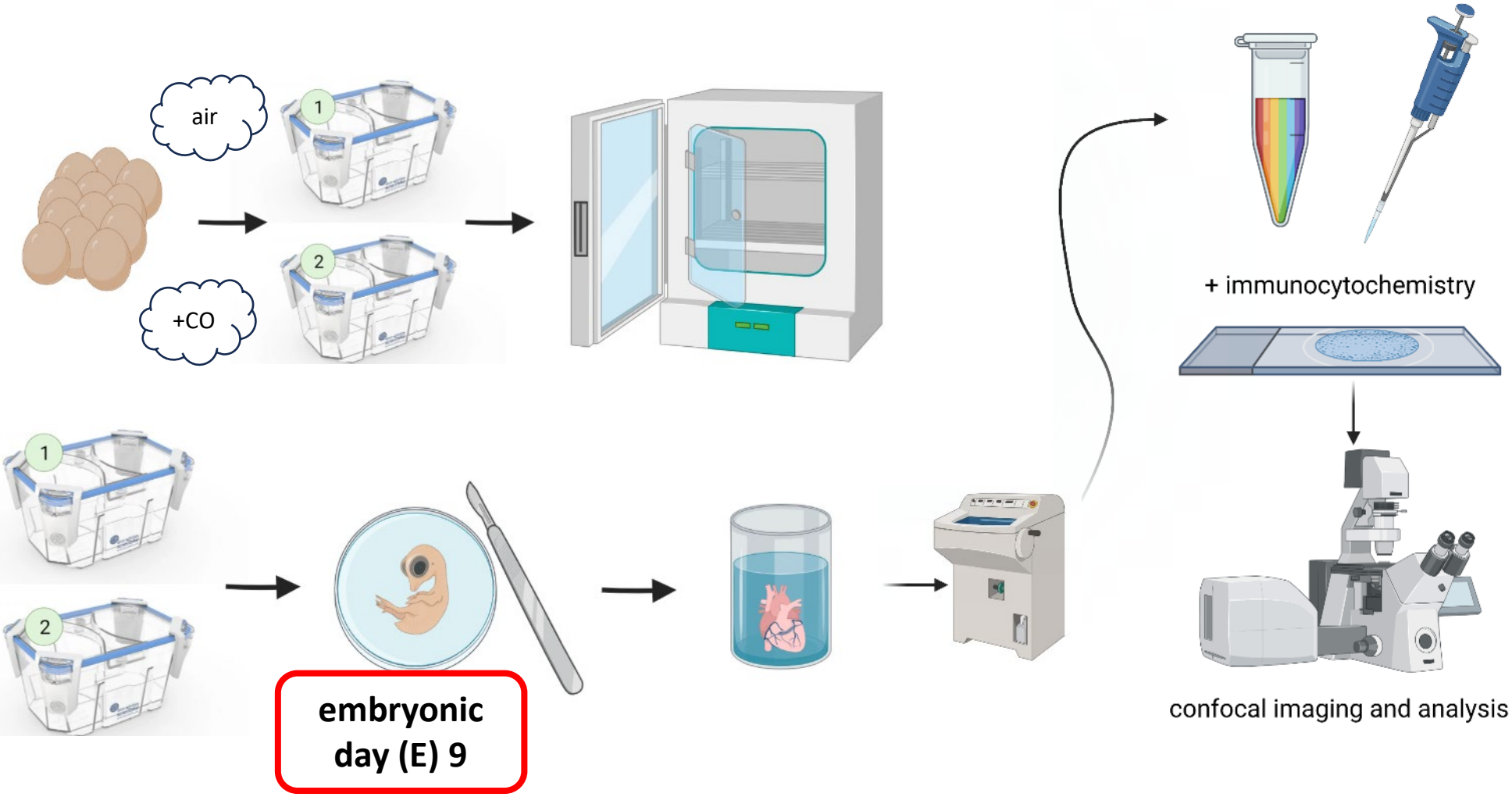
Experimental set up to study effects of low-dose CO...



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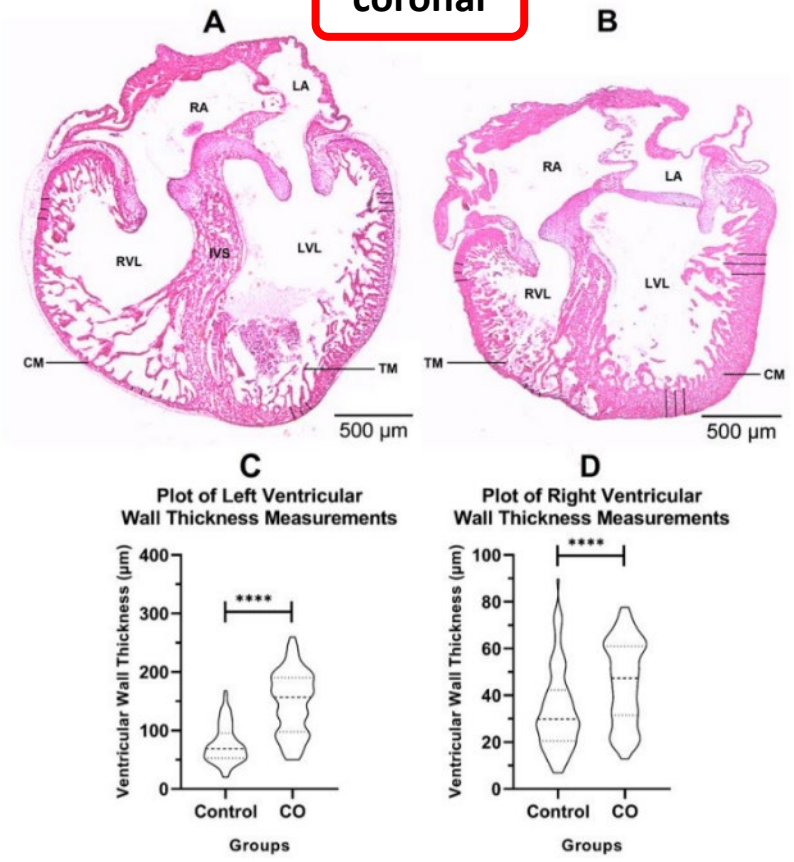
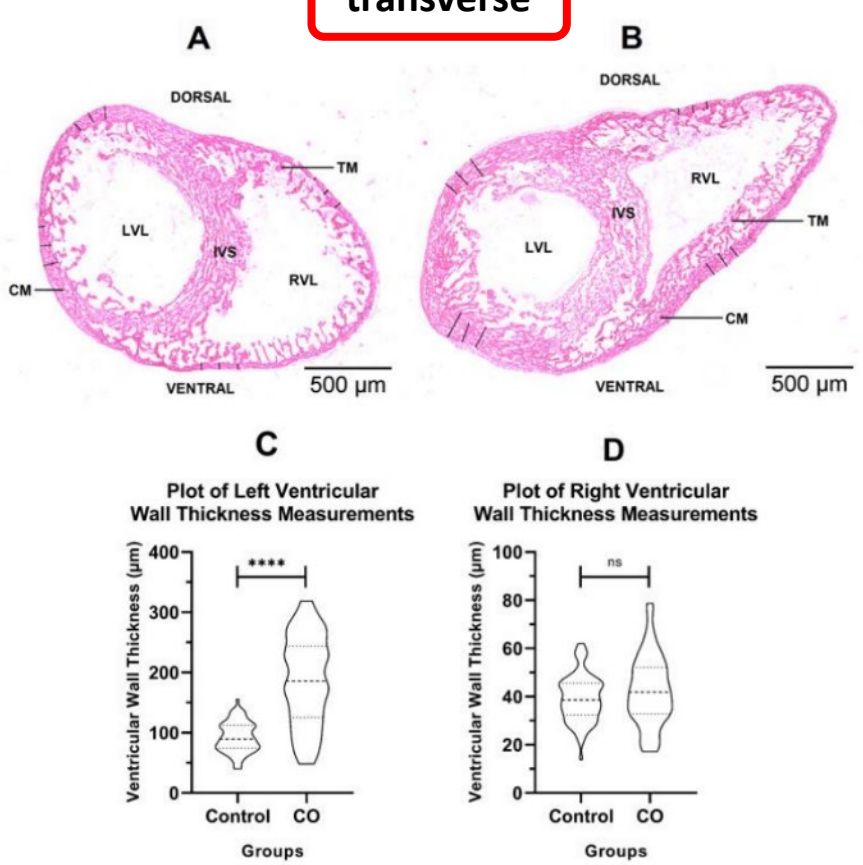
Histology to examine internal cardiac structure...

coronal



transverse



CO exposure results in thicken ventricular myocardial wall at E9

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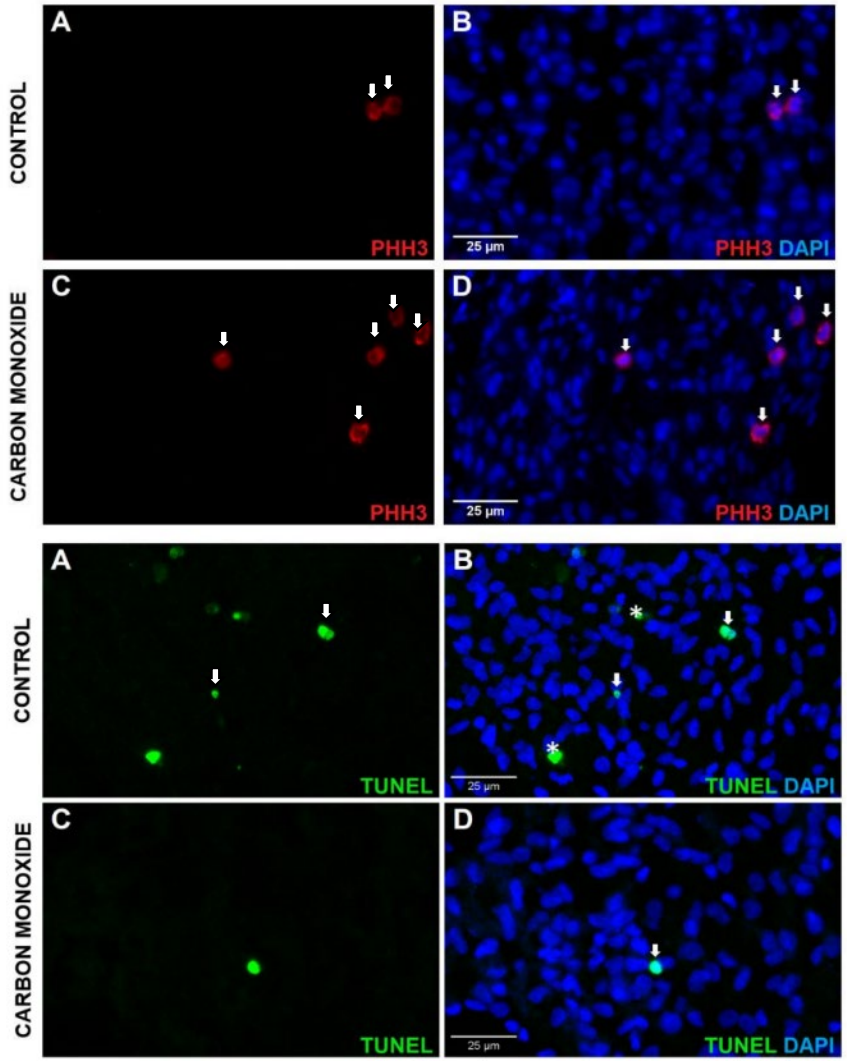
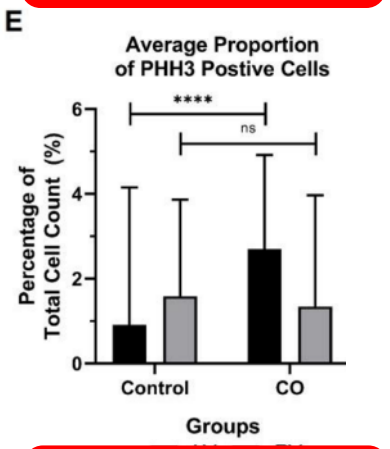
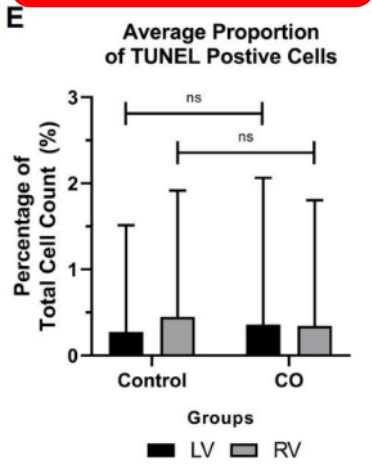
More cells? Fluorescent microscopy to assess cellular processes...

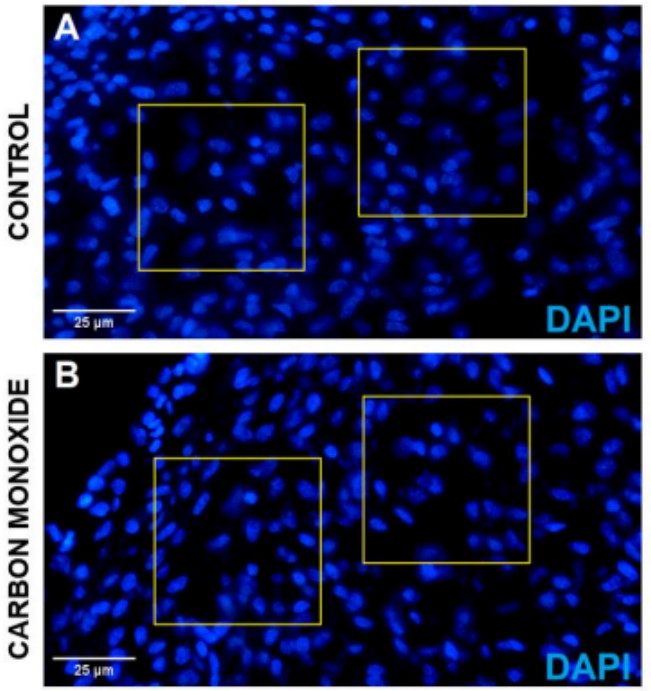


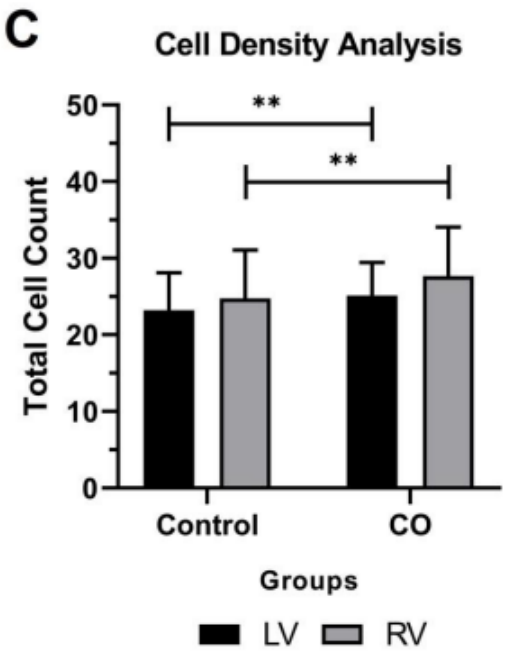
proliferation



apoptosis



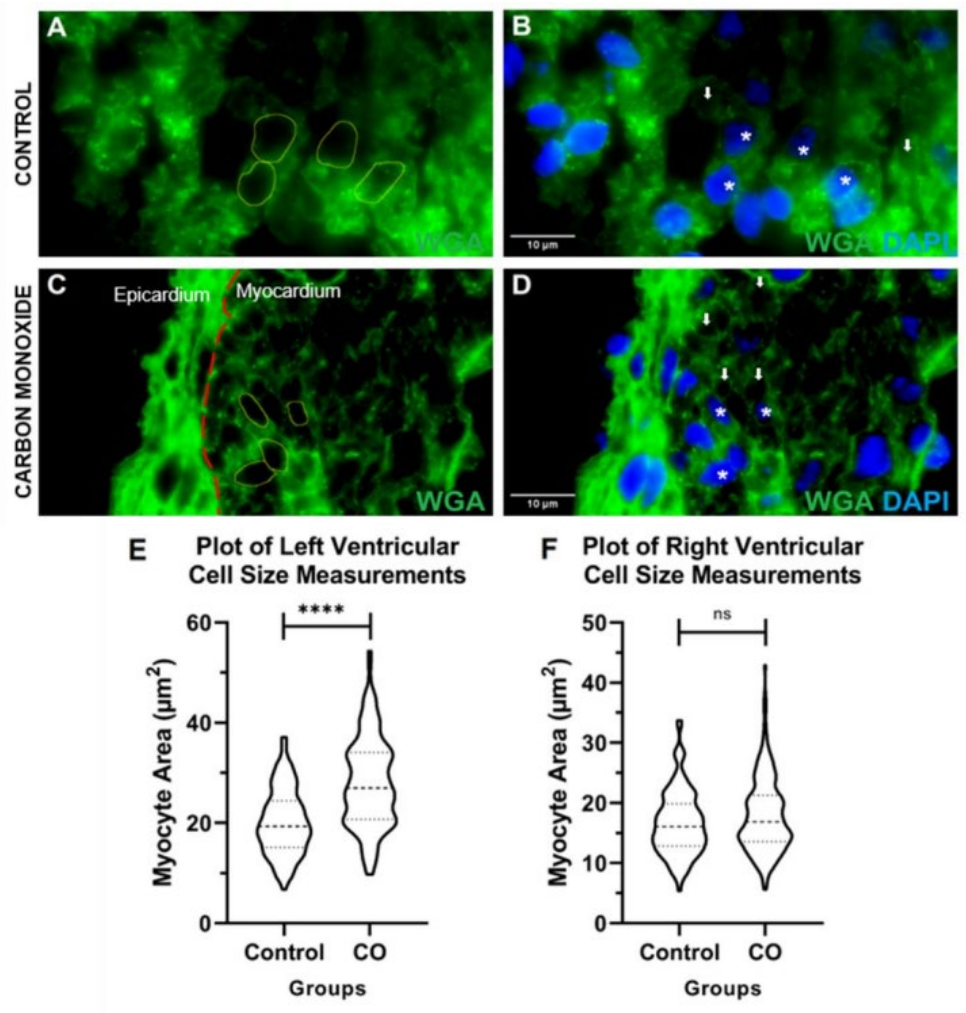




Increased proliferation and cell density in CO exposed myocardium

CO exposure does not induce cell death

Larger (hypertrophic) cells? Fluorescent microscopy to assess cell size...



Evidence of cardiac hypertrophy & increased cell number (proliferation) in left ventricular wall

New Results — Follow this preprint

Impact of carbon monoxide on early cardiac development in an avian model

Filipa Rombo Matias, Ian Groves, Mari Herigstad

doi: https://doi.org/10.1101/2021.12.22.473783

This article is a preprint and has not been certified by peer review [what does this mean?].

Impact of chronic low-level carbon monoxide exposure on the cardiovascular development of the embryonic avian model

*Joshua Durrans[1], Simon Clarke[1], Prachi Stafford[1], Mari Herigstad[1] and Liam Ridge[1]**

Affiliations:
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But how does CO induce these effects?

- Many more questions to define mechanism of action...
- Which cells effected? Cardiomyocytes, others?
- Developmental window of critical exposure?
- Phenotype exacerbated over time?
- Aberrant inflammation, cell signalling, ECM deposition?
- Important? Effect on cardiac physiology/systemic development?

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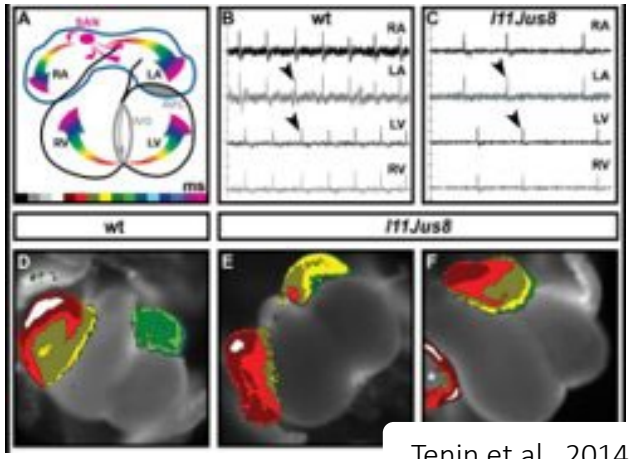
But how does CO induce these effects...?

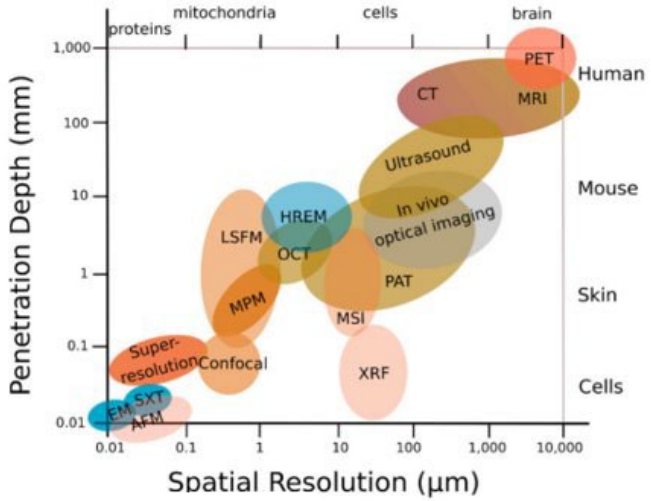
- Many more questions to define mechanism of action...
- Which cells effected? Cardiomyocytes, others?
- Developmental window of critical exposure?
- Phenotype exacerbated over time?
- Aberrant inflammation, cell signalling, ECM deposition?
- **Moreover, is this important?** Effect on cardiac physiology/systemic development?

Power of bioimaging to characterise potential CO-induced CHDs...

electrophysical mapping

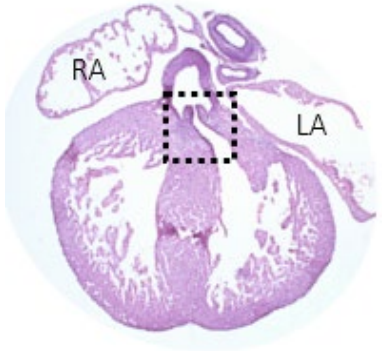


Tenin et al., 2014

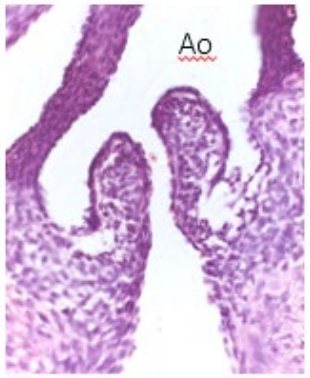


Keuenhof et al., 2021

brightfield (light)

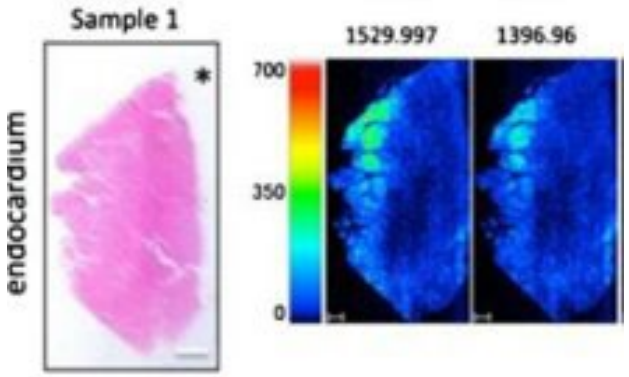


E15.5 H&E coronal section



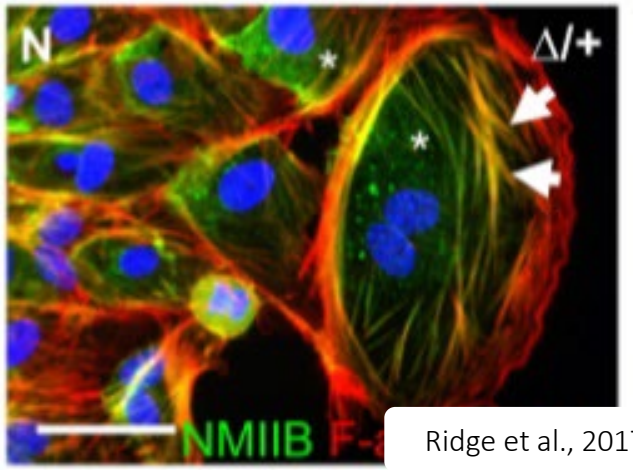
Page, Ridge et al., 2018

mass spec/proteomics



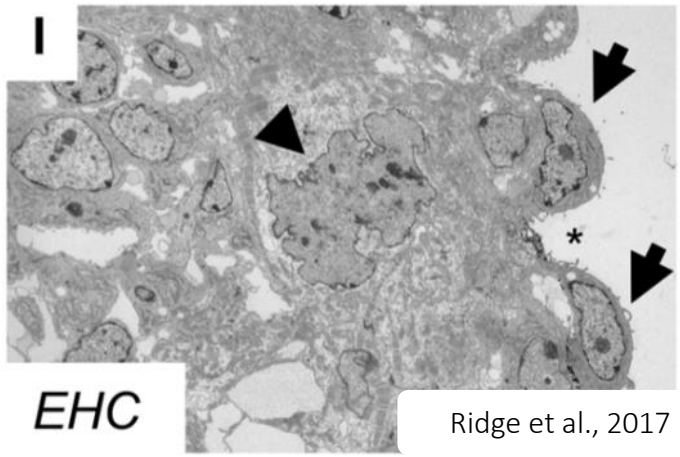
Mezger et al., 2019

fluorescent (confocal)



Ridge et al., 2017

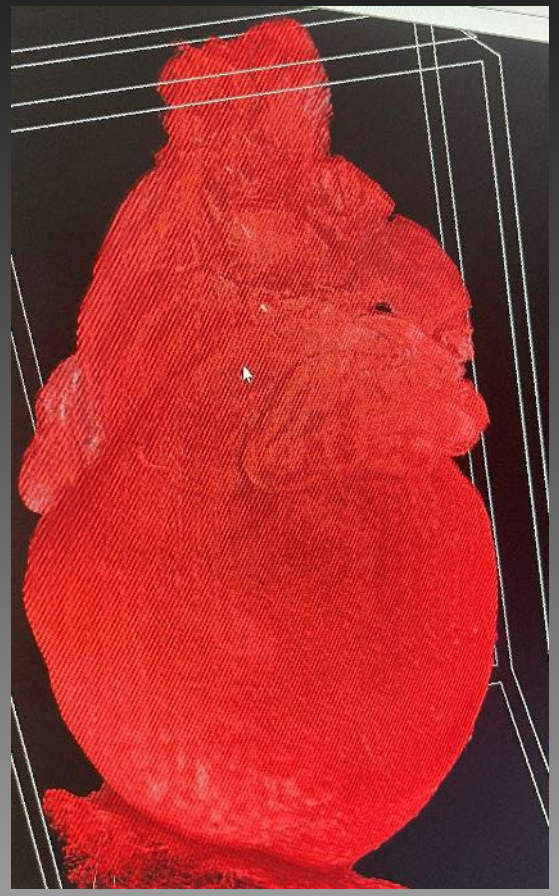
electron (scanning, transmission)



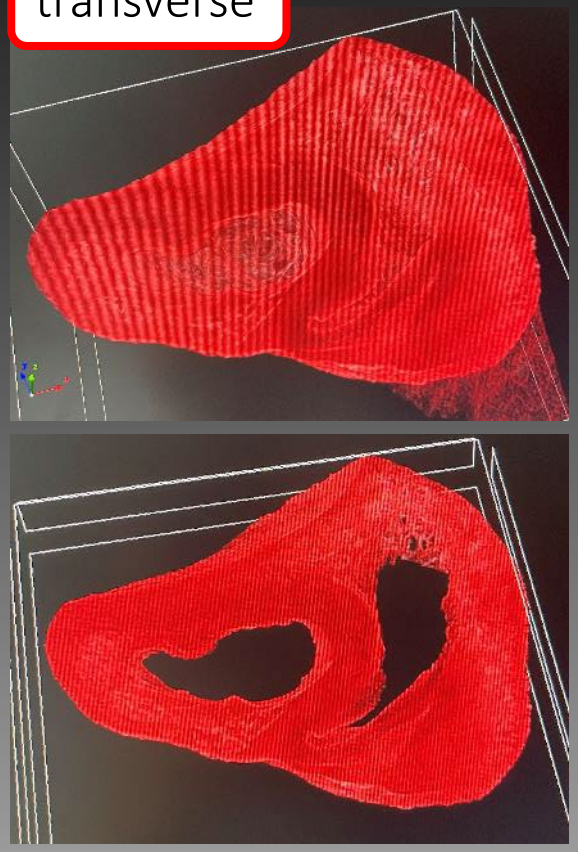
Ridge et al., 2017

Sheffield Hallam University

Ongoing work and future directions...



transverse



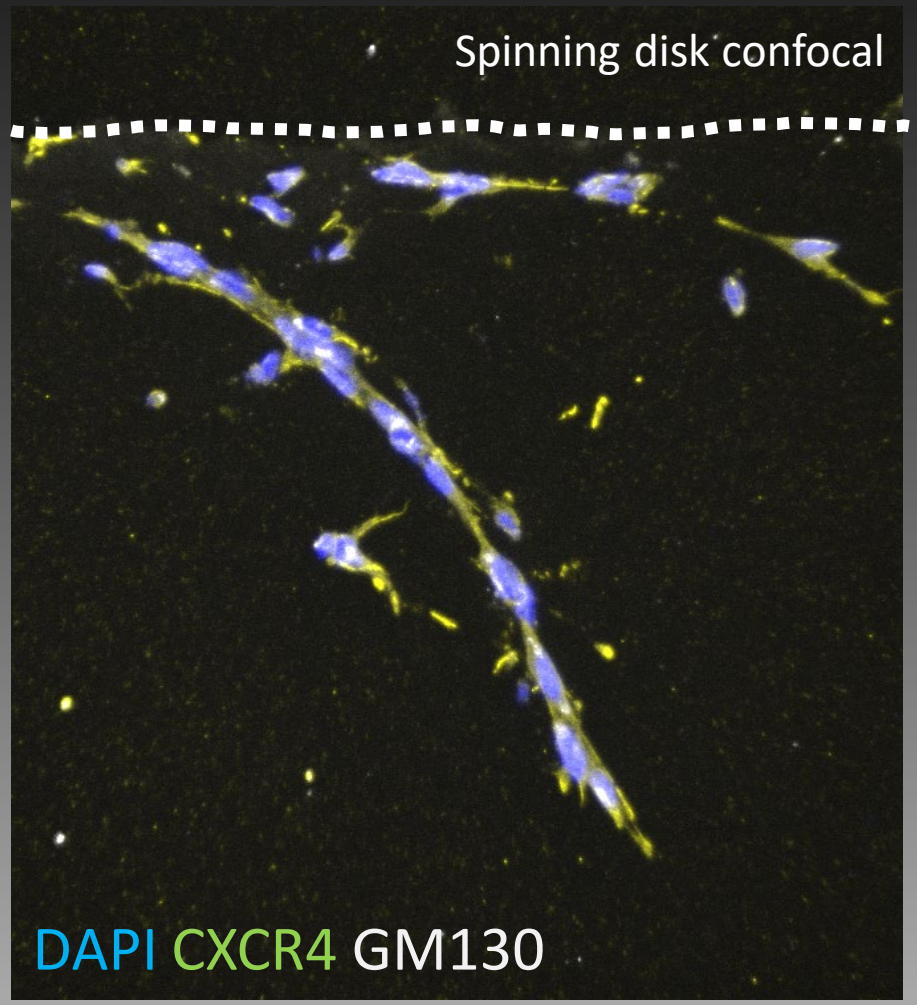
coronal

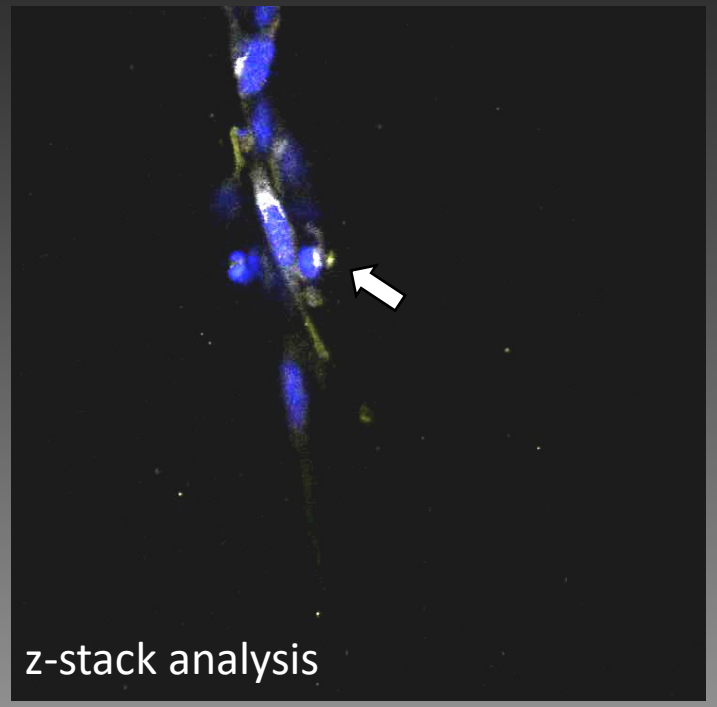
BSDB

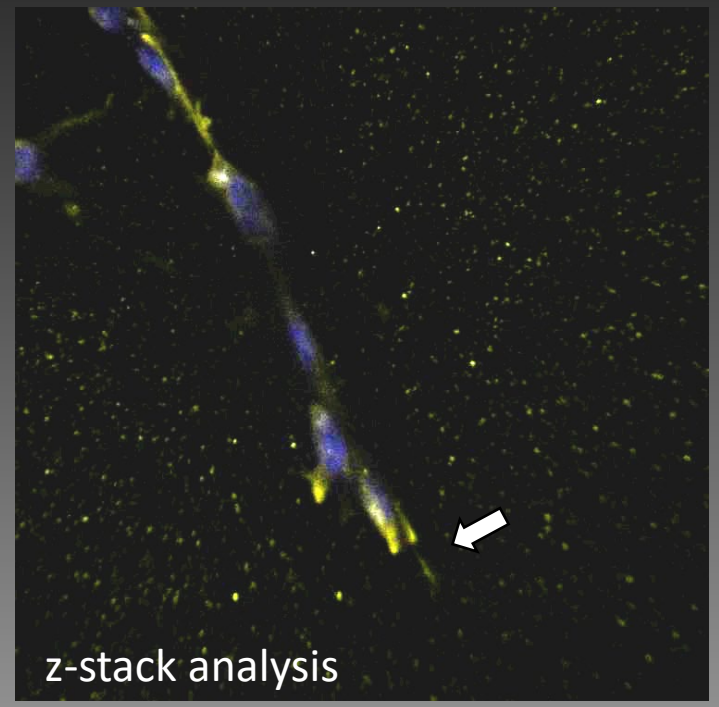
non-destructive microCT to optically section whole embryonic tissues (Josh Durrans, Dr Nicola Aberdein, Gurdon Summer Studentship funding)

Sheffield Hallam University

Ongoing work and future directions...







UCL

Imaging single progenitor cell dynamics (migration, differentiation, functionality) *in vitro* (Ridge et al., 2021)

Acknowledgements...

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