Identifying the ischaemic penumbra with BOLD-MRI oxygen challenge: Validation based on consequences of reperfusion

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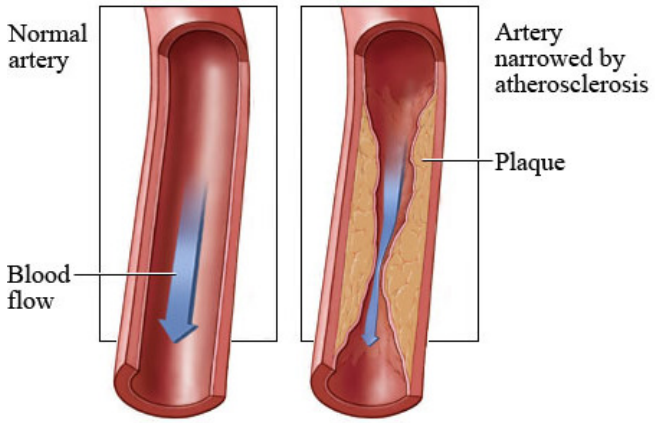
Ischaemic stroke

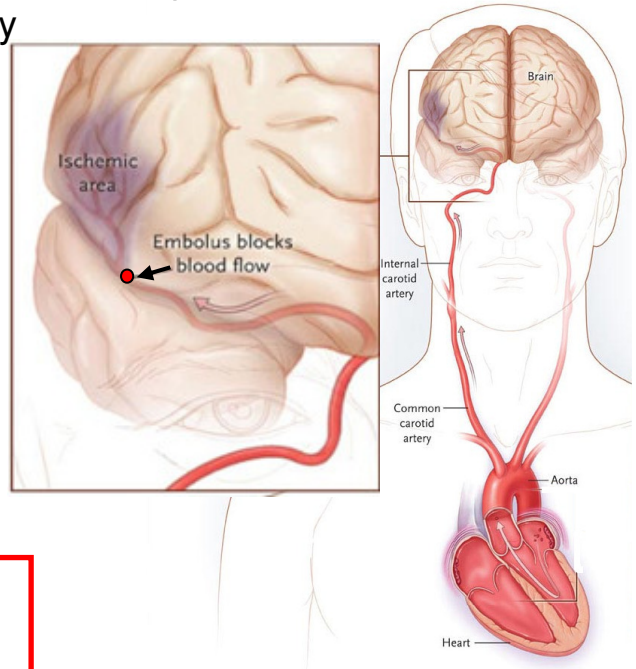
- In Scotland: Stroke is 3rd most common cause of death
- In Scotland, death rates from stroke : - highest compared to rest of UK
  - about 50% higher than in London
- Most strokes are not fatal – greatest cause of severe disability

Ischaemic stroke can arise from:

1. Atherosclerosis: Fatty deposits cause narrowing of an artery which preclude blood flow



2. A displaced blood clot that travels from the heart, for example, to the brain and blocks an artery



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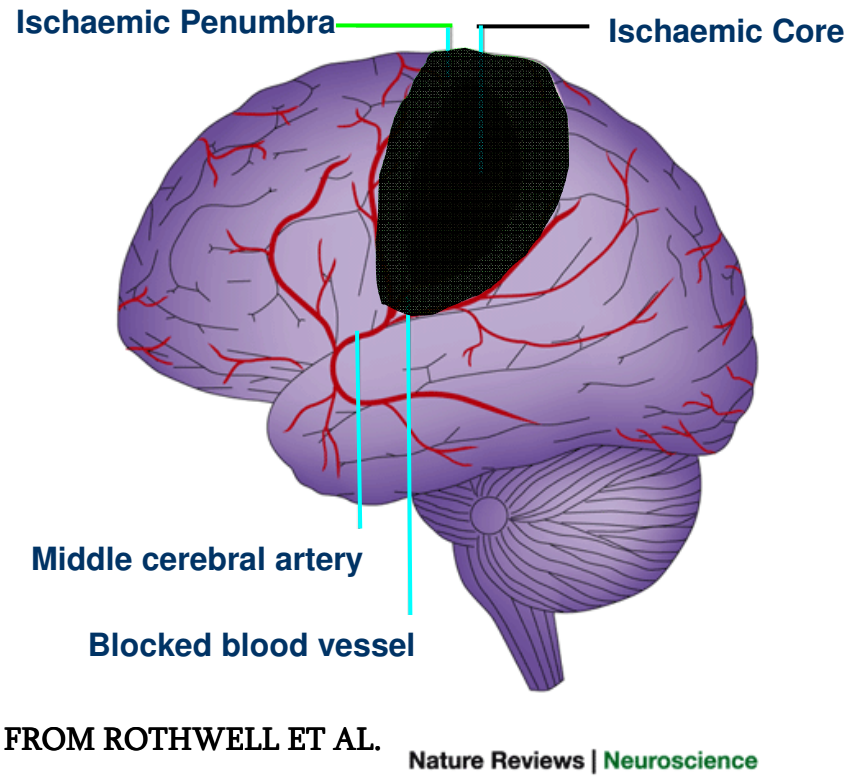
The severe reduction in blood flow causes almost immediate brain damage due to neuronal death

The Ischaemic Penumbra



FROM ROTHWELL ET AL.

The penumbra has a finite life span

The Ischaemic Core -

Tissue irreversibly damaged and cells are destined to die.

Unless blood flow is restored, tissue will eventually become incorporated into the infarct

The Ischaemic Penumbra -

- Tissue does not function

Stroke patients with penumbral tissue are most likely to benefit from acute therapy

restored or drugs given to support survival

A major method of identifying penumbra is with Magnetic Resonance Imaging (MRI)

- The tissue is also still metabolically active

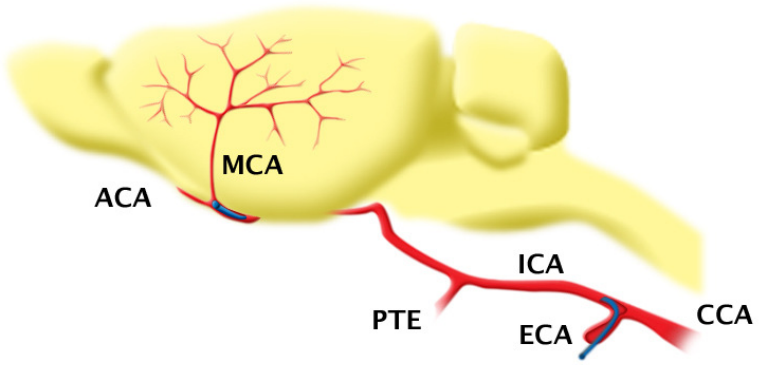
Rodent model of stroke

Stroke can be induced in the rodent using:

Intraluminal filament model of middle cerebral artery occlusion (MCAO)

MCA targeted because it is commonly occluded in human stroke patients

Sagittal view



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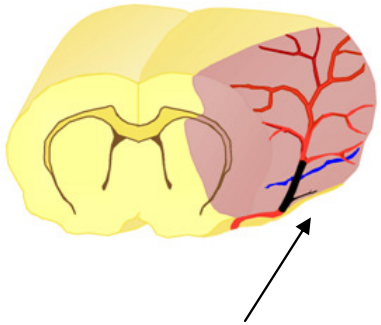
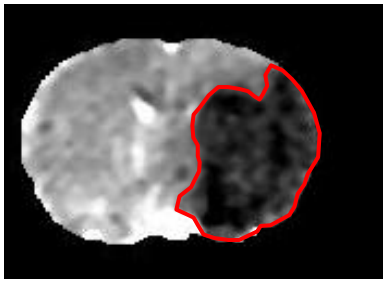
Coronal view



Ischaemic injury in MCA territory



Injury detected with MRI sequences

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Aims

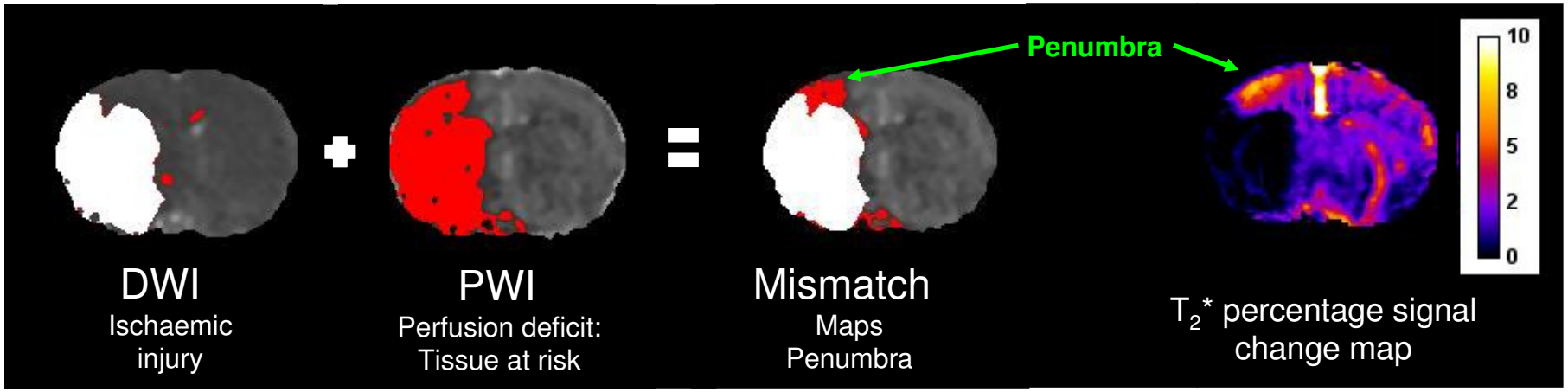
Develop and validate a novel MRI method of identifying penumbra

Rationale: Limitations of current MR model

Diffusion-Perfusion (DWI/PWI) Mismatch

T_2* Oxygen Challenge

BOLD MRI uses 100% oxygen inhalation as a metabolic biotracer



Metabolic characteristics of penumbra unaccounted for

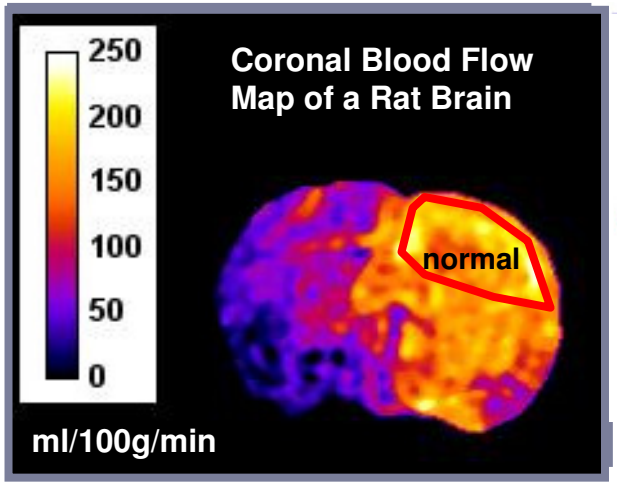
Defines penumbra based on oxygen-extraction fraction status **(Santosh et al, 2008).**

The Oxygen Challenge Paradigm

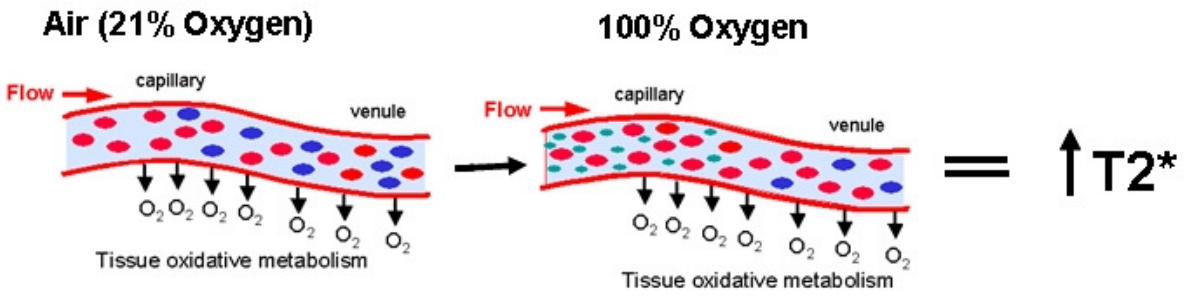
T_2* weighted MRI sequence

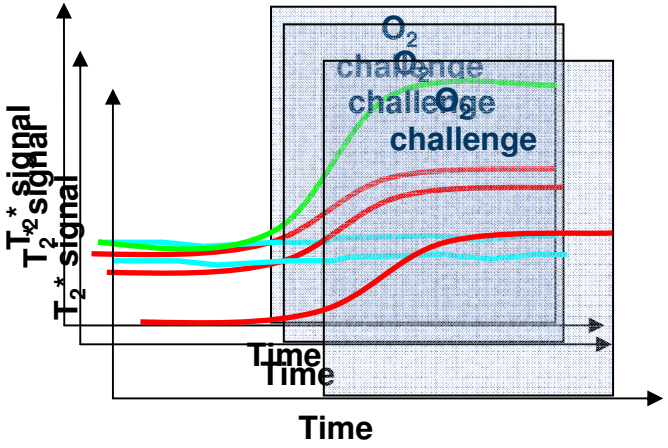
Air (21% O_2) 4 min	100% O_2 6 min

Key
- Oxyhaemoglobin
- Deoxyhaemoglobin T_2*↓
- O_2 Dissolved in Plasma



1. Normal metabolising tissue



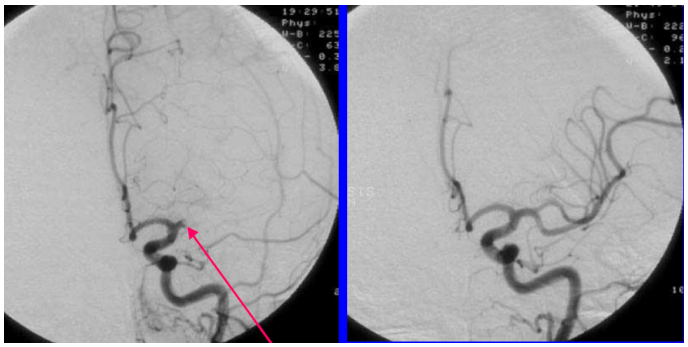


(Santosh et al, 2008)

Reperfusion Study

"Reperfusion of the ischemic brain is the most effective therapy for acute ischemic stroke ever known and ever likely to be discovered" **Molina and Saver (*Stroke.* 2005;36:2311.)**

MR angiogram



Occluded artery Restoration of CBF

Reperfusion restores nutritional blood flow to injured tissue before it progresses to infarction, thus

- Salvaging penumbral tissue
- Reducing final infarct size
- Enabling improved clinical outcomes

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Validating Oxygen Challenge (OC):

T_2* MRI sequences should map changes in penumbra associated with restoration of flow and its amenability to salvage

Study Aims

1. How does the Oxygen Challenge-defined penumbra respond to reperfusion?

   Reduction in signal change in OC-defined penumbra following reperfusion may signify recovery

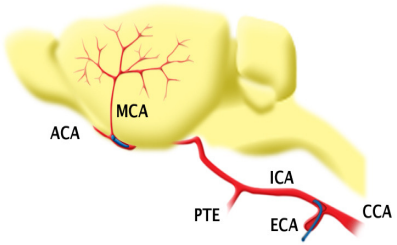
2. How does cerebral blood flow (CBF) change following reperfusion?

   Increases in CBF in the OC-defined penumbra following reperfusion may also signify recovery

Methods

Stroke surgery:

Male Sprague Dawley rats (n=7) underwent intraluminal filament model of middle cerebral artery occlusion (MCAO)



DWI
PWI
OC

DWI
PWI
OC

Ischaemia (MCAO)

Reperfusion

~1hr

~90 min

~2hr

DWI, PWI and OC scans carried out after MCAO to define the penumbra

Reperfusion induced at 90 mins post-ischaemia by removal of intraluminal filament

Series of scans repeated following reperfusion

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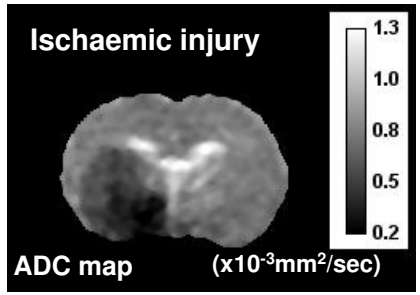
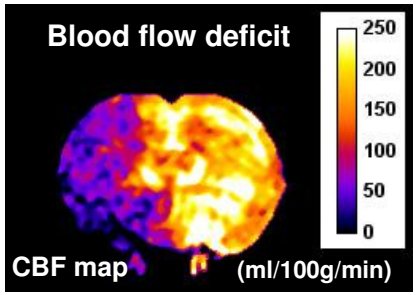
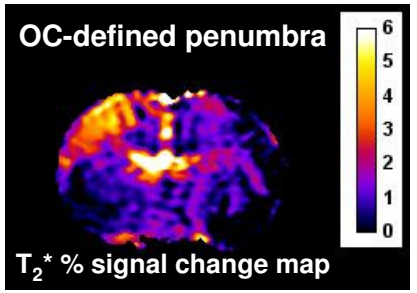
MRI scans

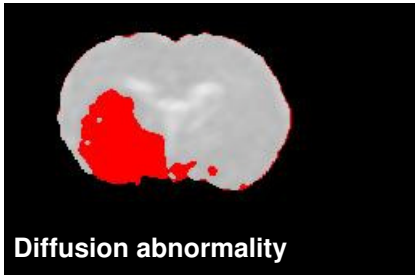
SCANS:

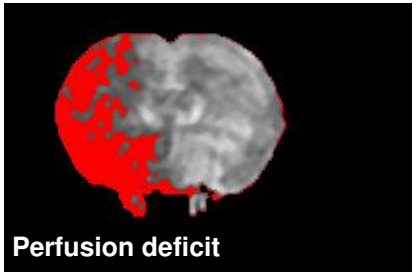
DURING ISCHAEMIA

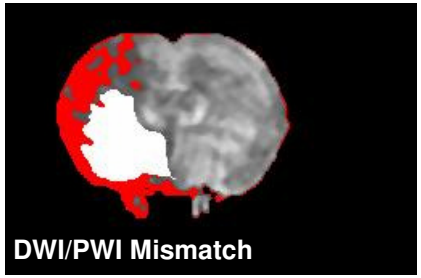






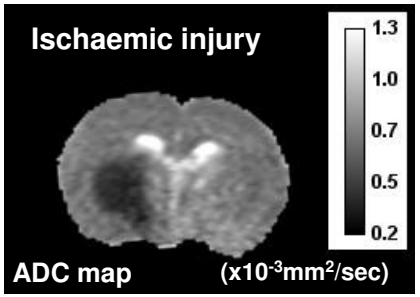


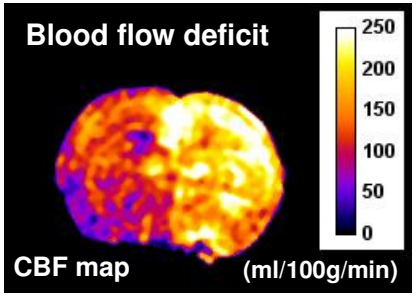


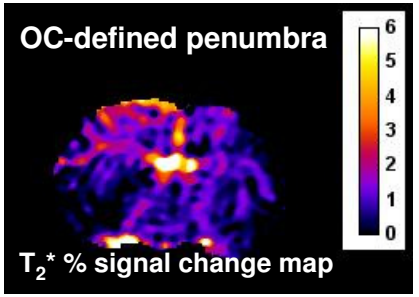


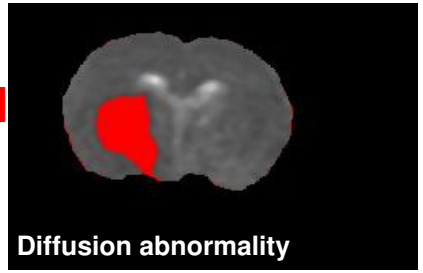
SCANS:

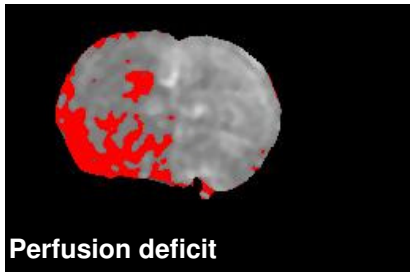
FOLLOWING REPERFUSION

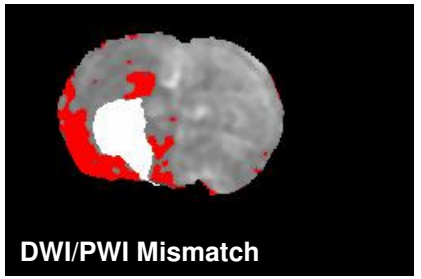












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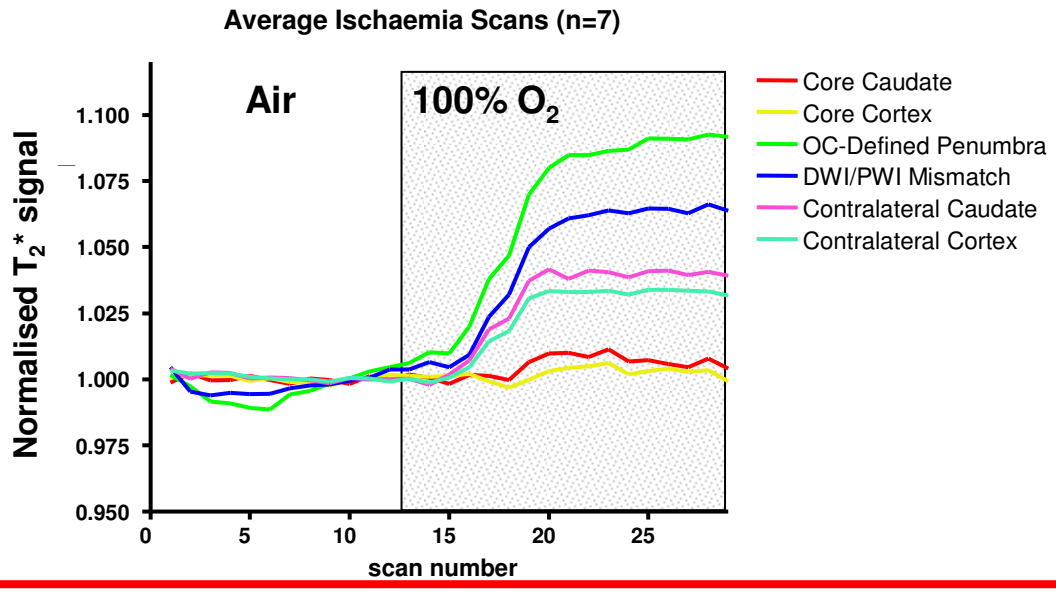
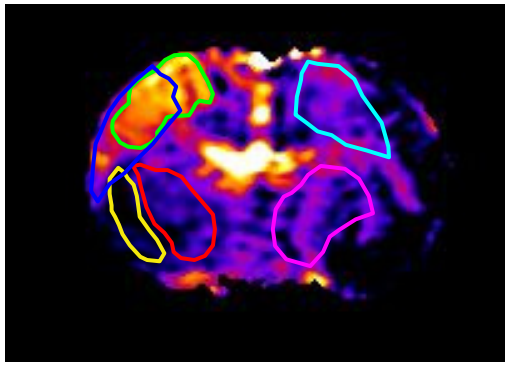
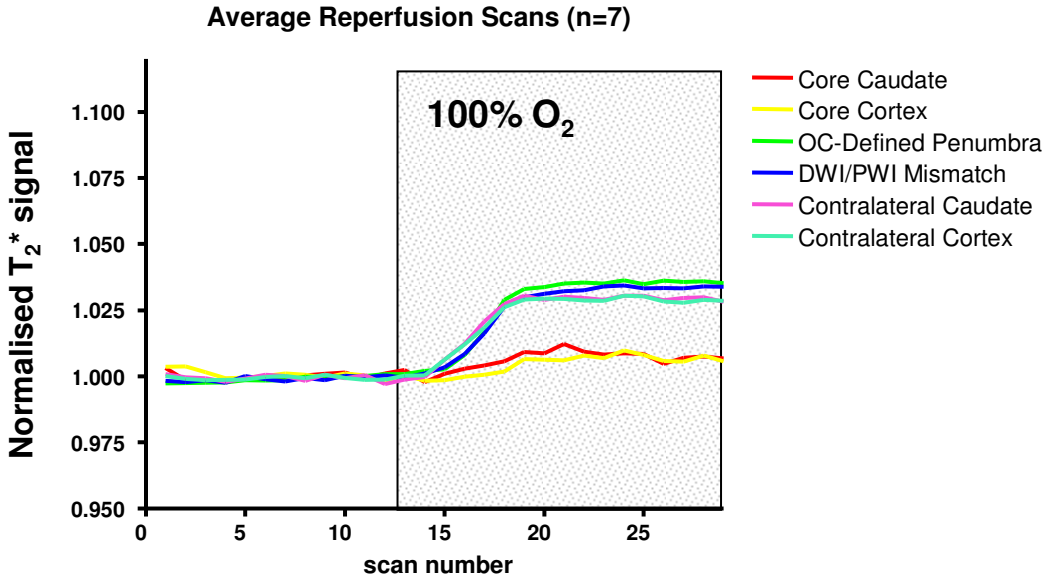
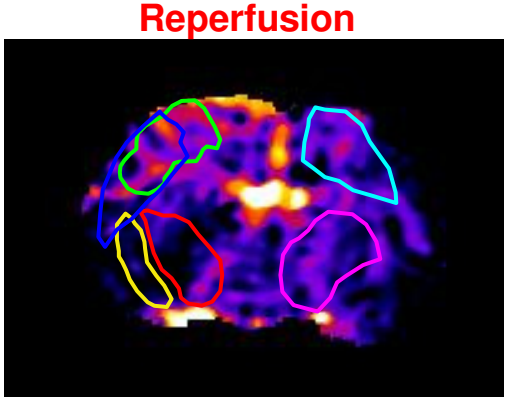
Results: T_2* Time course maps



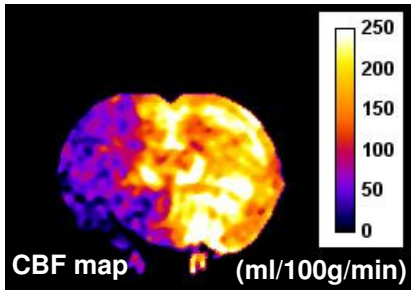


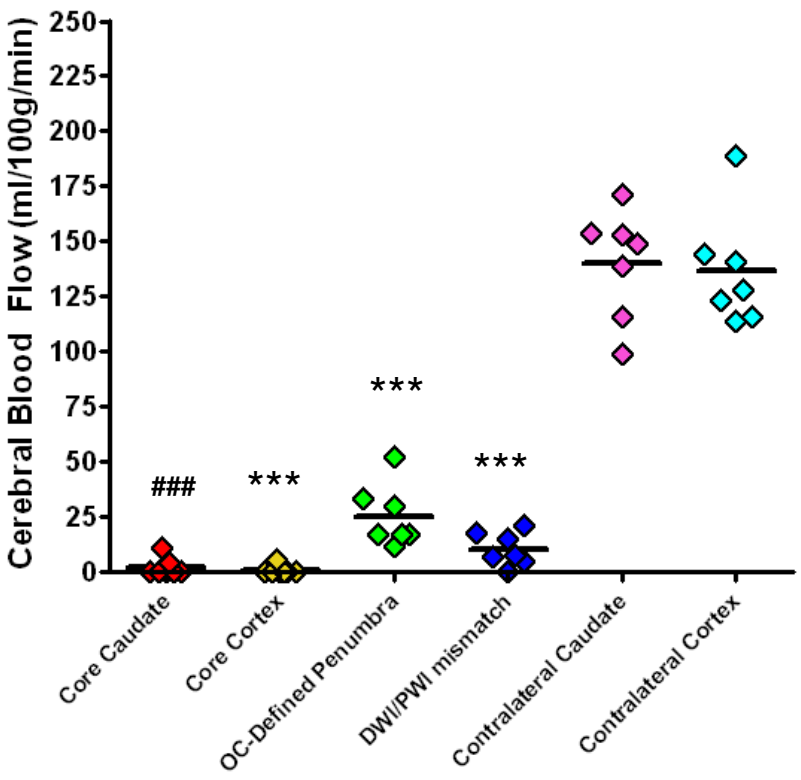




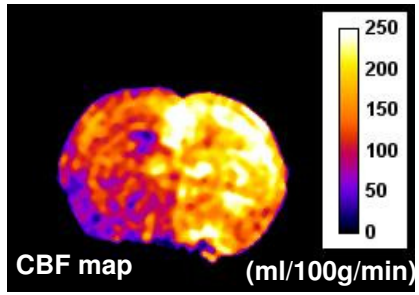
Results: Cerebral Blood Flow

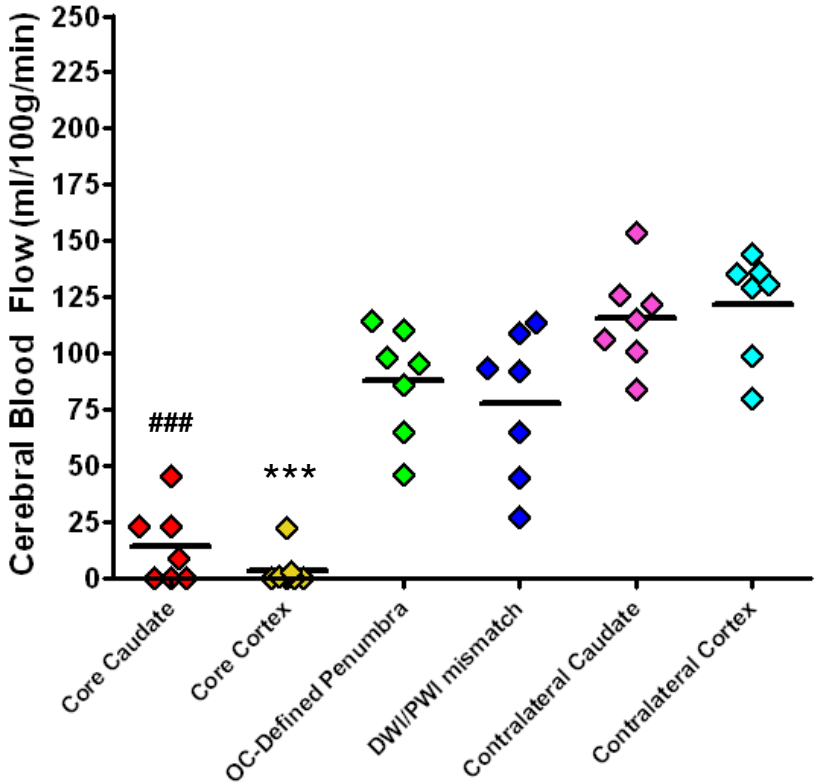
Ischaemia





Reperfusion





*****, p<0.001 and ###, p<0.001 compared to contralateral cortex and contralateral caudate, respectively. One-way ANOVA with Bonferroni Correction**

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Conclusions

Salvage of the Oxygen Challenge-defined penumbra may be evident by:

Attenuation of the T_2* percentage signal change in the Oxygen Challenge-defined penumbra following reperfusion

Restoration of CBF in the Oxygen Challenge-defined penumbra following removal of intraluminal filament

In conclusion:

Tissue identified as penumbra using Oxygen Challenge is capable of recovery when blood flow is restored

Technique provides further validation of the utility of OC MRI for acute stroke management.

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Acknowledgements

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