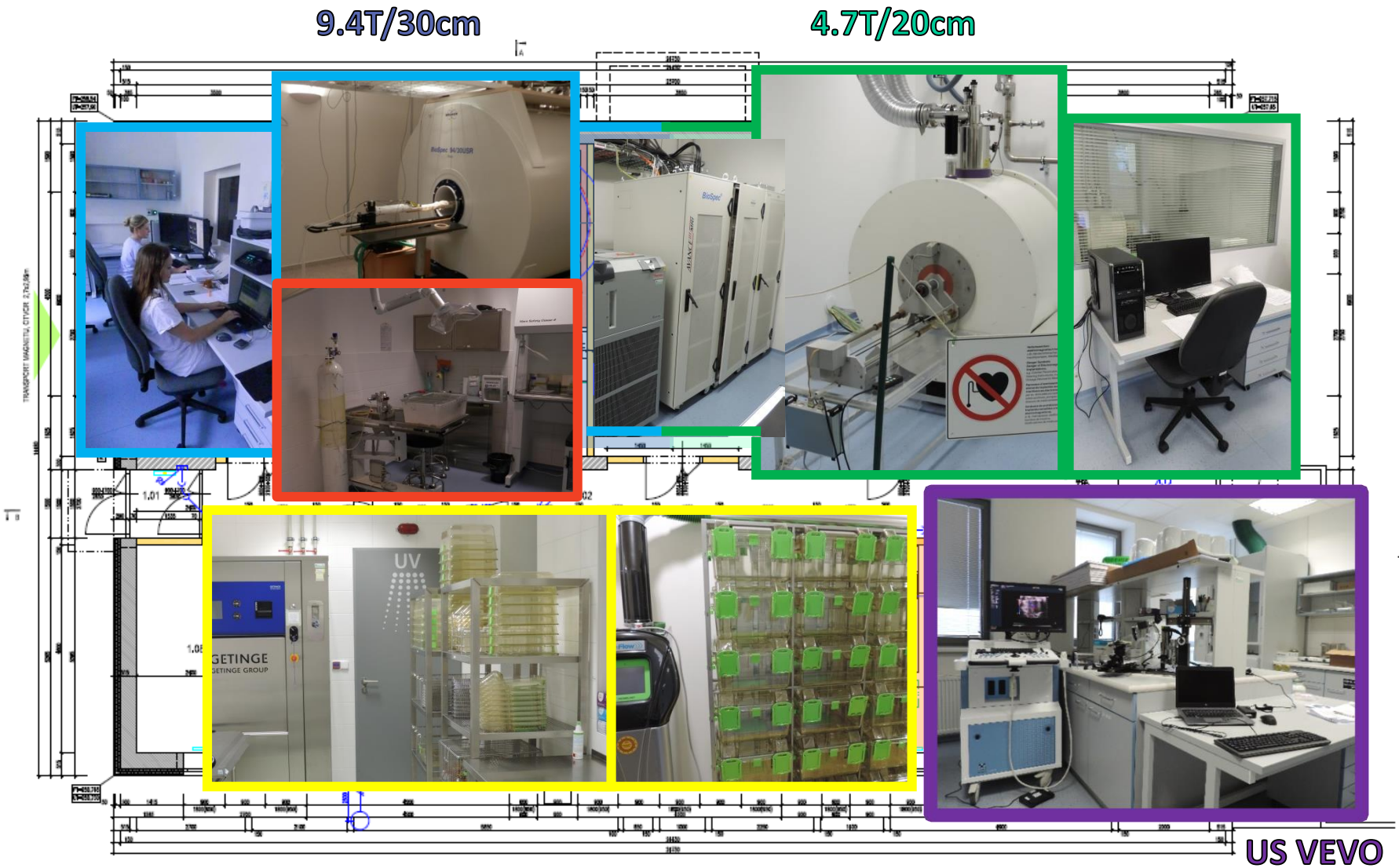
Practical Aspects of Animal MRI Studies, Legal and Ethical Issues, Applications

Eva Dražanová

MR systems



Kitchen/WC

Animal facility

Operating room

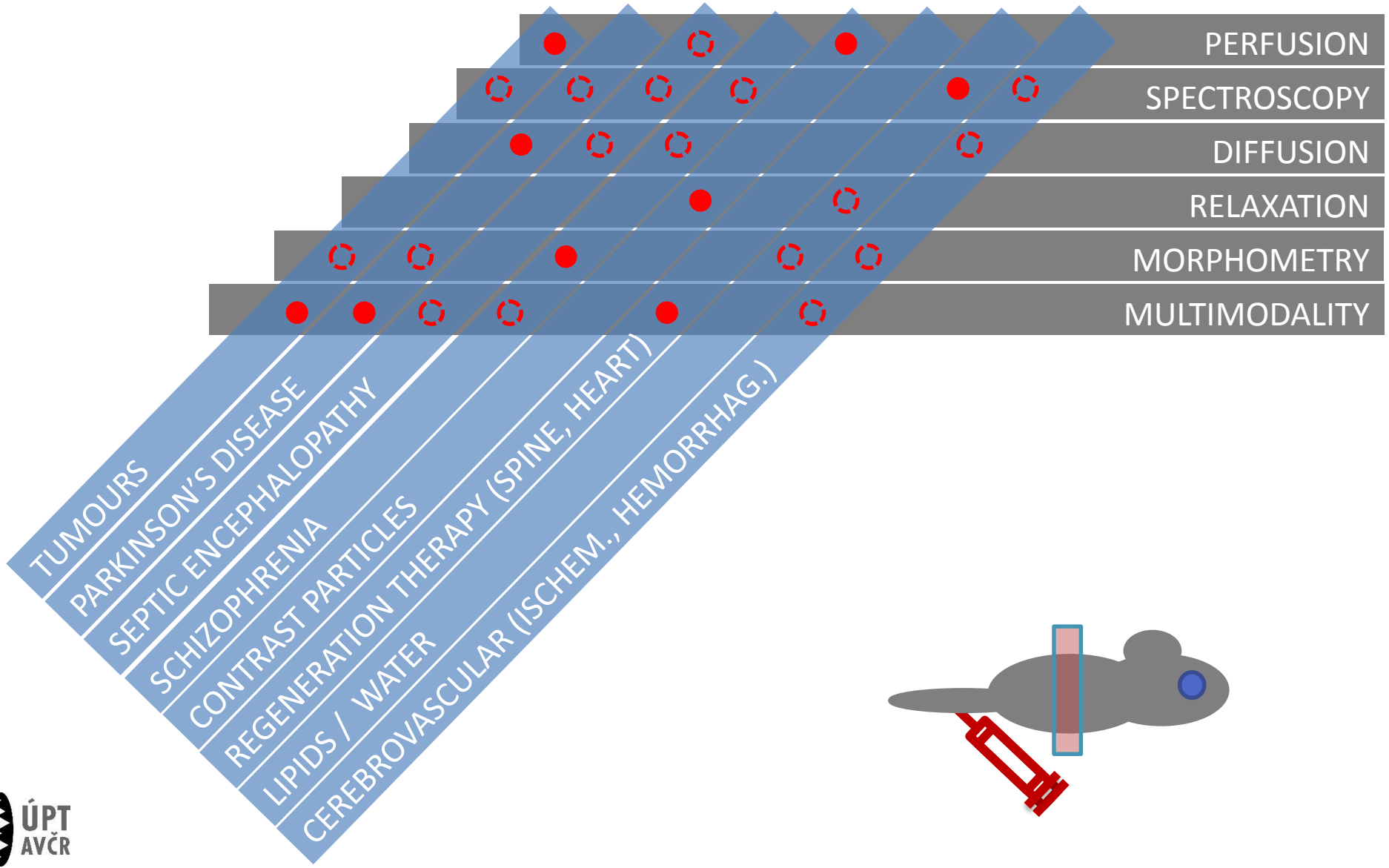
Technical facility

ÚPT AVČR

Principal research areas

- Study of pathophysiology
  - Neurodegenerative, psychiatric, cerebrovascular diseases in small animal models (mouse, rat, rabbit)
    - Parkinson's disease, schizophrenia (MU)
    - septic encephalopathy (University Hospital Brno)
    - colorectal carcinoma (Inst. of Biophysics CAS)
    - chicken embryos and nanoparticle effects
    - myocardium infarction (University of Veterinary and Pharmaceutical Sciences Brno)
- Drug and therapy development
  - Testing of nanoparticle carriers of imaging markers and drugs and their targeting
  - Nanoparticular markers for theranostics (diagnostics + therapy), farmacokinetics, farmacodynamics
  - Toxicity studies
- Measurement and analytical methods
  - Perfusion – diffusion - spectroscopy
  - Multimodal synergy: MR – US – … ? – optics – TEM – ...

Research & Service Topics



ÚPT AVČR

Animal model

- An animal with a disease either the same as or like a disease in humans. Animal models are used to study the development and progression of diseases and to test new treatments before they are given to humans.

Animal model - **Legislation**

- All procedures are performed in accordance with EU Directive no. 2010/63/EU
- Approved by the Animal Care Committee of Academy of Sciences, Czech Republic
- Czech Governmental Animal Care Committee, in compliance with Czech Animal Protection Act No. 246/1992.

→ **Ethical clearance**

Animal model - **Tricky stuff**

- Small size
- Fast breathing (mouse 60 – 90/min)and heart beating (mouse 450 BPM)
- Different metabolism
- Physiological abnormalities
- Bad collaboration

→ 3R

Animal model - **Anesthesia**

- **General anesthesia**

 - inhalation anesthesia

 - intramuscular anesthesia

 - intraperitoneal anesthesia

- **Drugs**

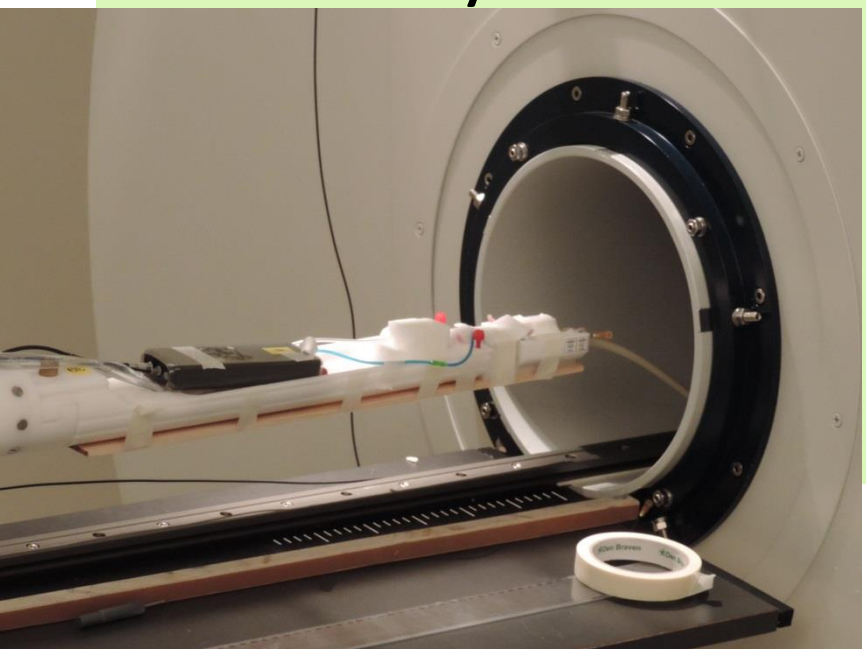
 - isoflurane

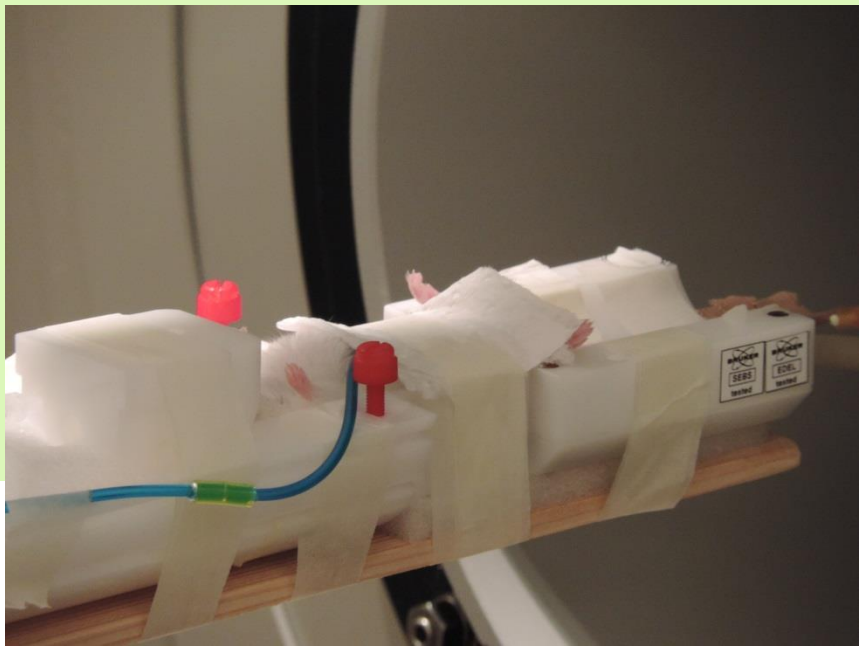
 - xylazine, ketamine, diazepam

 - propofol, medetomidine

Animal model

- temperature
- respiration monitoring
- heating
- oximetry





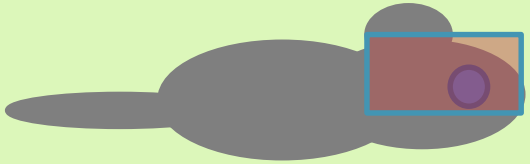
Happy Snappy Camera

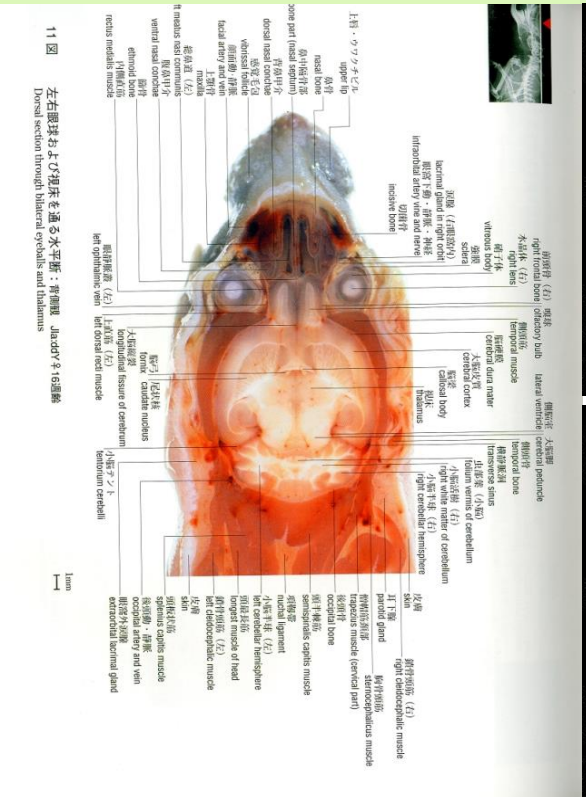
ÚPT AVČR

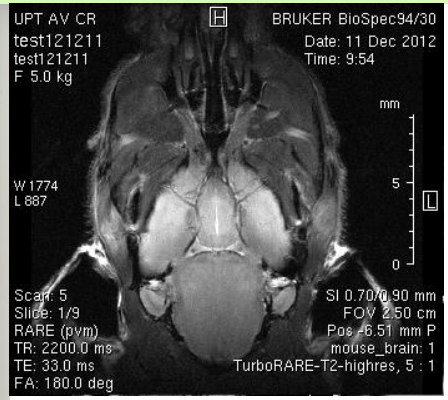
Anatomical imaging - brain

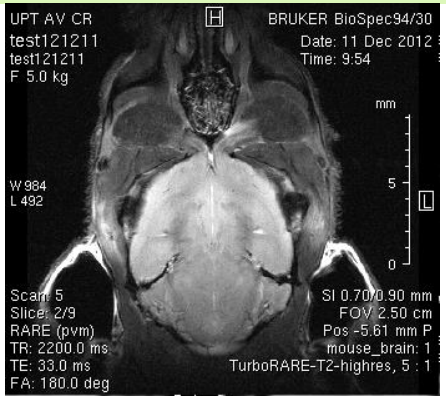
Brain with high spatial resolution

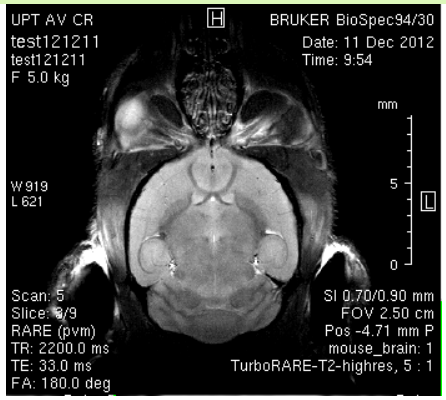
- **Aim**
  - Anatomical background for functional studies, volumetry
- **Limits**
  - Isotropic resolution of 90 μm in 10 min (water)

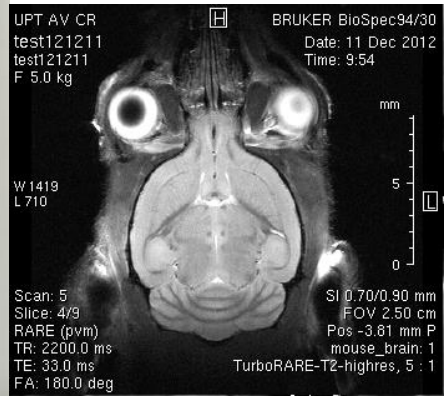


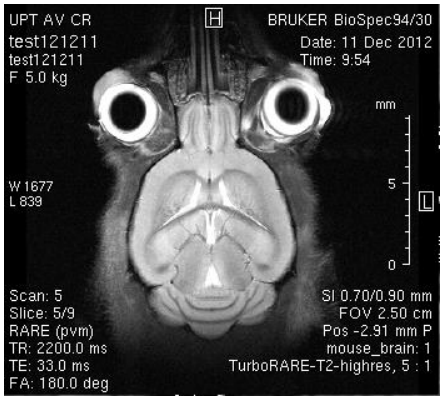


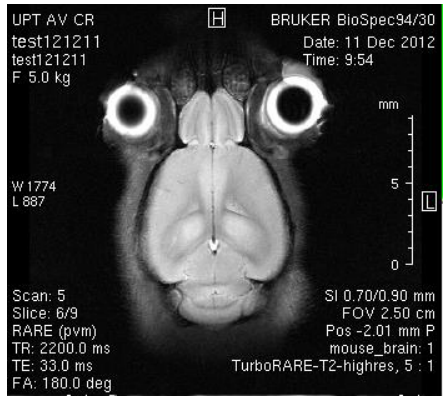




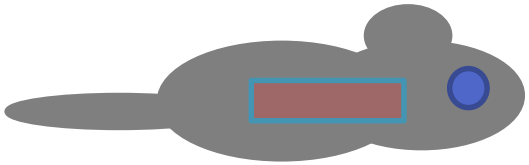


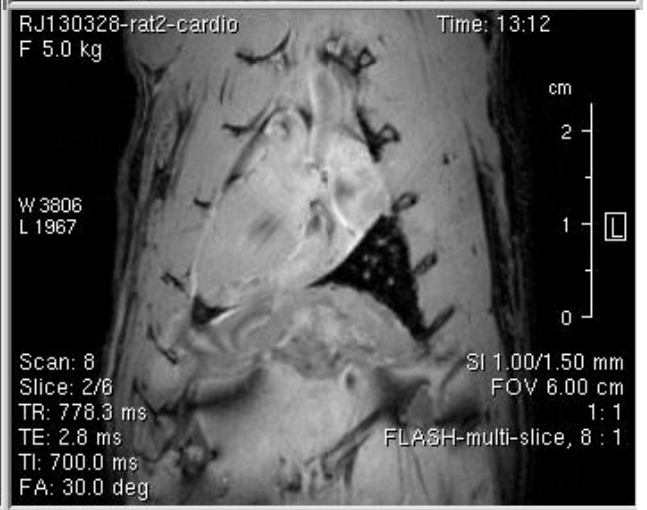


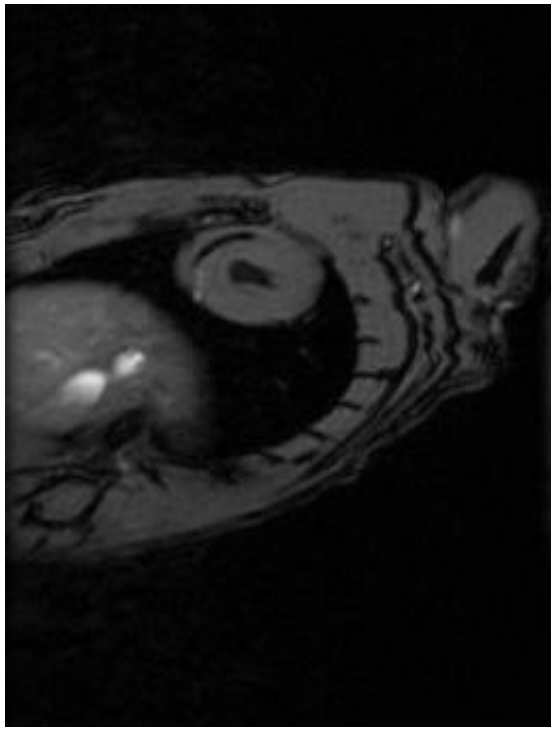




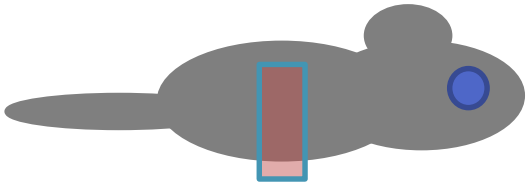
Anatomical imaging - heart

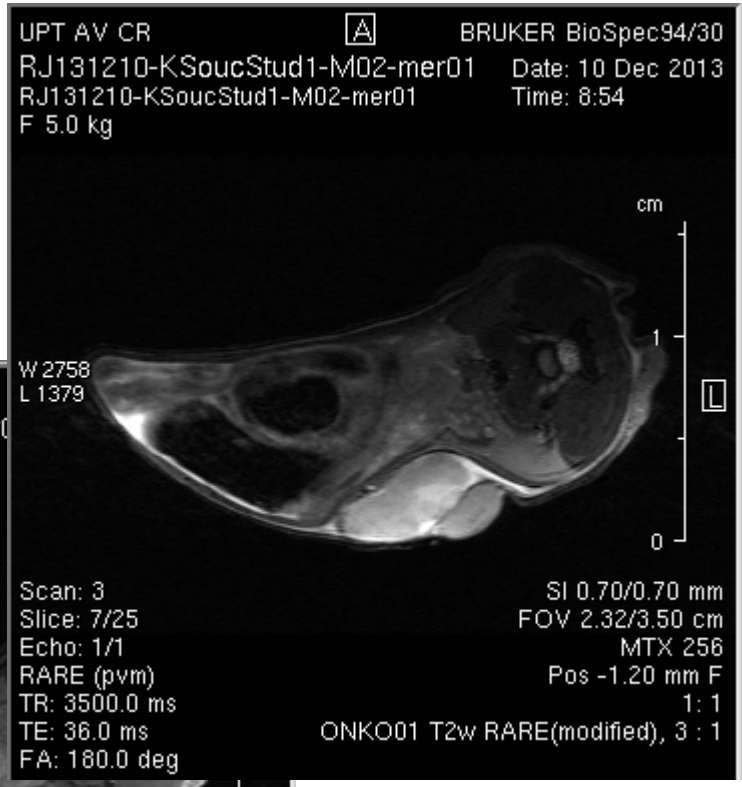


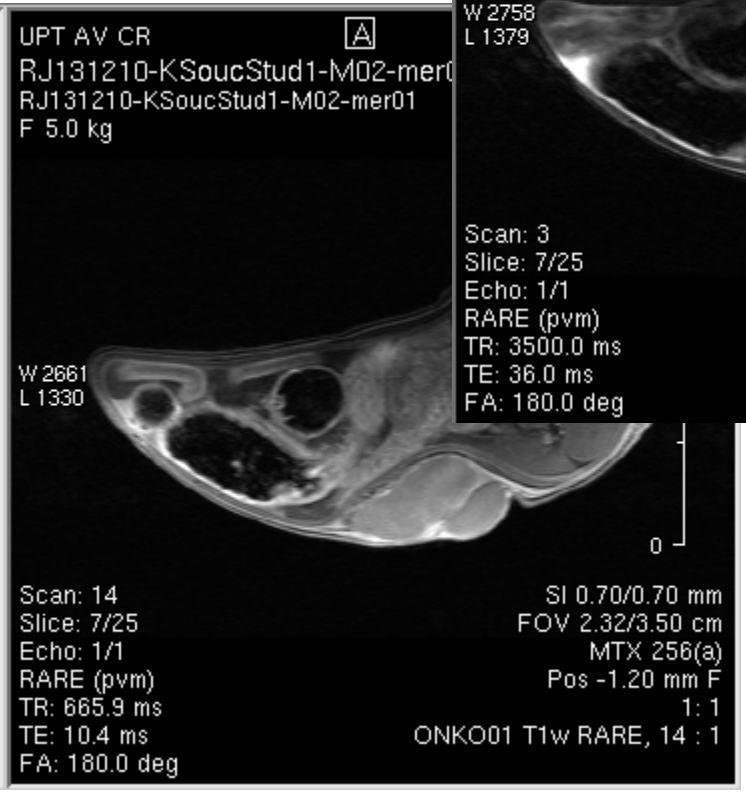




Anatomical imaging - tumor







ÚPT AVČR

Angiography - brain

- Detection of abnormalities in the vessel tree (stenosis, thrombus, …)
- Detection of angiogenesis (oncology)
- Ischemia
- Estimation of flow

ÚPT AVČR

Animal models of schizophrenia

- Pharmacological model
- Developmental model – POLY I:C model, MAM model
- Genetic model

Animal models

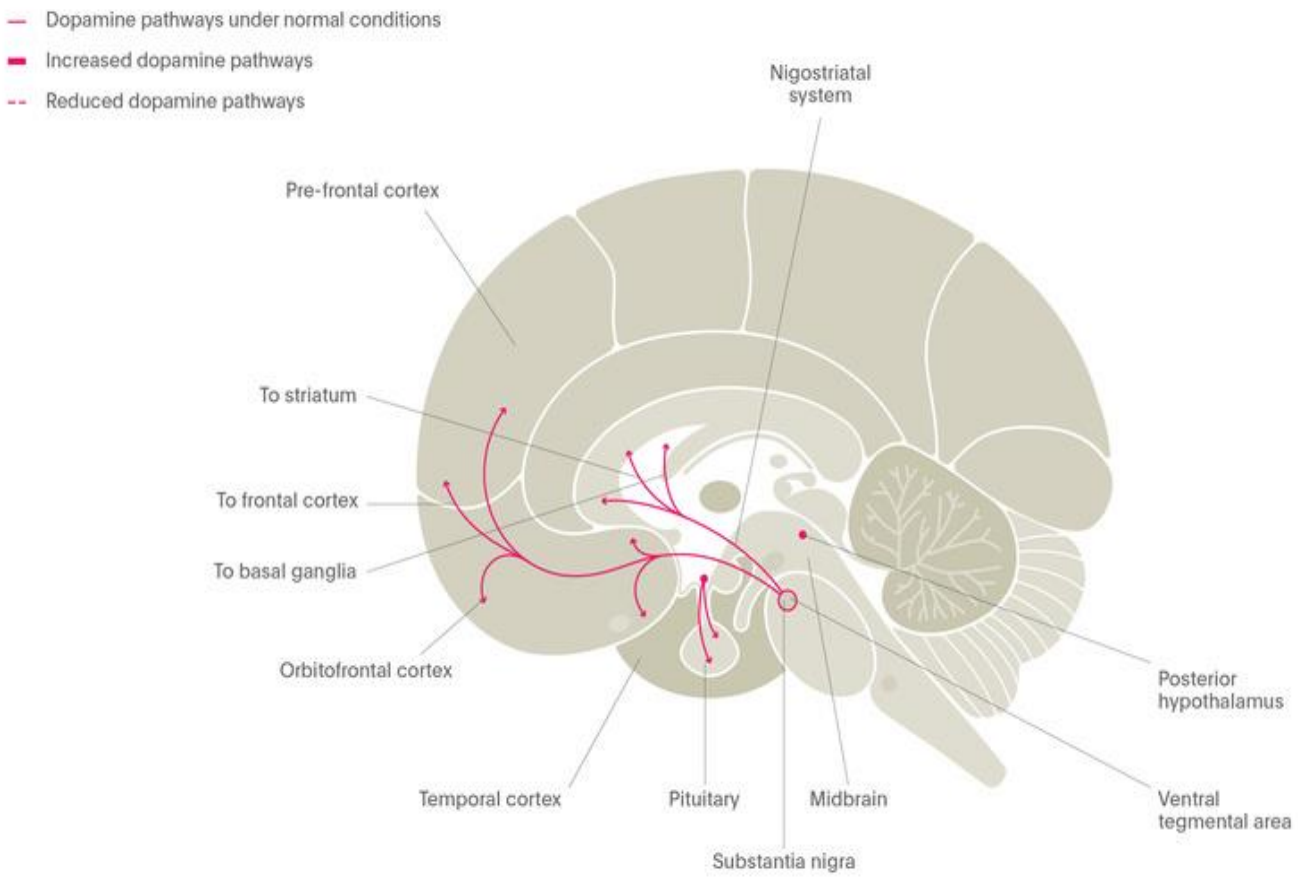
- **POLY I:C** - pregnant rat females, intravenous application
- 15th day
- offsprings

- **MAM** – pregnant rat females, intraperitoneal application
- 17th day
- offsprings

Animal models of schizophrenia

- Polyriboinosinic–polyribocytidilic acid (POLY I:C) mimics neonatal exposure to viral pathogens
- Mitotoxin methylazoxymethanol acetate (MAM) model mimics neonatal exposure to toxic substances
- **Dopamine** - influences all segments of cerebral circulation, dopamine dysregulation is a hallmark of schizophrenia

Schizophrenic phenotype



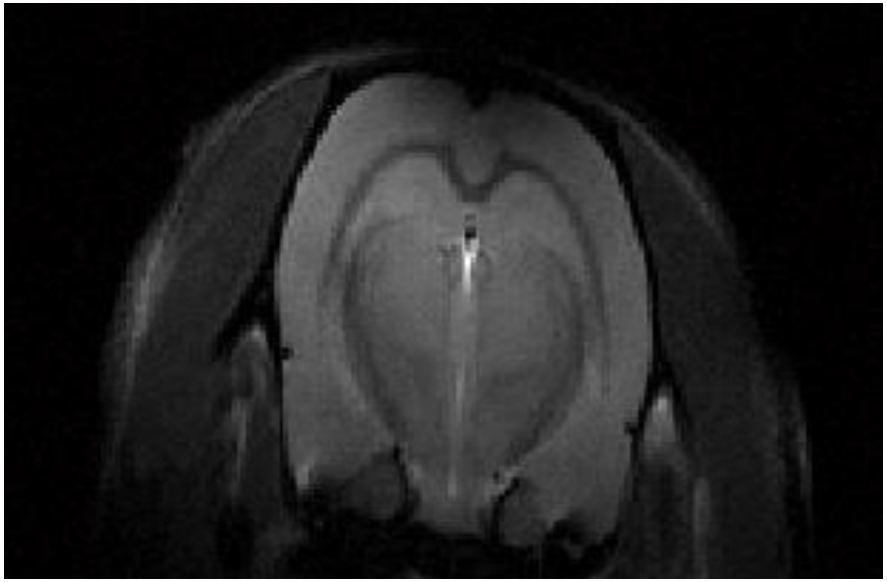
ÚPT AVČR

Schizophrenic phenotype

- Schizophrenia is associated with several structural and functional brain abnormalities
- Simulation of positive symptoms – hyperactivity of mesolimbic dopaminergic neurons
- Simulation of negative symptoms – hypoactivity of mesocortical dopaminergic neurons
- *In situ* application of dopamine produces vasoconstriction, but binding on D1 and D2 dopaminergic receptors induces vasodilation (*Iadecola*, 1998)

Anatomical images – T2w

Control



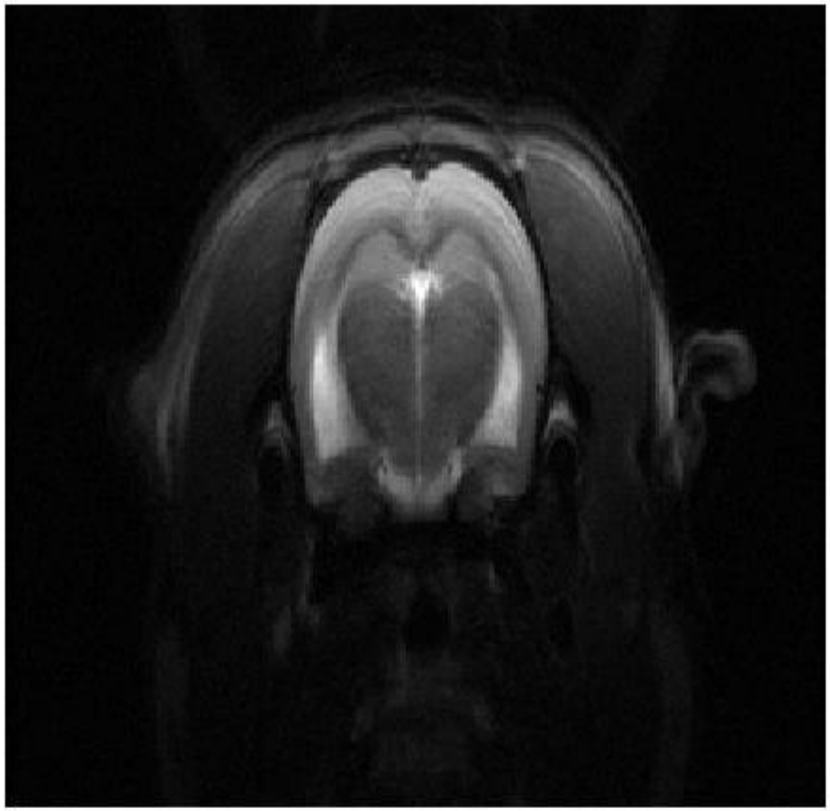
POLY I:C

ÚPT AVČR

Analyzing of data - ASL

- **ASL** gives absolute values of brain tissue perfusion of brain tissue by blood (cerebral blood flow) in ml blood/g tissue/min
- It uses magnetic labelling of inflowing arterial blood
- It is noninvasive, using no injected contrast medium, it can be repeated without limit, and can study normal physiology and its variation with time

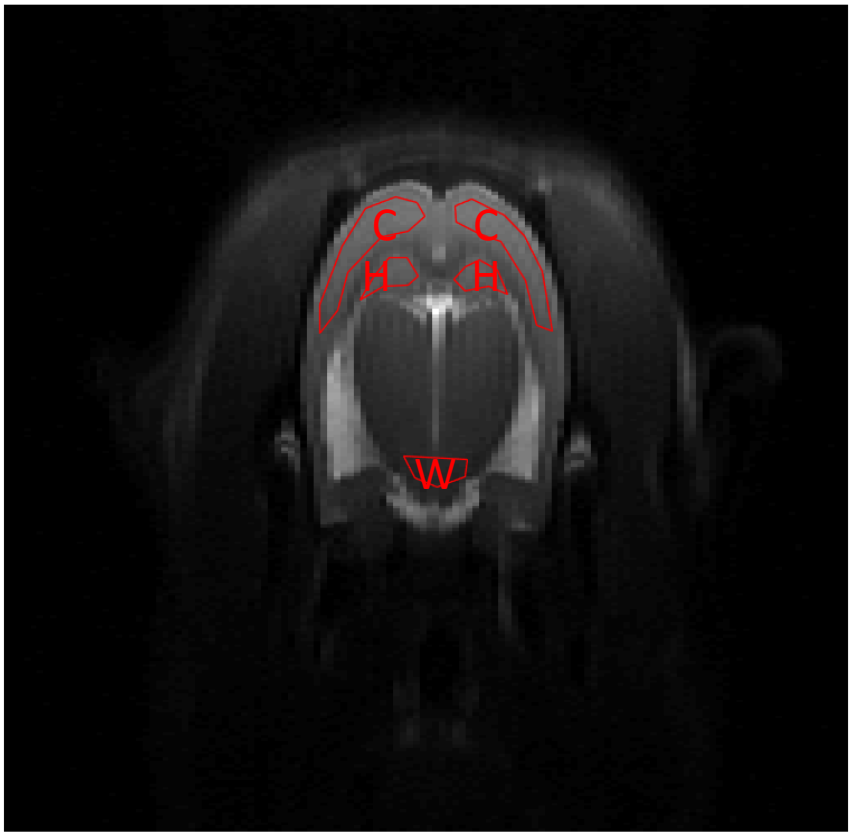
Acquisition – T2w



- T2w - image

UPT AVČR

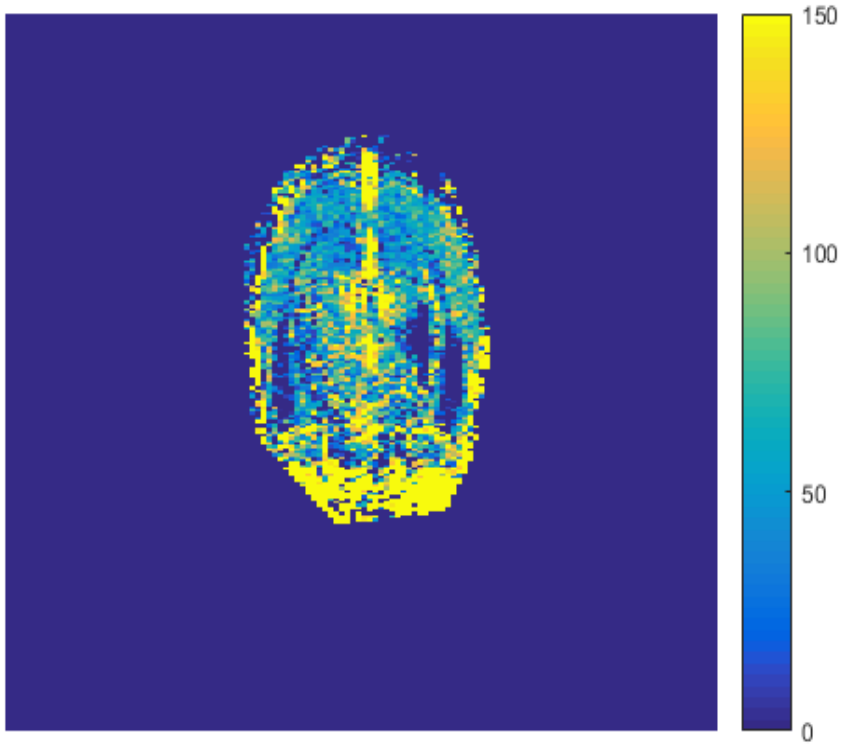
Acquisition - ASL



- **ASL** image
- FAIR-RARE
- ROI

- cortex
- hippocampus
- circle of Willis

Data processing - ASL



- ASL perfusion map
- Cerebral blood flow
- ml/min/100 g tissue

ÚPT AVČR

Data processing

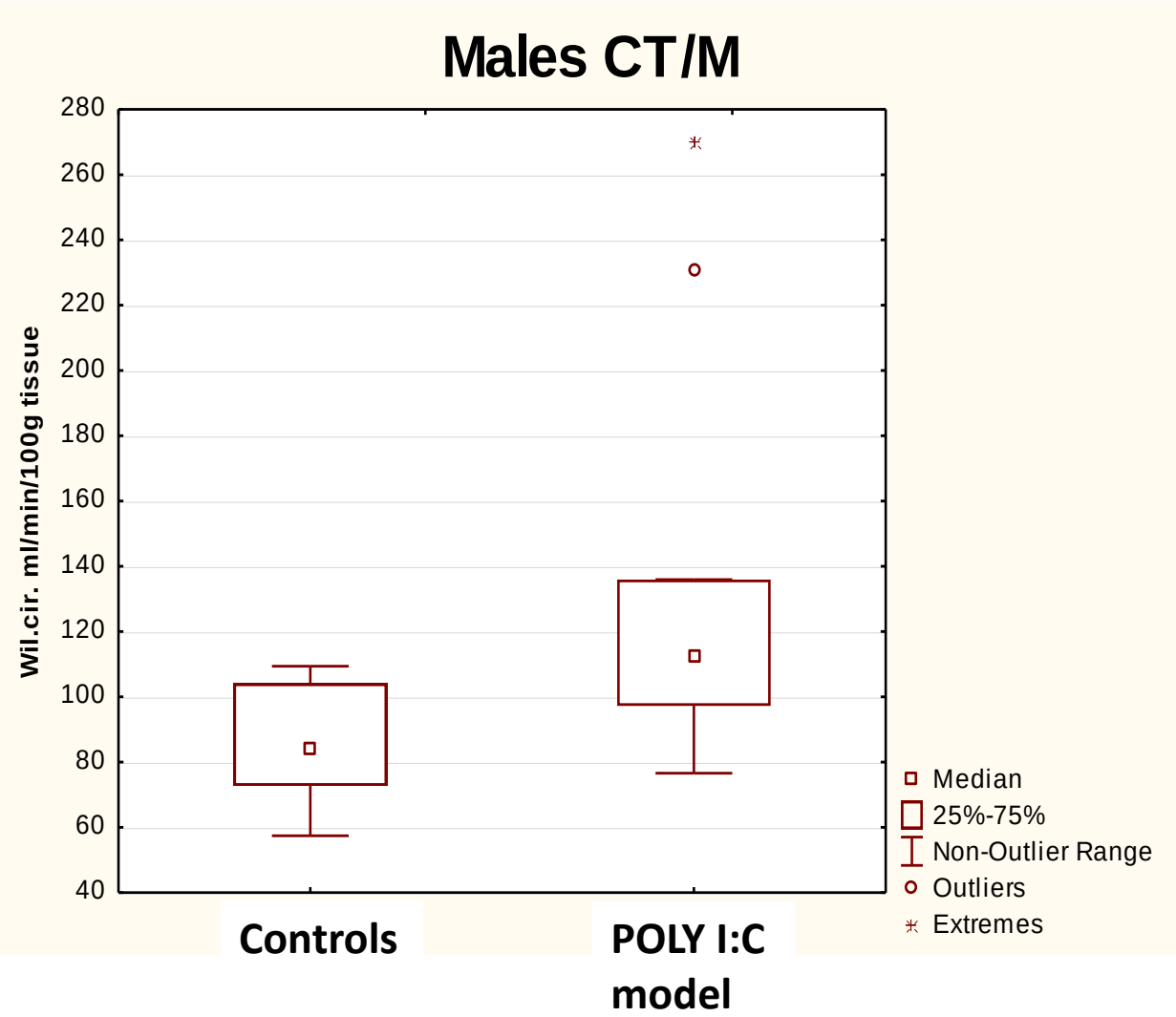
- ASL data were analysed in ParaVision 5.1 (Bruker)

$$CBF = \lambda . \frac{T_{1,\text{nonsel}}}{T_{1,\text{blood}}} \left(\frac{1}{T_{1,\text{sel}}} - \frac{1}{T_{1,\text{nonsel}}} \right)$$

- ASL blood flow maps were analyzed in manually drawn brain ROIs by own Matlab R2010a code

ÚPT AVČR

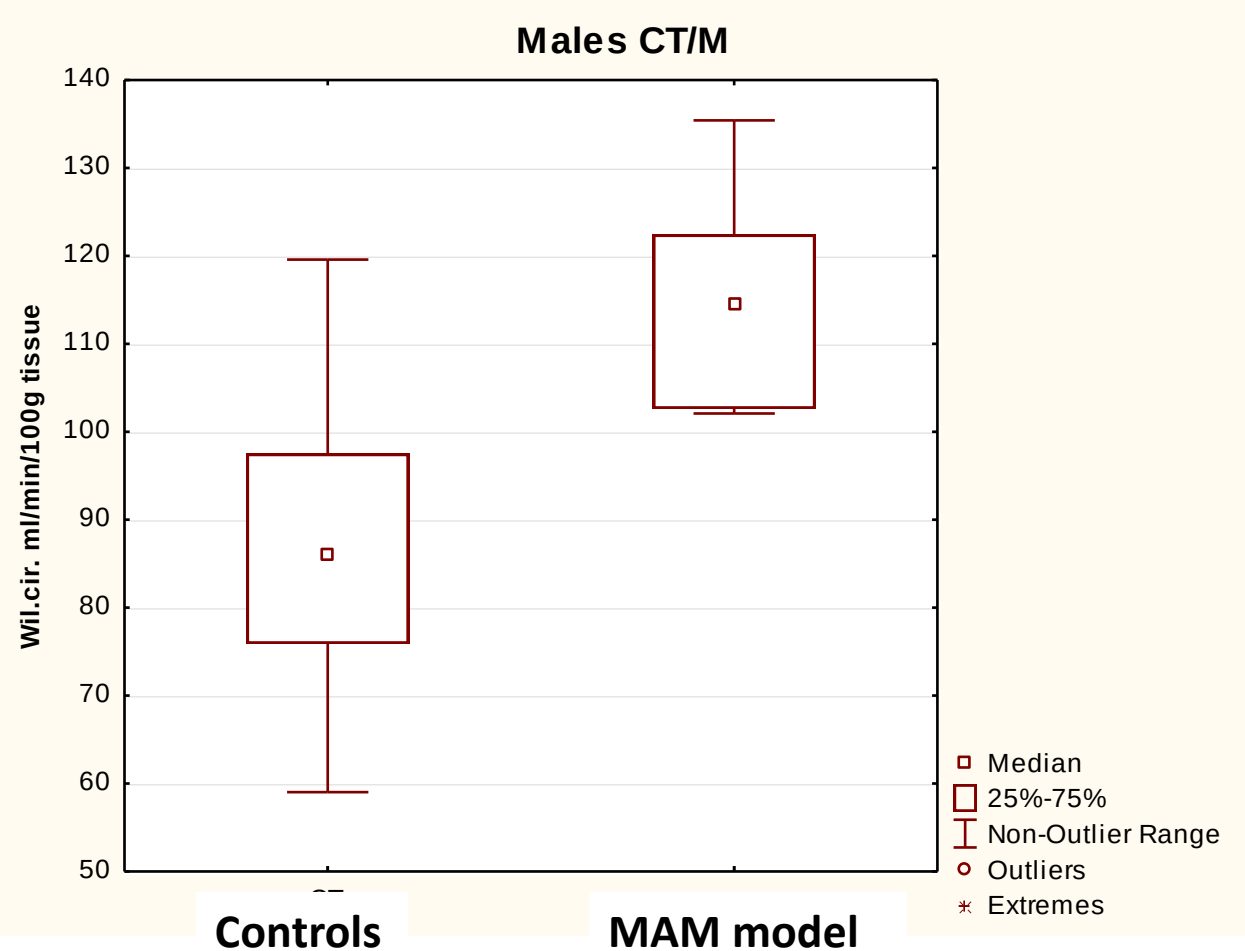
Results



- Circle of Willis
- Higher perfusion in **POLY I:C** model

ÚPT AVČR

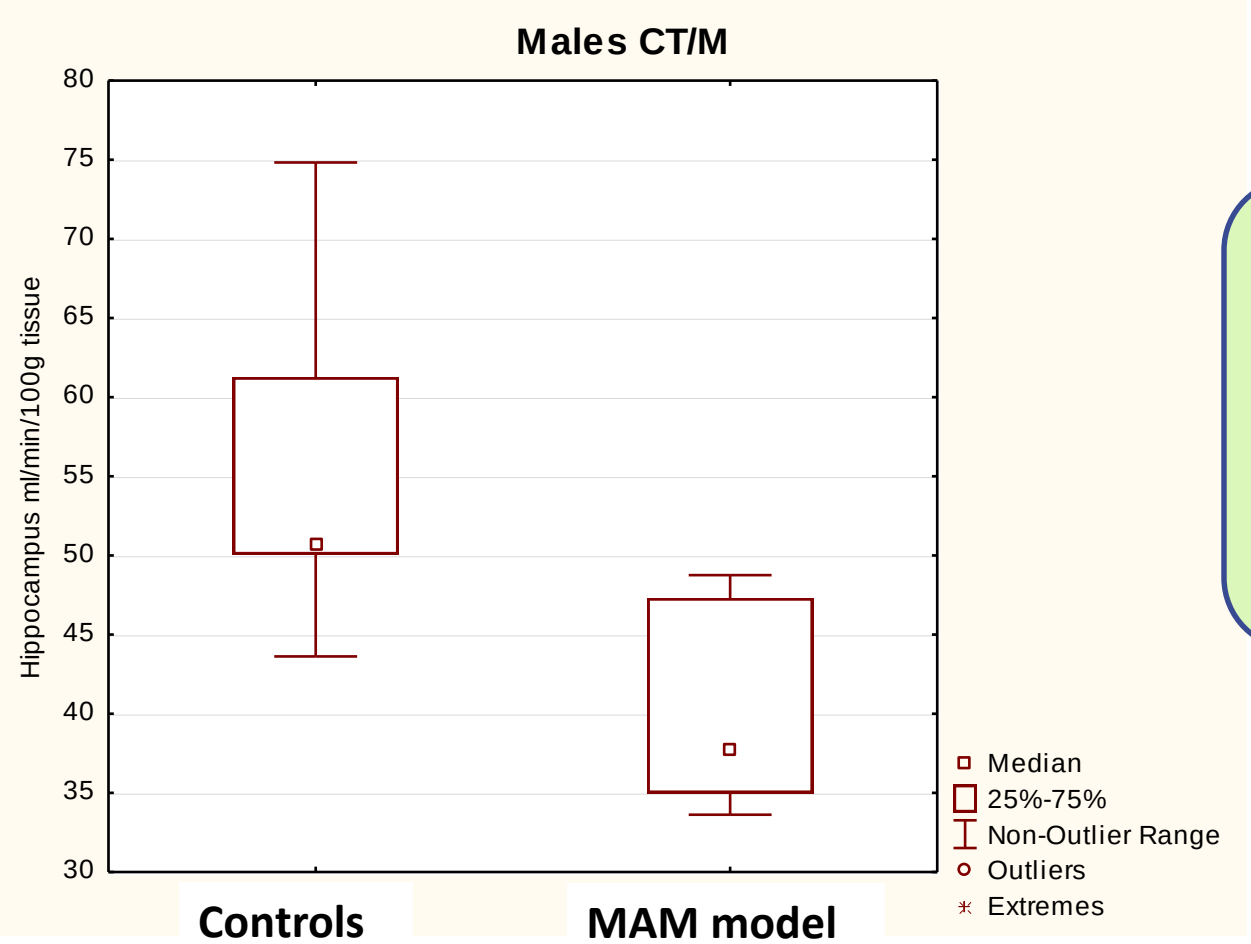
Results



- Circle of Willis
- Higher perfusion in **MAM** model

ÚPT AVČR

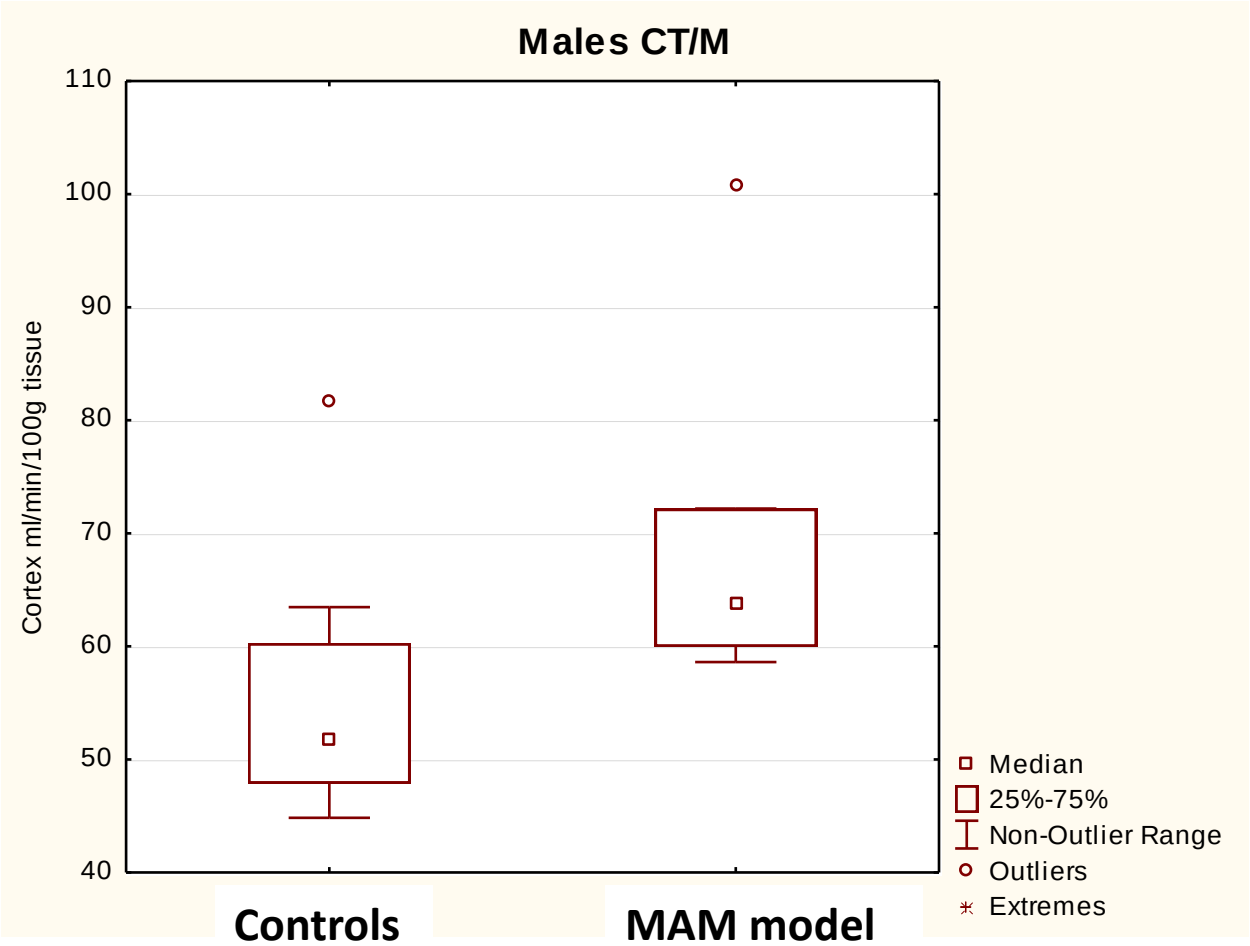
Results



- Hippocampus
- Lower perfusion in **MAM** model

ÚPT AVČR

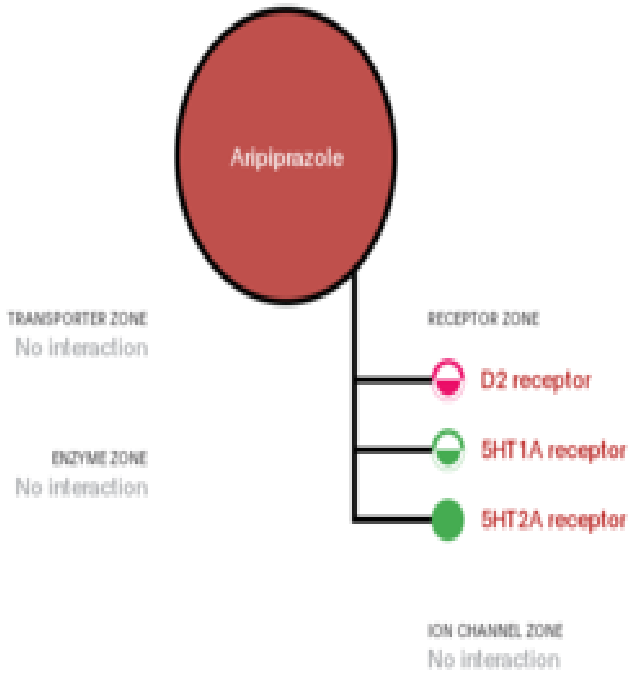
Results



- Cortex
- Higher perfusion in **MAM** model

ÚPT AVČR

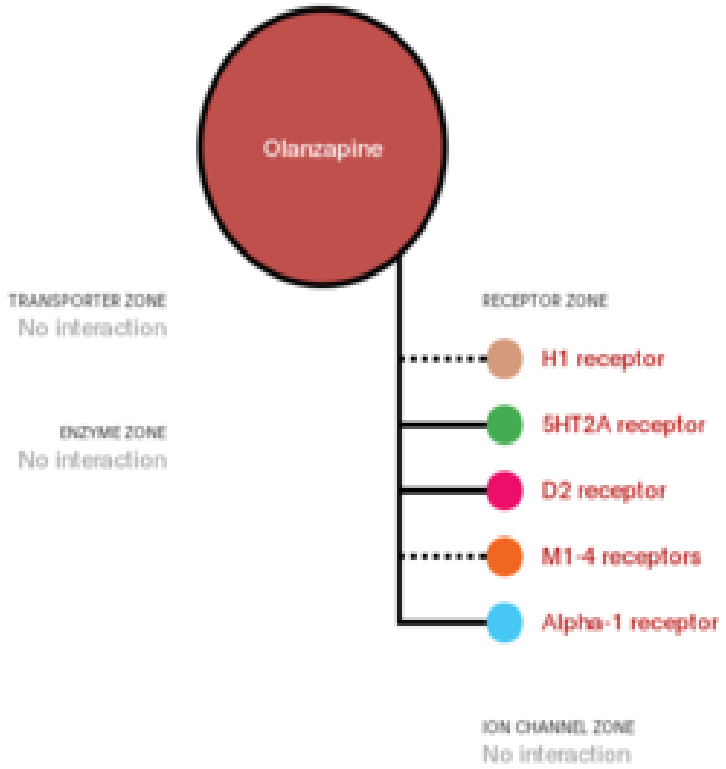
Pharmacodynamical experiments



- **Aripiprazole**
- Dopamine D2 partial agonist
- Serotonine partial 5HT1A agonist
- Serotonine 5HT2A antagonist

ÚPT AVČR

Pharmacodynamical experiments



- **Olanzapine**
- Dopamine D2 antagonist
- Serotonine 5HT2A antagonist
- Noradrenaline α1 antagonist
- Histamin H1 antagonist
- Acetylcholin M1-4 antagonist

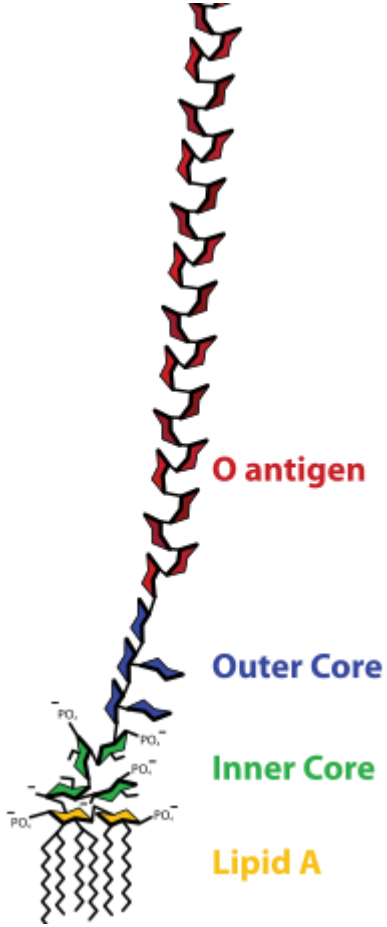
ÚPT AVČR

Septic encephalopathy (SE)

- Aim
  - early diagnostics of SE
  - research into physiology and therapy development for cerebrovascular encephalopathy etc.

- Animal models
  - induction by lipopolysaccharide

- Methods
  - ASL
  - contrast-enhanced (**DCE**, DSC): more accurate, testing BBB, carrier delivery



ÚPT AVČR

Septic encephalopathy (SE)

Native imaging (x CA)

Dynamic imaging

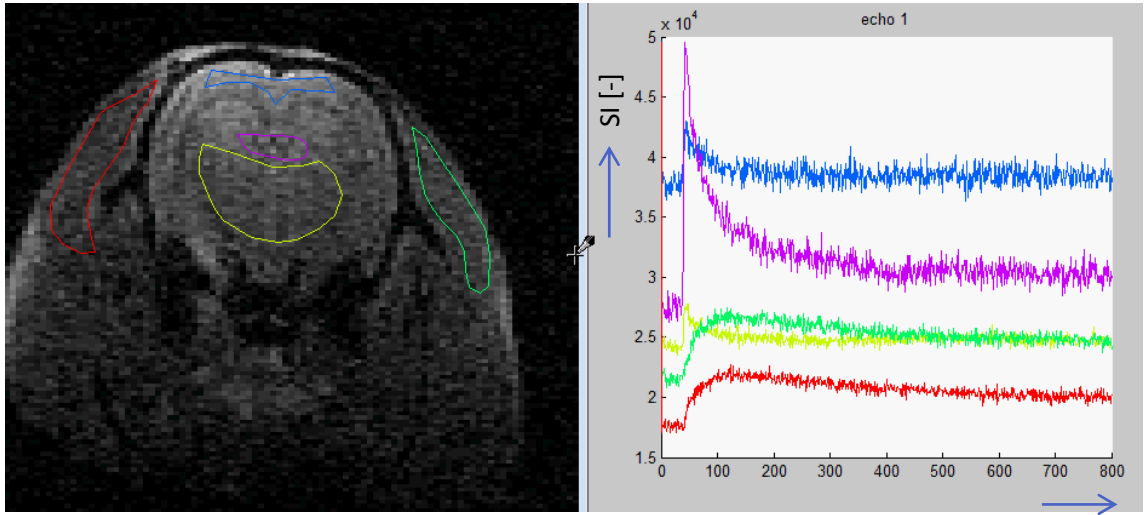
Conversion $SI(n)$ -> $c(n)$

Define ROIs $C_{ROI}(n)$ a $C_{AIF}(n)$

$$C_{ROI_{model}}(n,\mathbf{x}) = \frac{F_p}{1 - Hct_{LV}} \cdot (C_{AIF} * IRF)(n,\mathbf{x})$$

$$\min_{\mathbf{x}} \left\{ \sum_{n=1}^{N} \left[C_{ROI}(n) - C_{ROI_{model}}(n,\mathbf{x}) \right]^2 \right\}$$

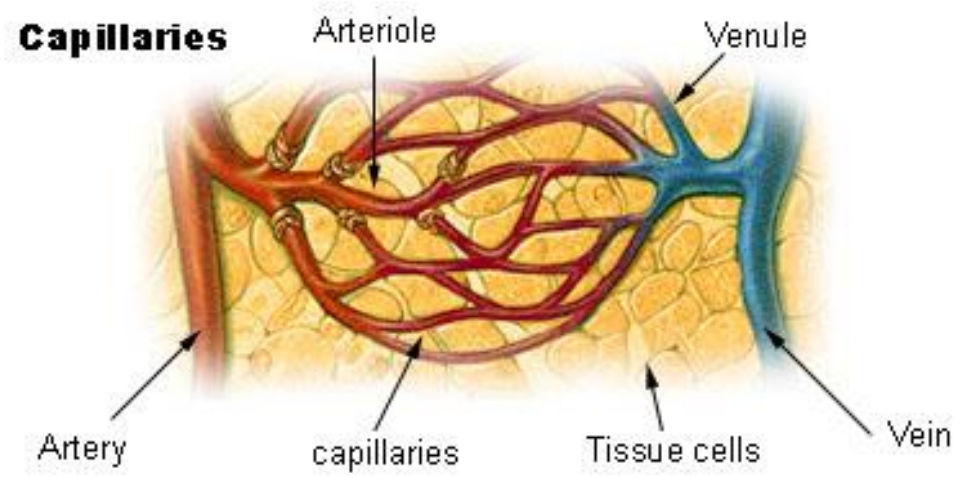
$$\mathbf{x} = [F_p, v_p, T_c, v_e, PS, E, K^{trans}, k_{ep}, BAT]$$

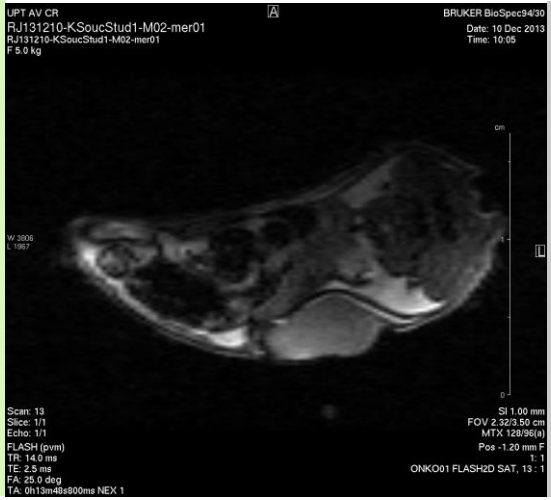


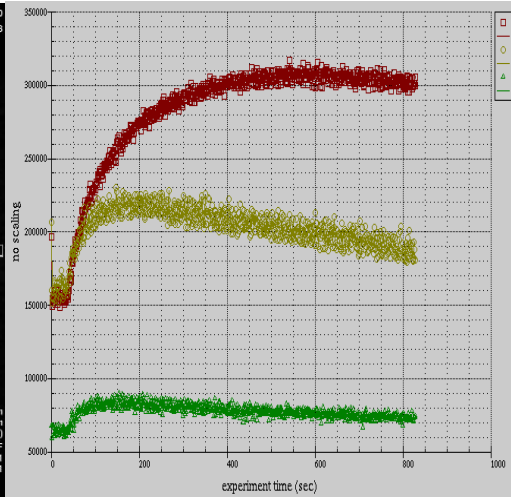
ÚPT AVČR

Perfusion

- Images of physiologic parameters characterizing blood supply
  - blood flow [ml/min/100ml tis.]
  - blood volume [ml/100 ml tis.]
  - EES volume [ml/100 ml tis.]
  - permeability-surface product [ml/min/100ml tis.]







ÚPT AVČR

Animal models

Oncology

- 6 BALB/c mice
- Murine colon tumor cells CT26.WT (ATCC, CRL-2638)
- Subcutaneously implanted into the left flank (1 000 000 cells in HC Matrigel)
- from Institute of Biophysics (CAS), Karel Souček, Ph.D.

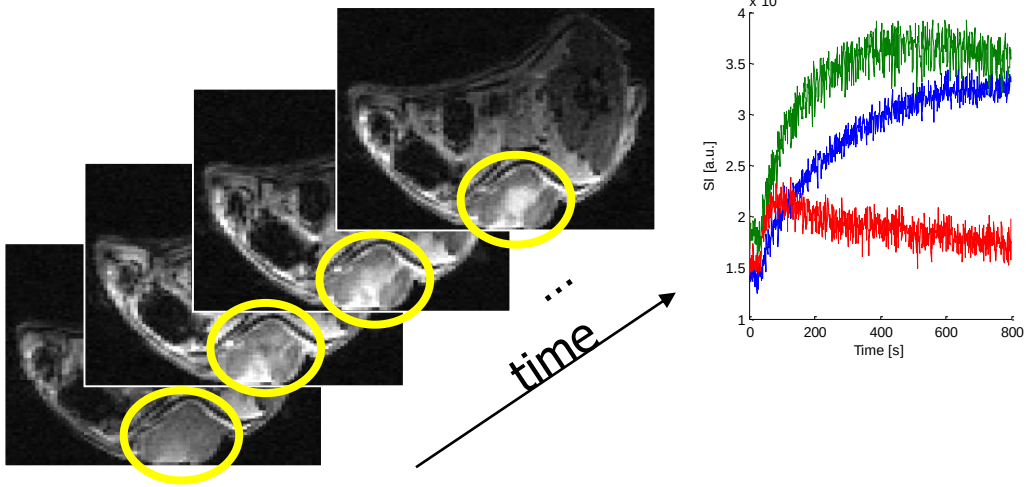
Cardiology

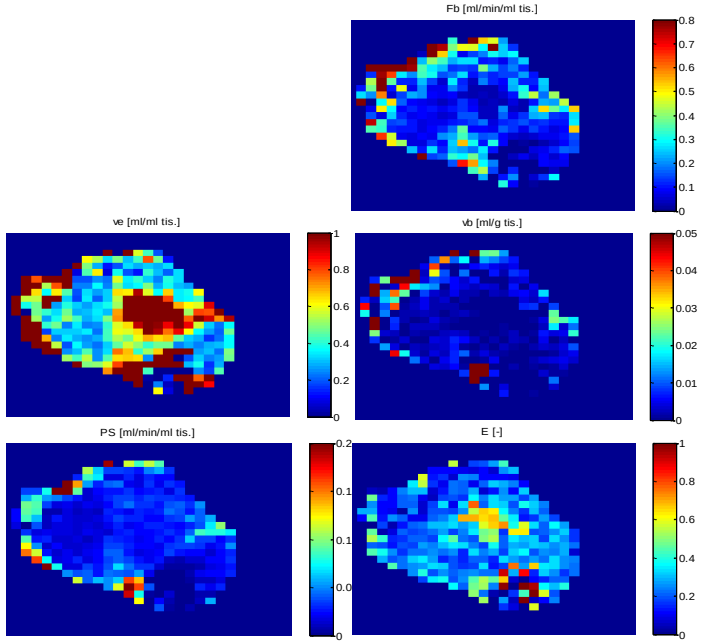
- Wistar rat
- Cryonecrotic model of infarction
- Total destruction of tissue by liquid nitrogen with injury of microcirculation but preserving major vessels in the heart
- from Veterinary and Pharmaceutical University (VFU), MVDr. Peter Scheer, Ph.D.

ÚPT AVČR

Perfusion

- Aim:
  - tumour diagnostics and therapy
    - angiogenesis, drug delivery tested by perfusion
  - other
    - research into physiology and therapy development for cerebrovascular encephalopathy etc.
- Methods:
  - contrast-enhanced (DCE, DSC):
    - more accurate, testing BBB, carrier delivery
  - native (ASL):
    - noninvasive, inexpensive, observing blood itself
  - qualitative images → pharmacokinetic modeling
    - calibration scans (B1, AIF)
    - multichannel blind deconvolution

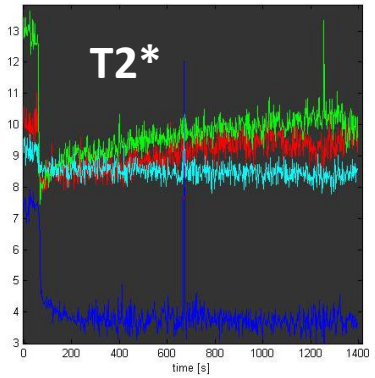


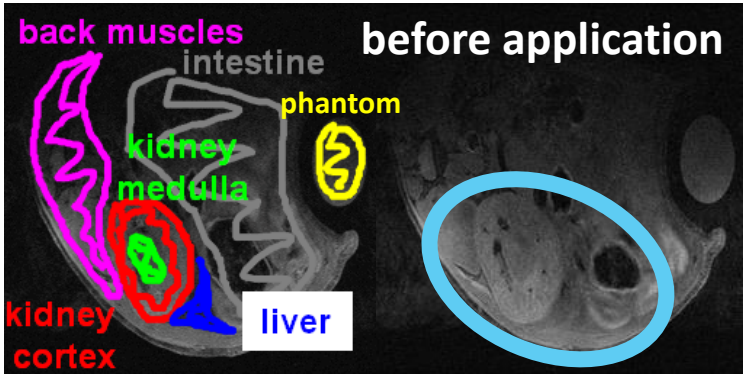


ÚPT AVČR

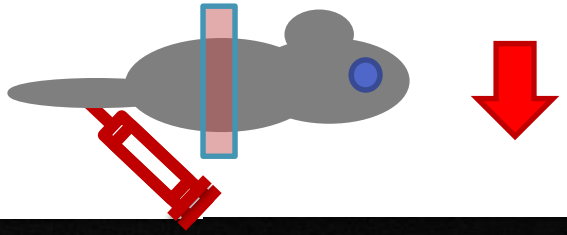
Relaxometry - experimental contrast nanomaterials

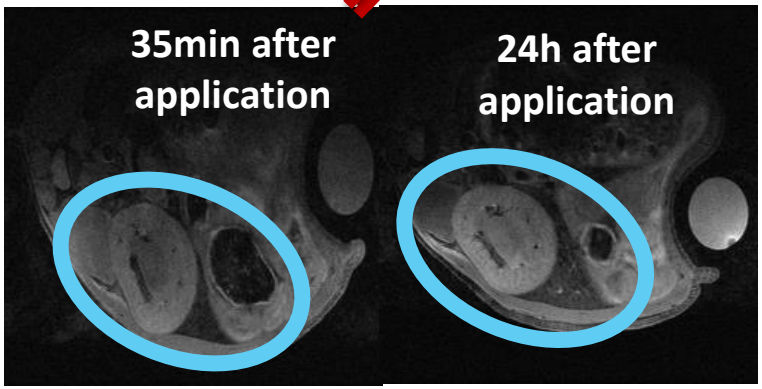
- Aim: targeted transport
  - diagnostics + therapy = theranostics
    - detectability of MR markers, concentrations needed
    - physiologic compatibility
    - stability, targeting, deposition, excretion, toxicity
- Methods:
    - relaxivity r1, r2, r2* in phantom
    - image intensity changes in organs in vivo





molecules/particles with Gd or Fe, v chelate, n a polymer skeleton, in dextrane, citrate, PEG ...



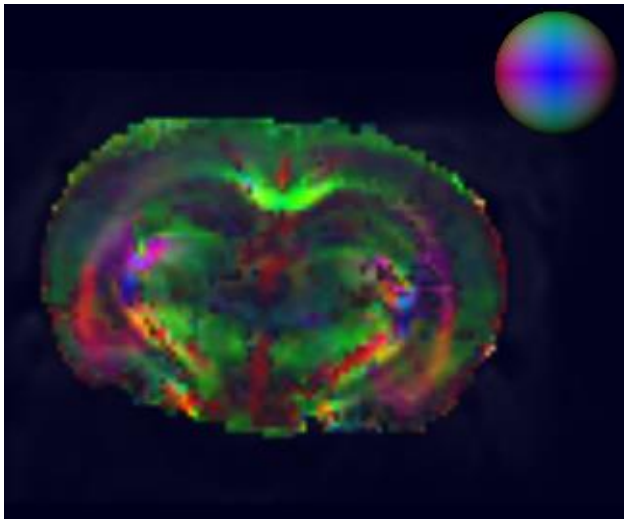


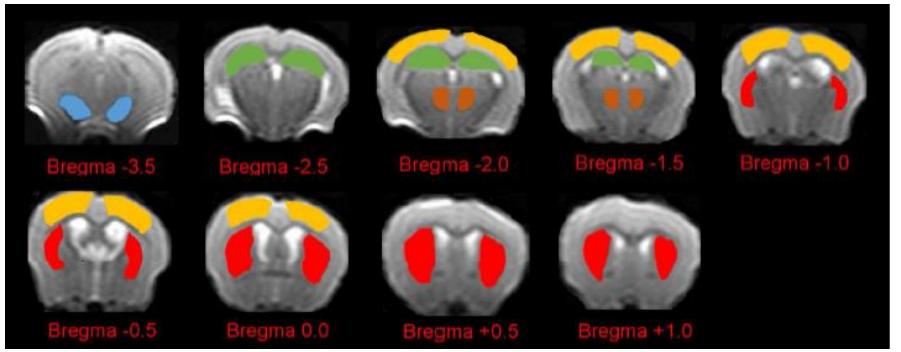
Neurodegenerative animal models

Animal models

- Methamphetamine-induced nigrostriatal neurodegeneration
- Transgenic mice simulate Parkinson's disease
  - Expression of α synuclein modify diffusion
    - Human Line 61 α-synuclein transgenic mice
- Rotenon-induced nigrostriatal neurodegeneration

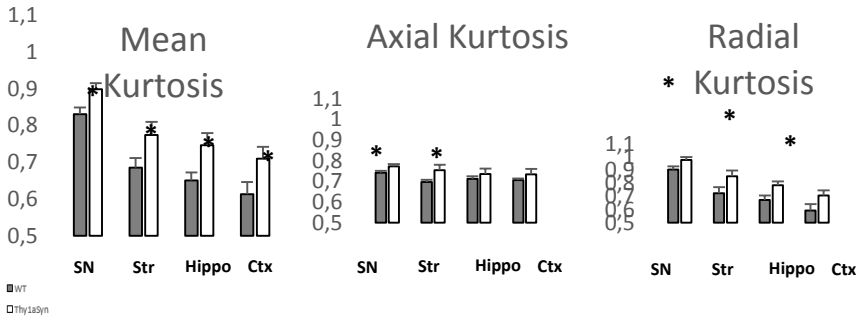
- Signal models
  - free diffusion
    - Gaussian distribution of
    - diffusion tensor, 0.5-1 h
  - restricted diffusion
    - nongaussian particlel scatter
    - diffusion kurtosis 3-4 h

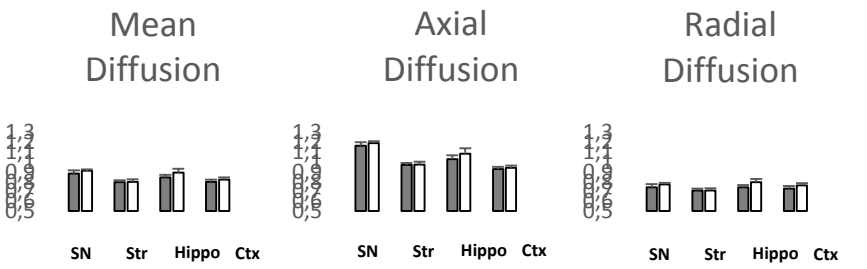




$$\ln[S(b)] \approx \ln(S_0) - bD(t)$$

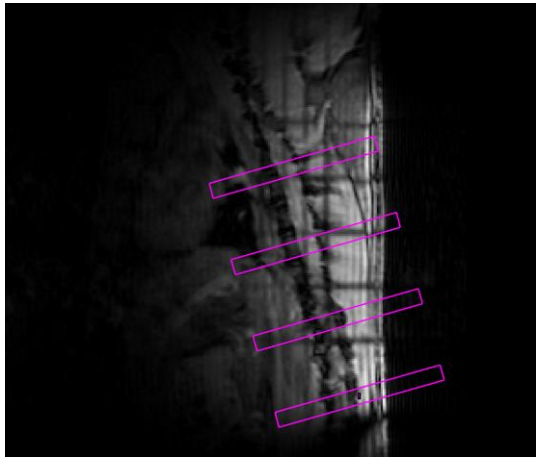
$$\ln[S(b)] \approx \ln(S_0) - bD(t) + \frac{1}{6}[bD(t)]^2 K(t)$$

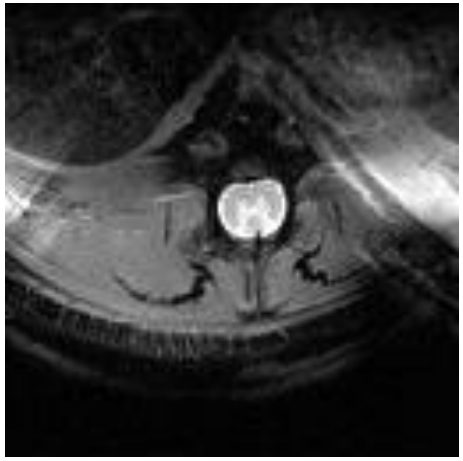


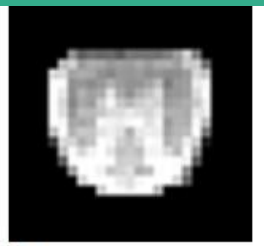


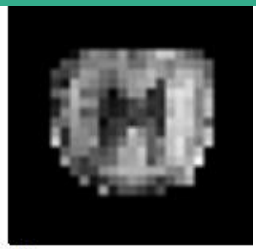
ÚPT AVČR

Diffusion imaging – spinal cord





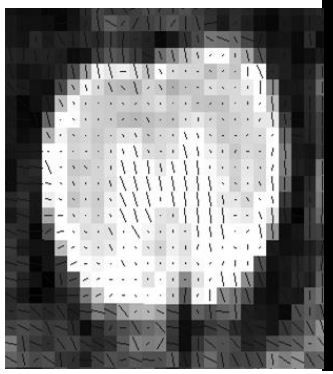


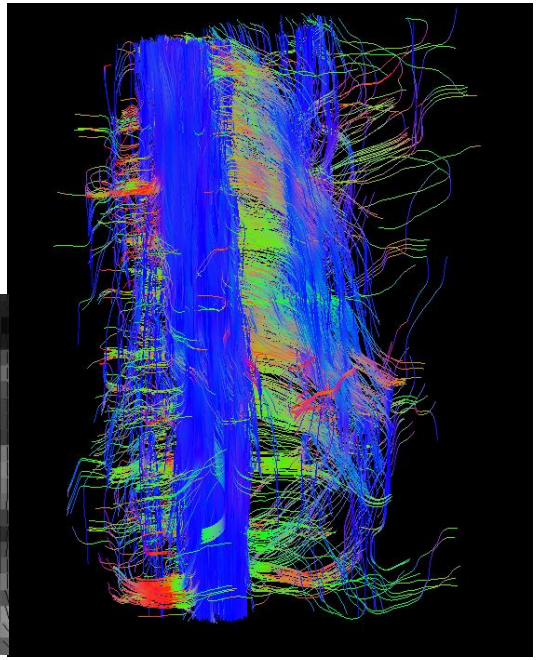


A B C

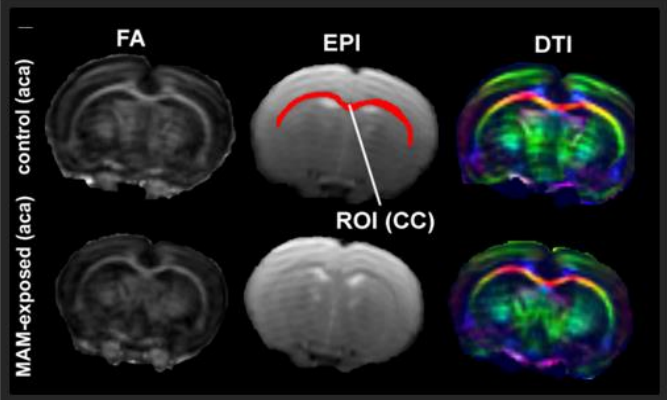
D E F

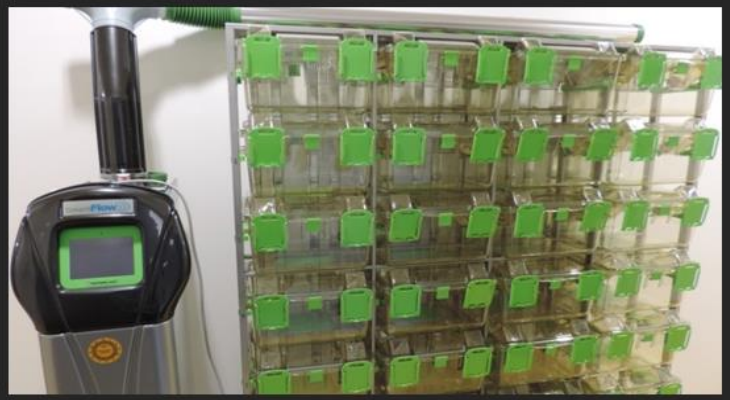
- Aim: regenerative medicine
  - prepare a technique for the assessment of connectivity restoration after therapy
- Experimental problems:
  - small volume in depth (sensitivity)
  - motion (breathing, heart)
- Solution:
  - RF coil, pulse sequence, physiologic gating
- Collaboration: ICRC, IKEM





Thank you for your attention!





ISI ASCR