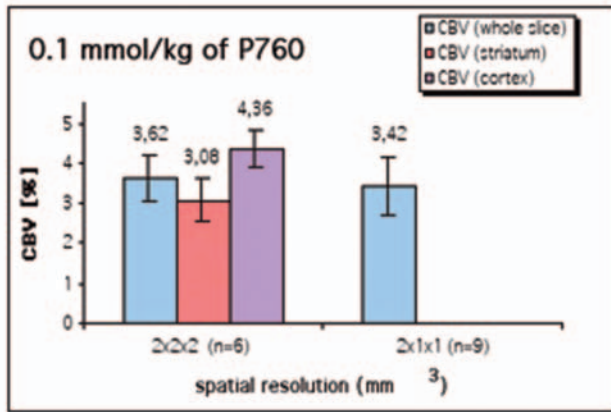


Fig. 2



Eq. 2

$$\frac{1}{T} = \frac{1}{650\text{ms}} \leq R_{1(iv)} - R_{1(ev)} = \frac{1}{46\text{ms}}$$

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In-vivo phenotyping of genetically engineered mouse models for amyotrophic lateral sclerosis is established by combining BT-MRI and CASL

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Introduction: Mice lacking the hypoxia response element in the Vascular Endothelial Growth Factor gene (*Vegf*^{fl/fl} mice) develop motor neurodegeneration reminiscent for Amyotrophic Lateral Sclerosis (ALS)(1). Carmeliet et al.(2) intercrossed mice expressing a SOD1G93A transgene (established mouse model for ALS) with *Vegf*^{fl/fl} mice generating 4 different genotypes of VEGF/SOD (Wt/Wt, Wt/He, Ho/Wt, Ho/He). The VEGF/SOD model is appealing creating an interesting link between angiogenesis and neurogenesis. We studied basal CBV and CBF with Bolus Tracking (BT) MRI and used Continuous Arterial Spin Labeling (CASL) to study the CBF response upon hypoxic challenge.

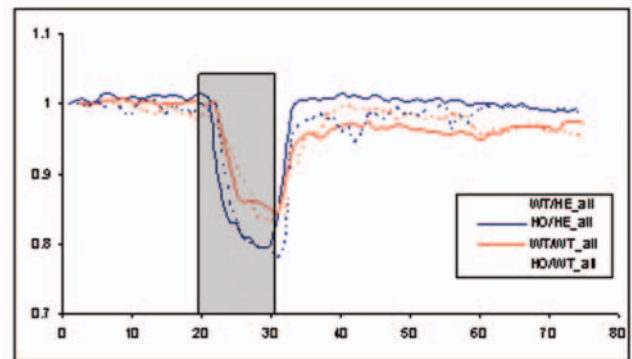
Subjects and Methods: VEGF/SOD mice anaesthetised with 0.7% isoflurane were monitored for end-tidal CO₂ (Capstar-100, Linton Instruments, UK), breaths per minute and body temperature (PC-SAM, SA Instruments, UK). MR experiments were performed on a 7T/8cm MR system (MRRS, UK). Intravenous injection of Gd-DTPA (0.2mmol/kg, Schering) during a single slice multi experiment GE-EPI sequence (TR 300ms) enables to explore basal CBV and CBF in absolute values (Medx, Software). GE-EPI CASL(3,4) images were acquired using a slice selective RF inversion pulse for labeling (post TI 500ms, TR 5s, TE 17.4ms). CASL experiments contained 150 pairs of images obtained under respectively normoxic (1-80), hypoxic (8%O₂) (80-120) and normoxic (120-150) conditions. Perfusion maps were generated for these 3 conditions (IDL Boulder, UK). Per genotype we analysed 8 BT experiments and 4 ASL experiments.

Results: CBV was observed to be unaffected in all genotypes,

while CBF was 50% reduced in the double transgenics Ho/He (20.7±3.3ml/100g/min) as compared to Wt/Wt (40.5±5.9ml/100g/min, p<0.05). The mean overall CBF increase as determined with CASL was significantly higher (26.1%) in Wt/Wt than in Ho/He (13.1%, p<0.05) during normoxic recovery. The global BOLD signal intensity changes during hypoxia were also different in Wt/Wt (16%) than in Ho/He (20%), p<0.05, illustrated in figure 1.

Discussion: BT-MRI illustrates that reduced CBF in Ho/He is associated with normal CBV. This supports previous findings showing that VEGF mutation impairs vasodilatation, rendering cerebral blood vessels more susceptible to vasoconstriction and reducing overall blood supply (1,5). The ASL results link the low basal CBF in the double transgenics to the smaller hypoxia induced CBF response. This means hypoxia induced deoxyhemoglobin increase dominates the global BOLD signal decrease within the ASL control images since less fresh blood is provided. This decrease in signal intensity during hypoxia is indeed most prominent in the Ho/He. The aberrant regulation of VEGF in response to hypoxia is involved in the pathogenesis of this animal model for ALS.

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Perfusion-based high-resolution fMRI in the primate brain using a novel vertical large-bore 7 Tesla setup

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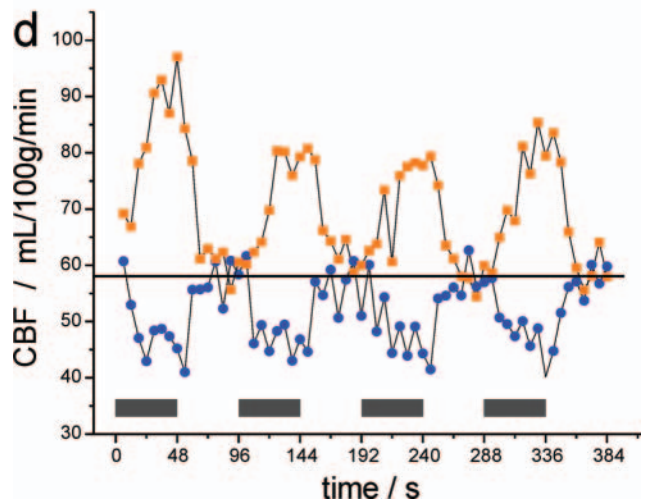
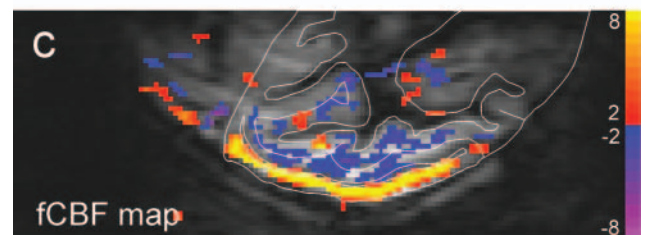
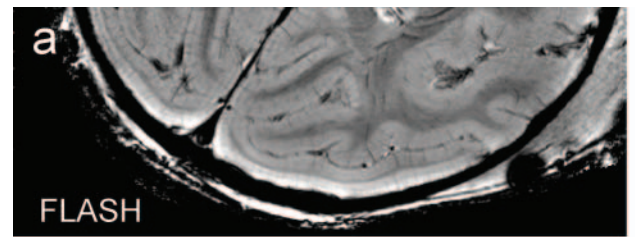
Introduction: Obtaining functional CBF maps with high spatial resolution is challenging, because the CBF signal is intrinsically low and the signal-to-noise is critical. Here we report the first high-resolution CBF maps in the *Macaca mulatta* that were obtained with voxel sizes as small as 0.5x0.5x3 mm³. High sensitivity was achieved by using a 7T system and custom-made RF coils in TORO mode. fCBF data were acquired and compared with BOLD data in the macaque primary visual cortex. The fCBF signal was entirely localized within cortex, providing unequivocal evidence for its high spatial specificity. This specificity is of paramount importance for studies seeking to understand the physiological basis of functional neuroimaging.

Methods: A novel large-bore vertical MR system (7T/60-cm,

Bruker) was set up for fMRI/MRS in the anaesthetized or the awake, behaving monkey. The 38-cm gradient insert (33-cm inner diameter with noise insulation) achieves 80 mT/m in <math><200 \mu\text{s}</math>. An actively-decoupled RF saddle coil was used for transmission and a 30-mm surface coil for reception. A full-field visual stimulus (8-Hz flickering LED array) was used in a block design with 4 repetitions of on- and off-stimulation-periods (48s, 8/8 images).

Single-shot zoomed GE-EPI was acquired at 500- μm in-plane resolution (128x48, FOV 6.4x2.4 cm^2) using outer-volume suppression. The FAIR module used adiabatic slice-selective / non-slice-selective inversion (TR=3s x2, TIR=700-1500s, inversion slice thickness 8-mm). Functional CBF and BOLD scans (FAIR off) were acquired interleaved with TE=12 and 20ms, respectively. For semi-quantitative analysis, a M_0 image was measured at TR=10s and CBF was calculated according $\text{CBF} = (S_{\text{SS}} - S_{\text{NS}}) / M_0 \cdot \lambda / (T_1 \cdot (2 \cdot \exp(-T_1/T_1) - \exp(-TR/T_1)))$, $\lambda = 0.9 \text{ mL/g}$. T_1 was measured for V1-GM to be 1.9s.

Results: Anatomical FLASH, inversion-prepared EPI, and CBF maps at 500- μm in-plane resolution are shown. Excellent single-shot EPI image quality was achieved by the use of OVS-aided FOV reduction in phase-encode. T2* blurring was still negligible at a readout duration of 31-ms, which is similar to T2* of (29 \pm 10) ms at 7T. Upon visual stimulation, CBF increased in average by 38% from 58.6(3.8sd) mL/100g/min at rest to 80.9(5.6sd) mL/100g/min during activation. CBF decreased by -21% in medial areas. A *t*-test revealed activated voxels along the whole visual cortex V1 ($t=2-8$, red...yellow). Robust functional CBF changes were observed, excellently localized within gray matter only. In contrast, the BOLD signal was spatially more spread. This observation is consistent with the fact that functional CBF maps are more localized to gray matter microcapillaries than BOLD maps, which suffer from contributions of proximal draining veins.



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Continuous arterial spin labeling (CASL) setup for the primate brain at 7 T using a three-coil approach

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Introduction: Arterial spin labeling is commonly used to measure cerebral blood flow (CBF) in the brain. Since CBF signal is intrinsically low, optimization of the signal-to-noise ratio (SNR) is critical. CASL with a separate labeling coil has the advantages of increased SNR, multi-slice capability, and absence of magnetization transfer. The CASL method has been applied successfully in rats¹⁻³, and in human studies⁴. Its wider application especially on

routine human MR systems is hindered by the advanced hardware and software requirements.

Here, we report the development of CASL for use on monkeys. Increased sensitivity (SNR) was achieved because of utilization of an custom-made three-coil setup and the use of high magnetic field (7T) with its favorable T1. The feasibility of this approach is demonstrated with a flow phantom and with initial experiments in the monkey.

Methods: Measurements were performed on a vertical 7T/60cm Bruker Biospec system dedicated for monkeys, which was equipped with a second 1H transmit channel. A saddle-shaped volume coil was applied for RF transmission and a 30mm surface coil was used for RF reception. For spin tagging, a 40mm concave-shaped surface coil was built according to the space requirements in the neck of monkeys based on angiographic scans. All three RF coils were actively-decoupled and switched with a self-built logic unit and current driver. The flow phantom consisted of a water-filled bottle with two tubes fed through, the water flow was adjustable from 20cm/s to 100cm/s.

Single-shot, multi-slice GE-EPI (PVM EPI, Bruker) was acquired at 0.75x1x2mm³ resolution (128x64x5, TR/TE=3500/12ms). The preparation module for ASL was self-written. The 2.5s labeling period was followed by a variable post-labeling delay prior to data acquisition. For CASL, the labeling frequency was switched in interleaved scans.

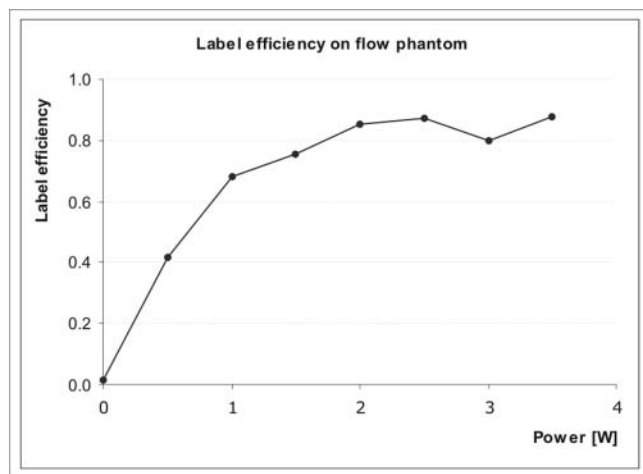
Results: The CASL three-coil setup was validated on the flow phantom. Label efficiencies of 0.7 were reached with a labeling power of 1W (Fig.1). Initial CASL experiments in the anaesthetized monkey were performed with a sensitive receive-coil placed on one hemisphere. The distance from imaging to labeling plane was ~6cm. CBF signal was observed predominately in the ipsilateral hemisphere with a maximum CBF at post-labeling delays of 600-1000ms. These first *in vivo* data promise that further functional studies to measure CBF, BOLD and CMRO₂ changes will gain from this setup.

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Perfusion measurement in the rat leg muscle with single-voxel fast FAIR

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Introduction: Arterial spin labelling has become a commonly used tool for measuring the perfusion in the brain and other highly perfused organs. In skeletal muscle, the perfusion is much lower and not within reach of most measuring methods due to their insufficient sensitivity [1]. A quantitative measurement for muscle perfusion would be highly valuable for medical and pharmaceutical research for peripheral artery occlusion disease (PAOD). We have implemented a method to measure the perfusion in the rat leg muscle at rest and exercise with precision and good temporal resolution.

Subjects and Methods: We have modified the FAIR technique [2] to measure the perfusion in the hindlimbs of rats. To cope with the low SNR due to the very low perfusion in the skeletal muscle, the sequence was optimized for maximum sensitivity:

A single-voxel PRESS sequence (voxel size 6 x 6 x 3 mm³) was used rather than an imaging readout with high spatial resolution [3]. The sequence timing was adapted to obtain maximum sensitivity and a good temporal resolution.

Measurements were performed on a 4.7 T Biospec. The rats were anaesthetised with isoflurane and N₂O. To measure the perfusion during exercise, the right gastrocnemius muscle was electrically stimulated. With 16 averages, a temporal resolution of 2.3 min was obtained.

Results: Fig. 1 and 2 show the time evolution of the measured perfusion at rest and during exercise. In Figure 1, the muscle had to work twice for about 22 minutes with a resting period of 15 minutes, the second stimulation period with a higher work load than the first. In figure 2, stimulation periods of 5 minutes were followed by resting periods of 10 minutes, the workload being increased for every period. The perfusion at rest was about 22 ml/100g/min, with a two- to threefold increase during exercise.

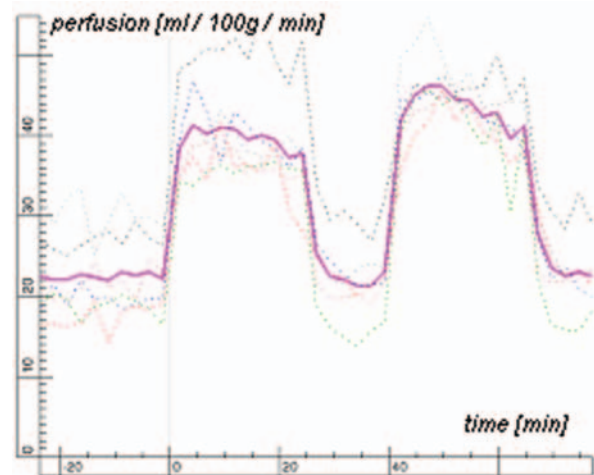


Fig. 1: Perfusion at rest and under two levels of exercise, measured in six rats. Dotted lines: individual animals, straight line: mean.