Nonlinear model for preprocessing of cerebral blood volume weighted functional MRI data and for evaluating pharmacokinetic properties of USPIO

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Introduction: Cerebral blood volume (CBV) weighted pharmacological magnetic resonance imaging (phMRI) examines the temporal changes of the tissue concentration of a blood pool contrast agent via its susceptibility effect as a measure for cerebral activity in response to a pharmacological stimulation in vivo [1]. The pharmacologically induced hemodynamic response can be sustained enough to be confounded by the elimination of the contrast agent from the blood pool. Signal recovery to pre-contrast baseline needs to be accounted for in the analysis of phMRI data to assure a valid assessment of the hemodynamic response function. A number of empirical detrending methods have been tested [2]. This work uses a nonlinear model for preprocessing of the phMRI signal time course. We apply it to investigate the properties of three ultra-small superparamagnetic iron oxide (USPIO) nanoparticles. Finally, we remove the drift from the R_2*-weighted signal to extract the hemodynamic response to the psychostimulant cocaine in mice.

Material and methods: The T_1 and T_2 relaxation times of 6 USPIO concentrations up to 0.3 mg Fe^{3+}/ml in rat plasma at 310K at 7T and 11.7T were measured with spectroscopic sequences to derive the r_1- and r_2-relaxivities of MION (Massachusetts General Hospital, MA), MoldayION (BioPAL, MA) and P904 (Guerbet Research, France) [3]. All animal experiments were approved by the Institutional Animal Care and Use Committee. In vivo MRI experiments on isoflurane anesthetized C57BL/6 mice (11-12 weeks, Jackson Laboratory, CA) were performed in a horizontal bore Bruker Biospec/Avance 7T/30 cm MR system using a linear birdcage RF coil for transmission and reception. Fourteen contiguous axial slices were acquired with a 2D multiple gradient echo sequence (TR = 600 ms, flip angle = 35°, voxel size = 0.18 × 0.18 × 0.75 mm^3, spectral line width = 60 kHz, 3 - 4 echoes at TE = 2.5, 6.0 and 9.5 ms (and 13 ms)) with 1 mn time resolution [4]. MoldayION (25 mg/kg, n = 3), MION (35 mg/kg, n = 5) or P904 (15 mg/kg, n = 3; 25 mg/kg, n = 3) was injected intravenously after 20 - 30 baseline acquisitions. Image acquisition continued for 80 - 90 mn. 30 mg/kg cocaine hydrochloride (Sigma-Aldrich, MO) was administered intraperitoneally 20 mn after 35 mg/kg MION injection [4] and 30 mn after 25 mg/kg P904 injection. Prior to image analysis with ImageJ [5] the time series were aligned (Automated Image Registration [6]). A two parameter model $S^{model}(t) = S_{pre}\cdot\exp[-TE\cdot\kappa\cdot\exp(-t\cdot\tau^{-1})]$, where S_{pre} is set to the average signal intensity before USPIO, was fitted to the measured signal intensity after USPIO injection S(t), excluding the time points within one hour after cocaine injection. The fitting parameter κ provides an estimate of the initial tissue ΔR_2* (∝ CBV) following USPIO injection, and τ^{-1} is the apparent elimination rate of the USPIO from the tissue. This model assumes a negligible T_1-effect, an instantaneous USPIO bolus and monoexponential decay in the plasma. The outer exponential results from the R_2* weighting. Maps of the relative CBV change were computed as $\Delta CBV(t) = \ln[S(t)/S_{pre}]/\ln[S^{model}(t)/S_{pre}] - 1$. The sensitivity is defined as $CNR(t) = (S_{pre} - S^{model}(t))/\sigma_t$, where σ_t is the temporal standard deviation of the signal over 10 mn following USPIO injection (at t = 0).

		7T	11.7T
MION	r_1	41 ± 1	18 ± 1
	r_2	848 ± 29	1035 ± 11
P904	r_1	25 ± 0	11 ± 0
	r_2	1526 ± 24	1692 ± 14
MoldayION	r_1	35 ± 0	18 ± 0
	r_2	1170 ± 9	1346 ± 35

Table 1: USPIO relaxivities in rat plasma at 310 K in (s mg/ml)$^{-1}$

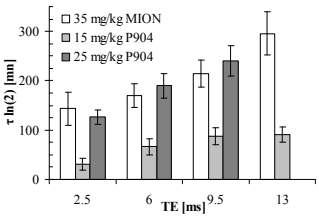

Fig 1: apparent USPIO tissue half-life in striatum

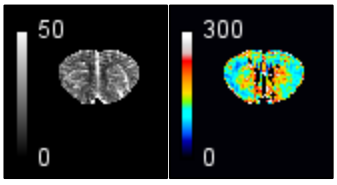

Fig. 2: ΔR_2*-map ∝ relative CBV, TE = 2.5 ms

Fig. 3: apparent tissue half-life [mn] of 25 mg/kg P904, at TE = 2.5 ms

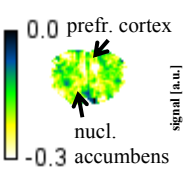

Fig 4: fractional ΔCBV 15 mn after 30 mg/kg cocaine injection

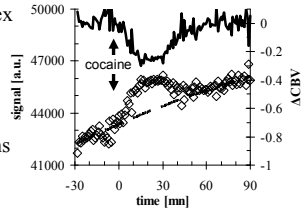

Fig 5:
▯ S(t) from striatum (4.2 mm^2)
-- $S^{model}(t)$
─ ΔCBV(t) (right axis)

Results and discussion: At both magnetic fields, P904 has the highest r_2-relaxivity and the highest r_2/r_1-ratio making it the preferable USPIO for a R_2*-weighted technique. We quantified κ and τ by analyzing the average signal intensity from cerebral ROIs (CNR(t=0) ≈ 24 at TE = 2.5 ms, ≈ 40 at TE = 9.5 ms) (Fig. 1) and voxelwise (CNR(0) ≈ 10 at TE = 2.5 ms, ≈ 17 at TE = 9.5 ms) to compute ΔR_2*-maps (Fig. 2) and maps of the USPIO tissue half-life τ·ln2 (Fig. 3). The signal recovery caused by USPIO elimination from the blood pool and the tissue varies with dose, TE and between subjects and tissue types (Fig. 3) necessitating detrending for each individual signal rather than using global detrending parameters [4]. 35 mg/kg MION and 25 mg/kg P904 had comparable tissue half-lives of > 2 h at TE = 2.5 ms and ≈ 4 h at TE = 9.5 ms. 25 mg/kg MoldayION had the longest tissue half-life of > 6 h at TE = 2.5 ms. The peak CBV response to cocaine was greatest in the nucleus accumbens -29.6 ± 0.5% and occurred at 12 mn after injection (n = 8, MION and P904 experiments combined). Figure 4 shows a typical ΔCBV map and Fig. 5 shows the striatal signal before detrending and the ΔCBV time course after detrending in a single mouse.

Conclusion: For acquisitions with low CNR such as at short TE or from individual voxels the proposed detrending model performs better than a constrained exponential model [2] for which the S_{post} signal after USPIO injection is difficult to determine. Our model directly yields estimates of the parameters of interest: the initial ΔR_2* and the elimination rate of the USPIO, both determining the sensitivity (= CNR(t)) to the activation-induced hemodynamic response over time. Mapping of the CBV response to cocaine using P904 at a dose of 25 mg/kg as USPIO is qualitatively and quantitatively comparable to using MION at a dose of 35 mg/kg. Under the described experimental conditions cocaine causes vasoconstriction in mice, which might be partially caused by direct vasoactivity of released monoamine neurotransmitters [7]. The demonstrated functional sensitivity of the ΔCBV technique in mice offers the opportunity to study centrally acting drugs in mouse models of disease.

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