Enhanced BOLD Effect in the Mouse Brain with fast CRAZED Imaging at High Magnetic Fields

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Introduction: High magnetic field strengths are advantageous for the fundamental BOLD effect and its application in fMRI. In particular, fMRI in small animals, which requires high spatial resolution, may benefit from very high field strengths (>7 T). However, short T_2^* and susceptibility artifacts impose major problems, and fast readout with EPI is problematic. Observation of enhanced BOLD effect has been reported with application of the CRAZED sequence (COSY revamped by asymmetric z-gradient echo detection [1]) [2]. Major challenge was the inherently low intensity of the CRAZED signal. We have developed a fast CRAZED acquisition scheme that affords very short acquisition times and allows for reliable observation of the BOLD effect in mice at 17.6 T.

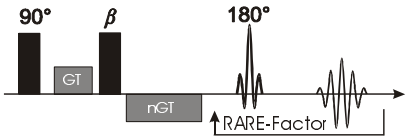

Fig. 1: CRAZED sequence with multiecho readout to create and select signal from iMQC.

Theoretical background: The CRAZED experiment is either described in terms of multiple-quantum coherences (iMQC) [1], or as formation of a nonlinear spin echo under local refocusing by the distant dipolar field [3], which originates from the spatially modulated longitudinal magnetization M_z. The echo builds up and reaches a maximum after a field strength-dependent time of typically tens to hundreds of milliseconds (see Fig. 2). CRAZED signal is inherently low, but strongly increases with magnetic field strength. To maximize SNR efficiency for image generation CRAZED signal was acquired as an echo train during signal build-up and an optimized k-space sampling scheme was devised, which takes into account the signal evolution. Since the observable signal depends on both M_z and M^+ it was essential to compensate for pulse errors and refocus all magnetization components.

Materials and Methods: All experiments were carried out on a Bruker Avance 750 WB spectrometer at 17.6 T. To observe the BOLD effect different blood oxygenation levels were generated by switching breathing gas between medical air (21% O_2) and carbogen (95% O_2, 5% CO_2) for spontaneously breathing, anesthetized mice (n=6). Images were acquired with the conventional RARE sequence (TR=4 s, TE=4 ms, RARE-factor 16, averages 2), the FLASH sequence (TR=100 ms, TE=3 ms, averages 1) and with the fast CRAZED sequence (TR=4 s, TE=9 ms, ITE=3 ms, RARE-factor 16, averages 4) (see Fig. 1). 15 consecutive images were acquired with the same method after each gas change. Signal intensities were averaged over all 15 images and changes verified to be significant by the T-test method.

After signal preparation with DQ-CRAZED, multiple echoes of an echo train were acquired with a sampling scheme based on RARE, with two fundamental modifications: 1. Magnetization had to be fully refocused and pulse errors compensated for, in both M_z and M^+. Two-step phase cycles were not suitable, because the CPMG cycle only corrects errors of M^+ along the pulse axis, and alternating phases (x, -x) do not refocus transverse components, which originate from M_z due to pulse errors. Only four-step phase cycles such as (x, x, -x, -x) or (x, y, x, y) fully refocus magnetization and compensate for pulse errors.

2. To maximize image intensity the most intense echoes during the rising echo train (see Fig. 2) were arranged in the central k-space lines. This intensity-ordered k-space sampling was implemented using the experimentally determined echo evolution, measured in a pre-scan. Since signal evolution depends on field strength and local relaxation times, the same sampling scheme was valid for all mice.

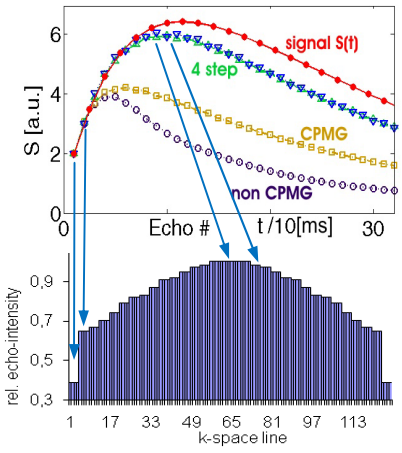

Fig. 2: Top: Signal intensities in echo trains acquired without phase cycle (nonCPMG), 2step (CPMG), and both 4step phase cycles compared to the maximum (i.e. single echo) signal S(t); Bottom: For image generation echoes were arranged using intensity-ordered k-space sampling with most intense echoes in the centre.

Results and Discussion: The impact of different phase cycles on echo amplitudes was assessed in a water phantom. Without phase cycling or with two-step phase cycles signal build-up was strongly disturbed, compared to the maximum signal measured with single echo acquisitions at different TE (Fig. 2). Only if both M_z and M^+ were refocused with a 4-step phase cycle, signal evolution close to the undisturbed case was reached. The impact of the intensity-ordered k-space sampling was assessed in fixed mouse brains in vitro. SNR reduction with increasing RARE-factors R was measured to be 14% at R=16 and 33% at R=32 compared to the initial SNR at R=1 (spin echo readout). Using the common linear segmented readout scheme more pronounced losses of 42% at R=16 and 83% at R=32 were observed. The fast CRAZED sequence dramatically increased SNR efficiency and allowed for acquisition of in vivo images of the mouse brain with high resolution (0.15 x 0.15 x 2.00 mm^3 – matrix 128^2) in 2:00 minutes, and images with a resolution of 0.6 x 0.6 x 2.0 mm^3 (matrix 32^2) in 0:30 minutes (see Fig. 3).

The achievable spatial and temporal resolution was sufficient to apply the fast CRAZED sequence for observation of the BOLD effect in mice. An average signal change of (6.3±1.1)% was detected in the CRAZED images of the mouse brain upon change of the breathing gas (Fig. 3). The T_2^*-insensitive RARE images showed a signal change of (4.4±2.3)% and the T_2^*-weighted FLASH images reached a signal change of (8.3±3.8)%. Since the CRAZED sequence was fully balanced, signal changes did not result from T_2^*-weighting. Therefore, it may be possible to combine both effects and observe higher signal changes using not fully refocused CRAZED acquisition [2]. Signal changes beyond 10% may become possible, rendering the method interesting for fMRI studies in small animals.

Conclusion: With the fast CRAZED sequence at 17.6 T, iMQC images of the mouse brain can be obtained in 30 seconds. A pronounced BOLD effect was observed upon breathing gas changes. Fast CRAZED makes fMRI studies in small animals at highest magnetic fields possible.

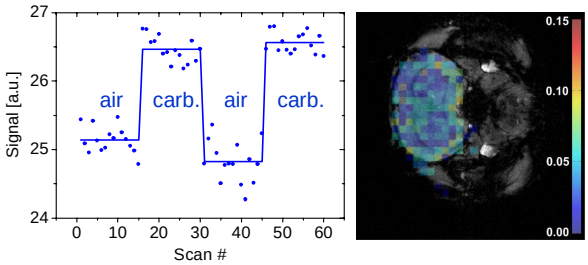

Fig. 3: CRAZED signal changes in the mouse brain with different breathing gases. Mean signal in the central brain region during 15 consecutive measurements per gas change (left). Map of relative changes overlaid with anatomical image (right).

References: 1. Warren W. et al., *Science* 265 (1993) 2005-2009. / **2.** Richter W. et al., *Magn Reson Imaging* 18 (2000) 489-494; Zhong J. et al., *Magn Reson Med* 45 (2001) 356-364; Schaefer A. et al., *Magn Reson Med* 53 (2005) 1402-1408 / **3.** Ramanathan C. et al., *J Chem Phys* 114 (2001) 10854-10859.