BOLD fMRI using a cryogenic RF probe: A concept for studying temperature perception in transgenic mouse models

Henning Matthias Reimann[1], Jan Hentschel[1], Babette Wagenhaus[1], Andreas Pohlmann[1], and Thoralf Niendorf[1,2]

[1]Berlin Ultrahigh Field Facility (B.U.F.F.), Max-Delbrück-Center for Molecular Medicine (MDC), Berlin, Germany, [2]Experimental and Clinical Research Center (ECRC), a joint cooperation between the Charité Medical Faculty and the Max-Delbrück-Center, Berlin, Germany

Introduction: Only little is known about the temperature perception and regulation mechanisms in mammals. The combination of fMRI and genetic modifications in rodents has great potential to help elucidating the role of the various (receptor and transducer) proteins involved in temperature perception and regulation mechanisms. Recently we introduced an MR-optimized thermo-stimulation system, which uses a water-tempered miniature peltier element and examined its feasibility in fMRI studies of temperature perception in rats, applying for the first time cold as well as heat stimulations [1]. Here we demonstrate the successful adaptation of our system to mice fMRI, which is of particular interest considering the numerous transgenic strains used in biomedical research of thermal perception. Signal-to-noise ratio was enhanced by using a cryogenic RF probe, which was shown to increase the sensitivity of BOLD-fMRI in mice [2].

Materials and Methods: ***Thermo-stimulation device.*** The stimulation system comprises a (10x10x2)mm^3 peltier element, a fiber-optic temperature sensor, two water reservoirs and a feedback control software. The peltiers heating/cooling performance was enhanced by a copper heat sink supplied with water of constant temperature (8°C/25°C) flows (Fig.1). The driving current was determined by a calibration (current vs temperature lookup table) and adapted/corrected in real-time (every 200ms) in a P-control algorithm based on the actual peltier temperature. Paradigms used for heat and cold stimulation were: 160s 33°C baseline, 15s rise time, 10s 48°C/18°C peak, 4x, error <0.5°C. ***Animal experiments.*** Three male C57BL/6 mice (weight 25-30 g) were studied using thermostimulation (48°C, 18°C) under isoflurane anaesthesia (1%, see [3]). The animals were intubated, artificially ventilated and paralyzed using the neuromuscular blocking agent pancuronium bromide (1-1.5mg/kg) in order to avoid motion artefacts [3]. Experiments complied fully with local institutional ethical and legal requirements. ***MR Imaging.*** Pilot images and high-resolution sagittal T2w images were used to position 10 axial T2*-weighted fMRI image slices (GE-EPI, TR/TE/FA = 2500ms/11.01ms/80°, FOV/mtx/res = 24x12x5mm / 90x60x10 / 0.1875x0.1875x0.5mm), 128 repetitions, TA = 16min. All images were acquired on a 9.4T Bruker Biospec (Ettlingen, Germany) using a transceive cryogenic quadrature RF surface coil (Bruker, Ettlingen, Germany). ***Analysis.*** fMRI data were motion corrected, registered to a mouse brain atlas, smoothed, and statistically analyzed (FSL).

Results and Discussion: The following activation patterns were observed (Fig.2): Anterior cingulate cortex (ACC), somatosensory cortex (S1/S2), medial thalamus (MTh), limbic system (LS). This distribution of activated areas is generally consistent with our previous findings in rats [1] as well as those known from different pain studies [3] or fMRI noxious temperature stimulation experiments in rodents [4,5].

Conclusions: fMRI of thermo-stimulation was successfully demonstrated in mice. The proposed concept for thermal stimulation supports rapid, stable and reproducible paradigms of various temperatures and rise times. fMRI activations for cold stimuli were reported previously for rats but this report is the first that demonstrates fMRI activations for cold stimuli in mice. Beside the usage of heat as a favored physiological stimulus in pain studies the implementation of this system in preclinical fMRI, particularly in mice, allows to examine a more comprehensive view of central nervous representations of thermal induced responses. Based on the concepts and results reported here we anticipate to extend our fMRI explorations into temperature perception and regulation mechanisms in mice with the ultimate goal to characterize the cold sensing transient receptor potential channel TRPM8.

References: [1] Reimann H et al., ESMRMB 2011; [2] Baltes C et al., NMR in Biomedicine 2010; [3] Bosshard S et al., Pain 2010; [4] Neely GG et al., Cell 2010; [5] Knabl J et al., Nature 2008.

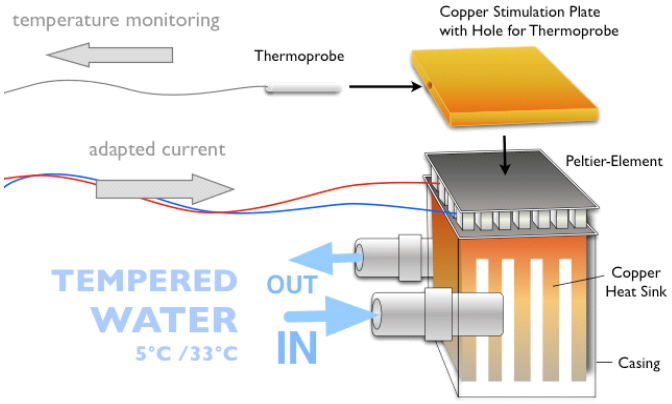

Figure 1: Schematic diagram of the thermo-stimulation system.

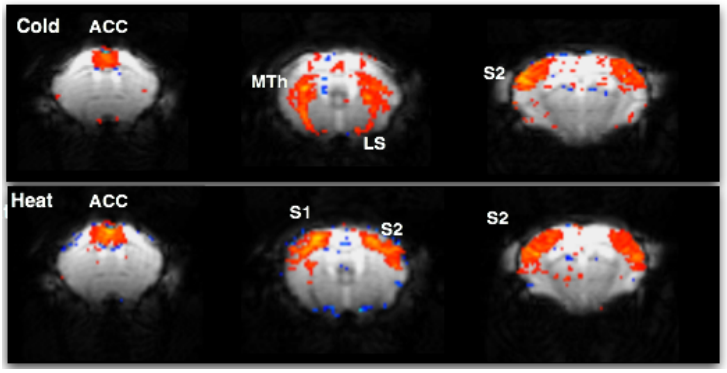

Figure 2: Bold activation maps derived from cold (left top) and heat (left bottom) paradigms showing activation for the anterior cingulate cortex (ACC), somatosensory cortex (S1/S2), medial thalamus (MTh), limbic system (LS).