Evaluation of pharmacological responses by quantitative T2 fMRI

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Introduction Pharmacological magnetic resonance imaging (phMRI) is a novel application of functional MRI where the activation or deactivation in the brain is induced by a pharmacological agent and the sequential changes in cerebral blood flow, volume and oxygenation can be measured with e.g. blood oxygenation level dependent (BOLD) contrast. Since the expected changes in signal intensity are usually small, this requires long and stable measurement environment. While slow drifts can easily be filtered from data, the fluctuations (e.g. room temperature, hardware drifts and animal physiology) in the time scale of the pharmacological activation are more problematic. Quantitative T2 maps are calculated from sequential images with different echo times. Therefore, the absolute T2 value decrease the influences of slow or intermediate scale fluctuations, which are presumed to be roughly similar in both datasets with two different echo times. The aim of this study was to use T2 maps to eliminate drifts in BOLD time series in order to detect activations caused by apomorfine, which is a drug used in treatment of Parkinson's disease and erectile dysfunction.

Materials and Methods 4 male Wistar rats (315 ± 6 g) were used in this study. Animals were anesthetized with isoflurane (4 % for induction and 1.5 % for maintenance during surgery) in 70 % N_2O -30 % O_2 mixture during femoral arterial and venous cannulation surgery. After surgery, anesthesia was changed to urethane (1.25 g/kg, i.p.) and the animals were tracheotomized and mechanically ventilated with a mixture of 70 % N_2 - 30 % O_2 and paralyzed with pancuronium bromide (0.5 mg/kg/h, i.v.). Data were collected with 7.0 T horizontal scanners interfaced with Varian DirectDrive. Anatomical images were collected with fast spin-echo (FSE) sequence (TR = 3 s, eff TE = 48 ms, echo spacing = 16 ms, echo train length = 8, FOV = 5 x 5 cm^2, 512 × 512, resolution 98 x 98 μm^2, thk = 0.75 mm, 40 slices). Functional data were collected with single-shot spin-echo echo planar imaging (SE-EPI) with TR = 4 s, FOV = 2.5 x 2.5 cm^2, data matrix of 64 x 56 (reconstructed to 64 x 64), spatial resolution of 391 x 391 μm^2 in plane with 15 slices (1.5 mm thick). The T2 maps were calculated as linear fit for two consecutive volumes with echo times of 32 and 50 ms yielding a temporal resolution of T2 maps as 8 s. A bolus of apomorfine (0.25 mg/kg, s.c.) was administered after 500 baseline images (250 T2 maps) and the scan was continued for 1000 images (500 T2 maps). The T2map data was analyzed with SPM8 along with in-house made Matlab-code using a block design model with onset at 250 T2 maps and duration of 150 T2 maps.

Results T2 values varied in the cortex between 32 and 57 ms with an overall average being 44.2 ± 4.3 ms (mean ± SD) with 125 pixel ROIs. Positive apomorfine responses were seen mainly in the lateral entorhinal cortex in all animals. The T2 values increased 3-4 ms during the activation. Negative apomorfine responses were detected in the motor cortices in all animals. The T2 values decreased 1-2 ms during the activation.

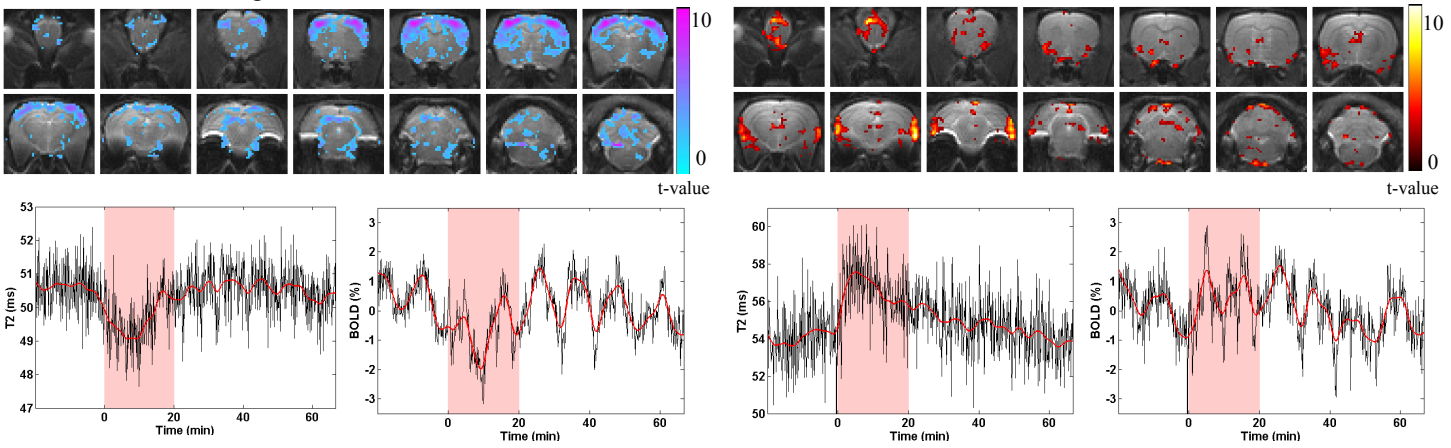

Figure 1. Statistical negative (left upper rows) and positive (right upper rows) apomorfine activation maps overlaid on EPI images of a representative rat. T2 and BOLD time series from activated pixels (T>4.5) (lower row). For clarity, low-frequency trends of signals (red) are shown on the time series.

Discussion Detection of small pharmacological responses relies on the stability of the signal intensity in time. Calculation of T2 maps from two sequential images diminishes fluctuations in the signal, and therefore allows more subtle activations to be detected. This method also allows quantification of the pharmacological response in absolute T2 values and not just as a relative response to a baseline. The T2 map method in pharmacological studies could be beneficial in studying new pharmacological agents with small or unknown responses in the brain.

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