Problems for motion correction: Paradigm correlated motion remains a confounding source for fMRI artefacts.

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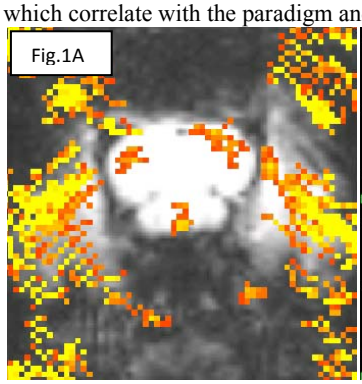
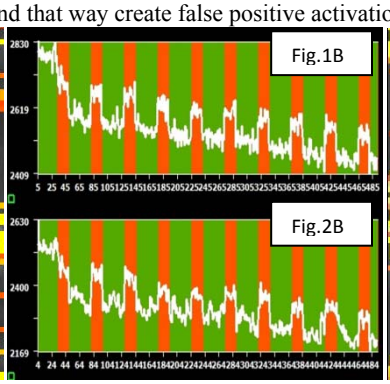
Introduction: Blood oxygenation level-dependent (BOLD) contrast fMRI is recently used extensively in small animal research. Great part of this research is done using echo planar (EPI) gradient echo imaging and massive statistical analysis of results. There are many factors influencing results in fMRI experiments (like type of anesthesia, optimization of stimulation protocol, and MRI sequences). Undesired motion of an animal is one important degrading factor, which is addressed by using different algorithms for motion correction applied before statistical analysis of the measured data. The motion is generally expected to be random. The aim of our study is to show how such undesired motion, which is correlated with stimulation protocol, can produce artifacts that are visually similar to normal BOLD patterns. Based on our fMRI experience we expect such motion especially in two types of fMRI experiments. First, experiments, which are using mechanical stimulation (e.g. whiskers stimulation) and second, experiments with very strong stimulus used, e.g. in pain research and to which even an anesthetized animal may react by some additional motion.

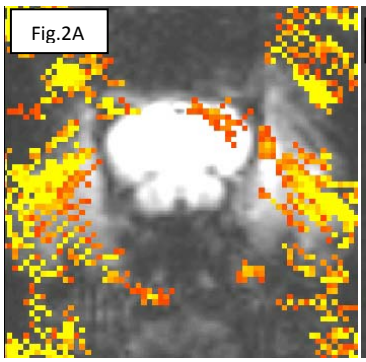
Materials and Methods: FMRI experiments were performed on a 4.7 T BRUKER Biospec scanner with a free bore of 40 cm, equipped with an actively RF-decoupled coil system on a dead Wistar male rats weighing ca. 350 g. A whole-body birdcage resonator enabled homogenous excitation, and a 3 cm surface coil array (4 channels), located directly above the head of the animal to maximize the signal to- noise-ratio, was used as a receiver coil. The scanning procedure started with the acquisition of T2 weighted spin echo horizontal anatomical reference images (slice thickness 1 mm, field of view 35 x35 mm, matrix 256 x128, TR = 2800 ms, TEef = 77 ms) using a rapid acquisition relaxation enhanced sequence (RARE, Henning et al., 1986). Functional images were acquired using Echo Planar Technique (EPI). A functional series of 500 sets of eleven axial GE EPI images (slice thickness 1 mm, field of view 25 x25 mm, matrix 64x64, TR = 1000 ms, TEef = 23.4 ms) was acquired. During EPI experiments motion was induced for 16 seconds and regularly repeated 10 times after 16 sec of no-stimulation. Functional analysis was performed using BrainVoyager and custom made IDL programs.

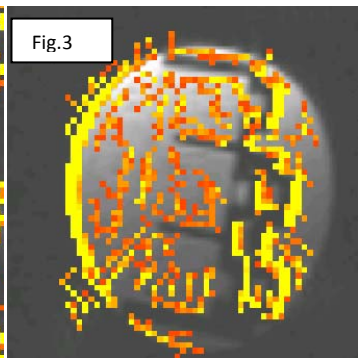
To demonstrate an effect of a motion correlated with the paradigm we performed series of experiments with dead animals and simple geometrical phantoms, respectively. The motion was induced by an air driven device integrated into the cradle which secures the animals in the scanner. Two inverted combs located at 2 cm of both sides of the snout allowed stimulations at frequencies between 0-15 Hz. For this study the head of the rat was connected with a soft rubber string to the combs. Different softness of the rubber string was used for the different degree of the coupling between the rat head and the moving combs. For minimal coupling no rubber string was used and the motion was induced just by vibration in the cradle. The amplitude of the comb motion was 10 mm and the stimulation frequency used was 7 Hz in all our experiments. Combs were driven from an external console running a custom stimulation software under LabView (Labview, National Instruments, Austin, TX).

Results and Discussion: Measured data were processed the same way like other fMRI data from different projects running in our lab (1,2). A typical result for the dead rat measurement with intermediated coupling between combs and the rat head is depicted in Fig. 1A. We can see "activated" area in the motor cortex. The correlations outside of the brain is caused by the motion of the whole head and correlated changes in EPI artifacts, which is not unusual in real fMRI experiments, too. Only positive correlation is shown. The time course (FIG. 1B) is a bit different to that of normal, physiological BOLD responses. The reason is, that our motion generating device is working with the maximal amplitude during the whole 16 sec stimulus. To simulate increase in the motion, which we expect e.g. for pain stimuli, we will have to use a more complicated device in the future, in which the amplitude of the motion could be controlled. As one major result, Fig. 2AB demonstrates that even after conventional motion correction not all false positive activated areas disappear. A result from the measurement of a gel phantom with a simple geometrical pattern in it (Lego brick) is depicted in Fig. 3. We can clearly see, that motion creates a false activation in the area of the change from the low to the high signal and vice versa. During the motion the bright parts of the phantom are partially moved to the areas of the low signal and this creates an enhancement on the edges, which correlate with the paradigm and that way create false positive activations.









Conclusion: Motion, which is correlated with or introduce by the fMRI paradigm can create false positive activations, which could remain real BOLD activity areas and a signal time course in these areas. Conventional motion correction algorithm are not able to remove these false areas completely. To avoid this problem, it is necessary to perform control experiments with the phantom or a dead animal in the case of mechanical stimulation experiments in order not to underestimate the motion. It is necessary to look for a typical "false" pattern of stimulated areas in experiments, which use strong stimuli (pain). In both cases, when one can see an undesired influence of the motion, the experimental setup has to be improved and validated by additional control experiments.

References: 1. Knabl et al. (2008) Nature 451: 330-335, 2. Hess et al. (2007) European Journal of Pain 11:109-119

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