Development of a 17.6T ultra-high field BOLD-fMRI method for amygdala related psychiatric disorders

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Introduction: Depression and anxiety disorders will prove to be the second leading cause of disability worldwide in the next years. The individual consequences and the lack of comprehensive therapies put a huge strain to the health care systems. To push research of this diseases and development of therapies, it is necessary to have an appropriate model organism and the corresponding genetic and environmental conditions. Known risk factors for the development of psychiatric disorders like depression and anxiety disorders are alterations in the function of the serotonergic system. A correlation between biased serotonin reuptake in humans and increased neuronal activity in the amygdala in response to fearful stimuli has already been proven. Since the amygdala is known for its key role in the development of fear and emotions, it is likely that an elevated activity in the amygdala has a strong effect on the development of psychiatric diseases. Therefore ultra-highfield MR at 17.6T promises very high resolution brain imaging paired with unparalleled high sensitivity and specificity for BOLD-fMRI studies. The goal was to overcome the drawbacks like susceptibility artifacts and to develop an appropriate method for the examination of the mouse amygdala. A special focus was the evaluation of a mouse handling method, which is as stress less as possible for a high comparability of the fMRI measurements.

Methods: A multi gradient echo sequence (MGE) sequence with 16 echoes was performed on a Bruker Avance 750 MHz wide bore NMR scanner (17.6T) to acquire T2* maps of a single slice encasing the amygdala for the most part. The field of view was 18mm x 18mm with a matrix size of 128 x 128 and a slice thickness of 1.5mm. A single T2* map was measured in 23s and were repeated 40 times to monitor a total time period of 15.2min. The experiment was designed in 4 blocks containing 40 repetitions each. The odd numbered blocks the mice got oxygen with 1.5% isofluran for anesthesia. During block 2 and 4 rat odor from used beddings was added to the oxygen isofluran mixture as predator stress. A boxcar function type paradigm to automatically process the regions with increased activity was applied to the data using Matlab (The MathWorks, Inc.). Therefore the increase of the T2* relaxation time based on the blood oxygenation level dependent (BOLD) effect was correlated to the stress. The T2* maps were compared to the maps of the first block as an unstressed reference. Prior to the MGE measurements the adequate slice orientation was selected by orientation in relation to the vesicles of the mouse brain. The tilt level of the head was given by placing a toothbrush underneath the front teeth and securing this position by foamed material. The anatomical images were done with a T1 weighted rapid acquisition with relaxation enhancement (RARE) sequence with a RARE-factor of 8. The activated regions are shown as an overlay image to these anatomical images with the same geometry. The time devolution is evaluated by averaging 10 repetitions proceeding from the first ten T2* differences maps to map 31-40 resulting in 30 averaged T2* maps in order to exclude short time effects. The starting time is therefore 1min 55s after the begin of the stressor exposure. The increment is 23s leading to the last time point of 13min 25s.

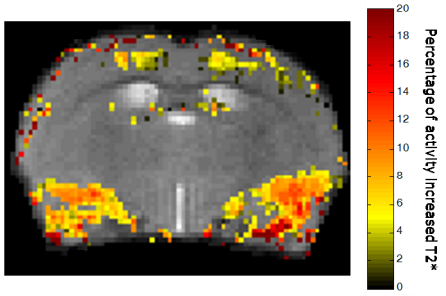

Fig. 1: BOLD activation of the mouse brain (increase in percentage of T2) induced by rat odor. The image is an overlay of the positive change on the anatomical image with the voxel size of 141 x 141 x 1500µm^3.*

Results: The observed BOLD effect shows a high sensitivity and specificity for the amygdala (Fig. 1). The increase of the T2* relaxation times based on the BOLD effect is up to 50% and shows some substructures in the amygdala. The measured time and location devolution of the activation, starting around the central nucleus of the amygdala and then shifting toward the lateral nucleus, was observed during the complete time period. Figure 2 shows several time points of the averaged T2* difference maps to visualize the proceeding of the activation shift.

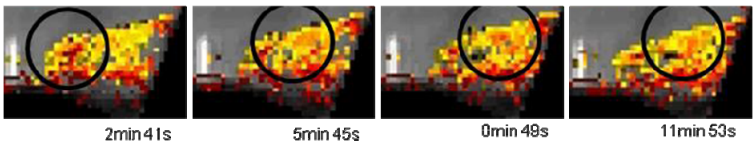

Fig. 2 Time and location devolution of the amygdala (lower right corner of the mouse brain). The overlay image shows the positive change in percent of the reference T2.*

Discussion: The BOLD effect with up to 50% increase of the T2* relaxation times was expected due to the high magnetic field of 17.6T. The quantification of T2* relaxation times strongly depends on a homogeneous field which is hard to obtain reproducible in vivo at this high field. For the comparability of the results we calculated the relative changes based on the stressor. The used paradigm is very simple but worked well for this method, but implies a lot of improvement potential. The observed starting reaction in the center nucleus of the amygdala makes sense, because it plays an important role in the regulation of the autonomous and endocrinal response of behavior and the development of anxiety. Since this reaction is important for the survival of the individual it takes place in front of the activation of the lateral nucleus which also has an output to the hippocampus and to the temporal lobe memorization system. This points to a processing and a retaining of the stress event.