Functional Atlas of the Rat Brain

Automatic Structure Assignment for Evaluation of BOLD fMRI

Andreas Hess[1], Silke Kreitz and Kay Brune[2]

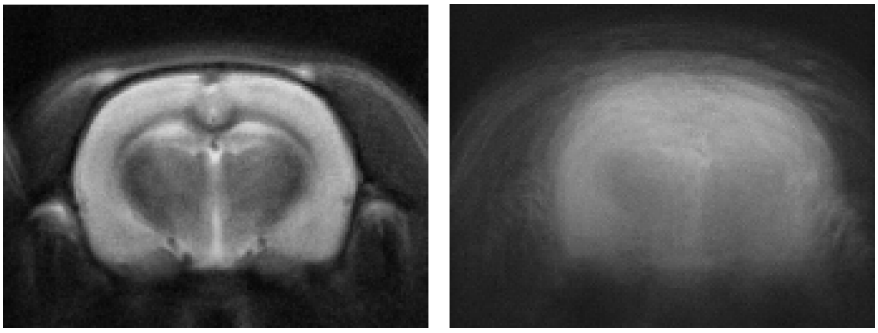
[1]Institute for Experimental Pharmacology and Toxicology
[2]Doerenkamp Professor for Innovations in Animal and Consumer Protection
FAU Erlangen Nuremberg, Fahrstrasse 17, 91054 Erlangen
Email: andreas.hess@pharmakologie.uni-erlangen.de

Abstract. For functional mapping of human brain activity the Talairach atlas provides the spatial reference system for structure identification of activated spots. No such common reference system exists for fMRI studies on animals. Therefore, the aim of this study was to establish a set of different image processing algorithms in order to generate for a given stimulation paradigm a functional standard atlas of the rat brain. The goal, which should be achieved, was an automatic identification and structure assignment of activated voxel groups based on such a labelled standard atlas. Due to the smooth brain structure of rodents even basic affine registration techniques greatly reduce the interindividual variations in brains and activated structures and allowed precise identification and labelling of the activated structures.

1 Introduction

For functional mapping of human brain activity the Talairach atlas provides the spatial reference system for structure identification of activated spots. Altough controversially discussed no such common reference system exists for fMRI studies on animals like rats or mices. Nevertheless such a spatial reference would be very helpful in evaluating the different activity spots. We established such a spatial reference system in rat fMRI experiments studying the effect of different analgesics on heat pain processing. Even today there is a continuous demand for development of novel analgesics to provide relief from different types of pain. Since traditional behavioral pain examinations are unlikeable for the animal as well as subjective, fMRI would significantly improve objective measurements of analgesic effects. Nowadays only a few groups perform fMRI studies on animals [1,2] compared to the numerous centres of human brain imaging. So far only Schweinhardt et al. [3] addressed the template spatial normalisation for anatomical MR rat images. To our knowledge no spatial normalisation approach for fMRI datasets exists for animal research. However, we do believe that this topic will be addressed in the near future particular for two reasons. First, the number of dedicated animal MRI scanners is strongly increasing and second due to the need of functionally characterising genetically manipulated mice a high demand

Fig. 1. Inset left showing the average of one anatomical slice before alignment, inset right after alignment.



will be created for matching individual functional datasets to spatial reference systems (e.g. wild type). A few groups already started to build pure anatomical brain databases of different knock-out mices based on single datasets. On the other hand, we could already prove the usefulness of geometric normalisation procedures for functional imaging experiments in animals using dedicated warping procedures on functional autoradiography animal datasets [4]. Therefore, the aim of this study was to establish a set of different image processing algorithms in order to generate for a given stimulation paradigm a functional standard atlas of the rat. The goal, which should be achieved, was an automatic identification and structure assignment of activated voxel groups based on such a labelled standard atlas as it is done in human studies by the Talairach reference system.

2 Material and Methods

FMRI was performed on a 4.7 T BRUKER Biospec scanner with a free bore of 40cm, equipped with an actively RF-decoupled coil system. A 3 cm surface coil, located directly above the head 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 coronal anatomical reference images (slice thickness 1mm, field of view 35x35 mm, matrix 256x128, TR 2800 ms, TEeff 77 ms) using a rapid acquisition relaxation enhanced sequence (RARE). Functional images were acquired using Echo Planar Technique (EPI). A functional series of 1800 sets of 20 axial EPI images (field of view 25mmx25mm, matrix 64x64, TR 2000 ms, TEef 23.4 ms, slice thickness 0.5 mm) was recorded. The initial 120 scans covered a 4 minutes period without any stimulation, and the following five 60 scans covered first 2 minutes of stimulation. The next 60 scans covered the second 2 minutes no-stimulation period and so on. Finally, a set of anatomical scans with a high spatial resolution in the same area as the functional set was acquired with GEFI (matrix 256x256, TR 400ms, TE =18 ms, number of averages 8). The stimulation of the left hindpaw of 300 g SD rats (n = 54) was performed using the MRI-ThS1-2ch, which is a computer controlled peltier heating and cooling

device. The stimulation system does not introduce any disturbances in the MR scanning and is also not influenced by the gradient pulses. At the beginning of each of the 4 stimulation cycle the peltier element was switched on for 20 sec. With a computer adjustable current resulting in temperatures of 35, 40, 45 and 50 degree C at the end of the 20 sec.

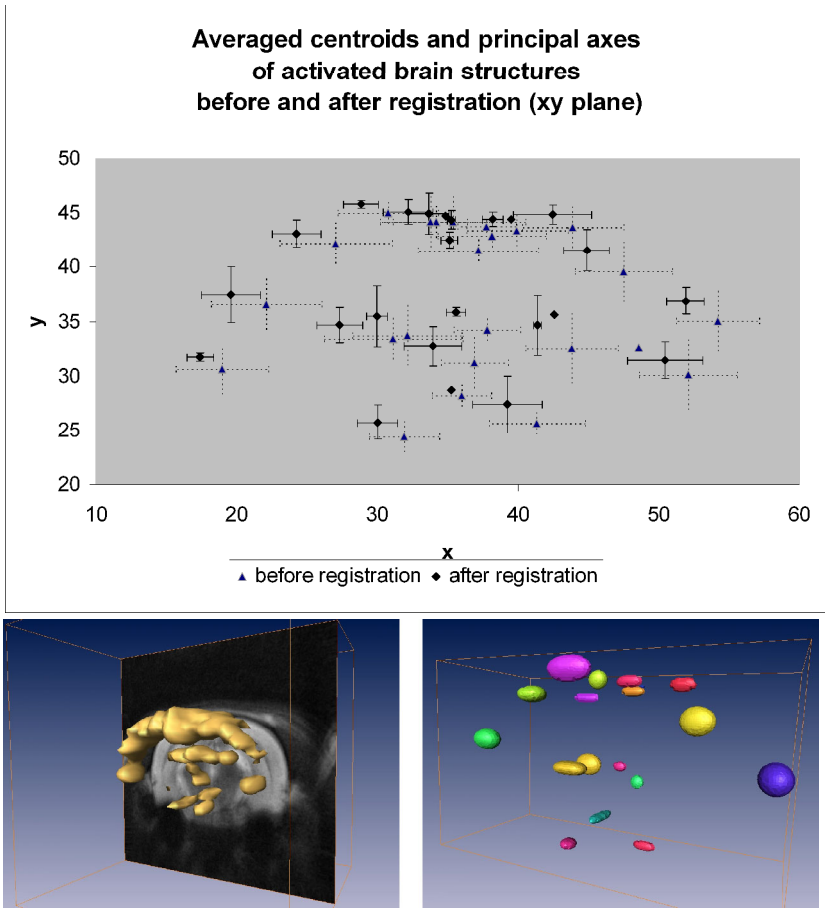
Functional analysis was performed using BrainVoyager 2000 (V 4.8.5.0) or our MRIan respectively at threshold for the p-values >= 0.15. By doing so the activated voxels in the complete brain were obtained. First, the voxel groups were manually identified as certain brain structures and accordingly labelled. From each voxel group the centroid was determined. Next, the anatomical scans were corrected for field inhomogeneity by an iterative homomorphic filtering algorithm. The inhomogeneity is due to imaging the brain with a surface coil. Afterwards, the brains could be automatically segmented by a classical segmentation approach as introduced by Höhn et al. 1988 with minor modifications for animal brains. Based on these binary brain masks an affine transformation matrix was obtained for registering the individual brains into a common reference system. This transformation matrix was applied to the anatomical scans as well as a downscaled version to the functional datasets (correlation coefficients or p-value matrix). In result the anatomical as well as the functional images were brought into register by affine transformations. The quality of the alignment was statistically evaluated by several coefficients. The geometrical match of different brain parts (cortex, cerebellum, thalamus, hippocampus, striatum) was evaluated by structure specific (manual segmentation) volume of overlap indices and geometrical variance or probability maps. Correlation coefficients were determined in order to obtain a grey value based intra-modality estimate of the registration goodness. Mean average brains of anatomy and functional labelling were obtained by averaging across the registered datasets. Most important for us was the visual inspection of small activated structures of the thalamus or e.g. hypothalamus in the resulting average datasets.

3 Results

The single fMRI experiments revealed various brain areas, already known to be involved in sensory and pain processing (somatosensory cortex, hippocampus, cingulate cortex, insular cortex, hypothalamus, periaquaeductal grey and small nuclei in the thalamus). Figure 1 demonstrates the effect of the alignment procedure comparing the average of a single anatomical slice across all 54 experiments of this study before and after the alignment procedure. Clearly one can see that only in the average across the aligned slices (Fig. 1 right side) brain structures can be identified.

The main result presented here is shown in Figure 2. Here for each brain structure, which was manually labelled, the average centroid (only x and y for better visualisation) is plotted. The x and y error bars mark the standard deviation of the centroid position across all experiments. As can be seen for each voxel group the cross is smaller after alignment indicating a more confined spa-

Fig. 2. Top: showing the averaged centroids and their standard deviations (x and y coordinates) per activated brain structure before and after alignment. Bottom left side shows these averaged structures after alignment in a 3d surface visualisation. Bottom right shows a representation of all centroids and their standard deviation from top as ellipsoids in space. Note that all structures are separated from each other.



tial description of the brain structure. During the alignment the mean position of the activated areas were shifted on average 3.84 voxels in x, 2.45 in y and 3.47 in z direction which is up to 16% of the image resolution. After the fit the standard deviation of the centroid position was 1.4 pixels in x, 1.5 in y and 0.95 voxels in z direction. This is a reduction on average of 63.58%.

As the most important result we found that after the alignment procedure no spatial overlap remained between any two voxel groups. The only exception was the cingulated cortex which was separated in 2 different parts. Moreover, the high registration quality allows identification of the small thalamic structures on the averaged dataset. This indicates that the labelled brain structures can be

uniquely identified. Consequently activated voxel groups of a single measurement can now be automatically labelled after registering this measurement into the functional atlas of the rat brain.

4 Discussion and Outlook

We conclude that even by affine transformation brain datasets of rats a functional standard brain or atlas can be generated with a spatial accuracy of 1 to 2 voxels reducing the standard deviation after registration of about 63%. Future studies will evaluate, if this can be further optimized by non-affine registration like warping procedures. Moreover, by using functional standard atlases which can easily be generated out of given experimental groups a more precise and dynamic analysis tool for automatic structure assignment of activated brain regions in animal research may be established.

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