Resting-State Functional Connectivity of the Cortical Pain Matrix

M. Amann [1], S. Becker[2], D. Kleinboehl[2], L. R. Schad[1]

[1]Medizinische Physik in der Radiologie, Deutsches Krebsforschungszentrum, Heidelberg, Germany, [2]Otto-Selz-Institut, Labor für Klinische Psychophysiologie, Universität Mannheim, Mannheim, Germany

Introduction

In resting state brain, low frequency oscillations in the BOLD signal have been detected. They have been shown by many investigators to be synchronized between functionally related areas, e.g. in the sensorimotor cortex [1,2], and the auditory system [3]. Another functional connected system of interest is the matrix of cortical pain processing. It can be hypothesized that chronic pain changes the interaction between the involved areas and that these changes may be detected by functional connectivity analysis. However, cortical pain processing is not clearly distinct from the sensorimotor system, so the concept of a "pain matrix" including both sensorimotor and pain related areas has been developed [4]. To separate both fractions, T2*w MR images with high spatial resolution are needed. This is, on the other hand, accompanied by lower temporal resolution. As a consequence, cardiac and respiratory signal could alias into resting state signal. In this study, we performed two different functional connectivity experiments: one with appropriate TR of 0.9s and another with high spatial, but low temporal resolution (TR=3.2). The ROI taken for connectivity analysis was the nociceptive part of the right anterior insula. The results were compared in terms of detecting the cortical pain matrix and in terms of signal aliasing.

Methods

The functional connectivity experiments were performed with four healthy volunteers (2f, mean age 28±4 years). Each subject underwent two different imaging sessions on a 1.5 T MR scanner (Siemens Symphony) with an 8-channel head coil. In both sessions, a resting state T2*w data set was acquired while the subjects were inactive (scan time = 12min). Afterwards, a painful thermal stimulation fMRI experiment was performed to identify regions of the cortical pain matrix. The functional connection to one of these regions (contra-lateral anterior insula) was then evaluated by examining low frequency temporal fluctuations in the resting state data set.

For the heat stimulation, an MR compatible thermode system (TSA2001, MEDOC) was fixed to the left thenar of the subjects. During the stimulus period, the temperature was oscillating between the individual pain threshold and 2.5°C above, whereas in the baseline period the temperature was fixed to 40°C. Seven baseline periods alternated with six stimulus periods, each lasting 15 s. All T2*w data were scanned with a GE-EPI sequence using TE=50ms, α=70° (session 1) resp. α=90° (session 2). In the first imaging session, both resting state and pain task data were acquired with high temporal (TR=0.9s) and moderate spatial resolution (9 transversal slices, $3.8 \times 3.8 \times 8mm^3$). In the second session, low temporal (TR=3.2s) and high spatial resolution (25 transversal slices, $1.9 \times 1.9 \times 4mm^3$) was obtained.

Data evaluation using AFNI [5] was performed for each subject and each session separately. The analysis included motion correction, spatial smoothing and realignment to the resting state images. Furthermore, the resting state data set was low-pass filtered in time (cut-off frequency 0.08 Hz). Based on the heat task experiment, a ROI of significant activation (p<0.001) in the right anterior insula (RAI) was copied to the resting state data set. Then the average signal time course of all voxels in the activation-defined region was calculated [3]. To prevent cardiac and respiratory coupling to the resting state signal, voxels in the vicinity of large vessels were censored [2]. The relevant voxels were identified by 3D TOF-MR angiography (TR/TE/α=39 ms/5 ms/25°, FOV=240x180mm^2, matrix=512x192). A multiple linear regression (MLR) was performed for each resting state pixel to the averaged time course of the RAI. In the MLR, the whole brain time course and the calculated motion parameters were treated as confounds of no interest. The resulting corrected (p<0.001) F-statistics correlation maps were then transformed to z-scores of the standard normal distribution, reflecting functional connectivity [3]. Functional connectivity maps were normalized to Talairach coordinates [6] using a high-resolution anatomical whole head data set taken at the beginning of each scanning session (MPRAGE: TR/TE/TI/α=1.9 s/4 ms/1.1 s/8°, FOV=256x256 mm^2, matrix=256x256). A group combined z-map for each temporal resolution was then calculated and overlaid to the MNI anatomical template [7]. Positive and negative correlations of RAI oscillations with resting brain activity were analyzed separately.

Results

In both experiments, symmetrical positive correlation was found in homologous areas such as left and right anterior insula (Fig 1a,b), SII (Fig 1c,d), and SI (Fig. 1e,f). In the maps of experiment 1 (TR=0.9s), additional correlation was found in the anterior cingulate cortex (ACC) and in the premotor area (PMA) (Fig. 1c,e). Correlation of SII seems to extent to the parietal lobe in experiment 1 at both sides (Fig. 1c). In experiment 2, additional correlation was found in the mid cingulate cortex (MCC) (Fig. 1f). Negative correlations were not related to somatosensory processing, lying in occipital regions for experiment 1 (Fig. 2a), and in prefrontal cortex (PFC) and in posterior cingulate cortex (PCC) for experiment 2 (Fig. 2b).
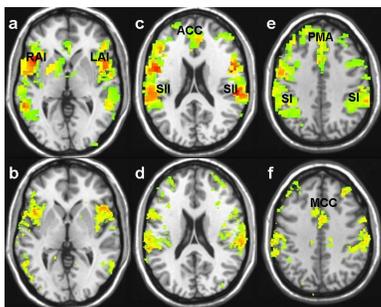
Fig. 1 (left): Composite map of positive resting state correlations with the right anterior insula (RAI). Upper row: experiment 1 (Δt=0.9s, Δx=3.8x3.8x8mm^3); lower row: experiment 2 (Δt=3.2s, Δx= 1.9x1.9x4mm^3). LAI: left anterior insula; ACC: anterior cingulate cortex; PMA: premotor cortex.
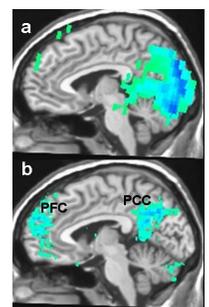
Fig. 2 (right): Composite map of negative correlations with the RAI in experiment 1 (a) and experiment 2 (b)
PFC: prefrontal cortex; PCC: posterior cingulated cortex

Discussion

In this study, we were able to detect positive correlations of resting state brain activity between nociceptive parts of the right anterior insula and brain areas related to pain processing. Despite of the low temporal resolution of experiment 2 (3.2s), a similar activation pattern was found compared to experiment 1 (0.9s). This is an evidence that aliased cardiac or respiratory signal has less impact on resting-state brain experiments with low temporal resolution, provided that regions with possible cardiac coupling are excluded from analysis [2]. Negative resting state correlations could not be interpreted in terms of functional connectivity. Differences in the correlation maps between both experiments can be explained by the small number of subjects under investigation yet. The high spatial resolution of experiment 2 may provide the opportunity to differentiate between sensorimotor and pain processing cortices. For this, we are planning further resting-state brain experiments where the reference ROIs are obtained by pure sensory and/or pure thermal pain (laser) stimulation.

References

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