Condition Specific Frequency Patterns in rs-fMRI measurement of a Neurodevelopmental Rat Model of Schizophrenia

Ekkehard Küstermann[1], Vani Thimmashetty[1], Jannis Gundelach[2], and Lena Wischhof[2]

[1]"In-vivo-MR" AG, FB2, Universität Bremen, Bremen, Bremen, Germany, [2]Department of Neuropharmacology, Brain Research Institute, University of Bremen, Bremen, Bremen, Germany

Introduction: Maternal exposure to infection during mid-gestation increases the risk for the offspring to develop schizophrenia. Here, the critical initiating factor appears to be the activation of the maternal immune response that follows infection. In rodents, this process can be induced by exposure of pregnant dams to lipopolysaccharide (LPS), a cell wall component of gram-negative bacteria [1]. Rats born to LPS-challenged mothers show structural, functional and behavioral alterations that have been associated with schizophrenia symptomatology. Since schizophrenia has also been described as a disorder of neuronal disconnectivity which may underlie positive, negative and cognitive symptoms, we studied the effects of prenatal LPS-exposure on brain functional connectivity in rats using resting state functional magnetic resonance imaging (rsfMRI). RsfMRI aims at detecting frequency fluctuations in the Blood Oxygen level Dependent (BOLD) signal and temporal correlation of these fluctuations between different brain regions are thought to reflect functional connectivity. As the processing technique to estimate functional connectivity in the brain we used the Independent Component Analysis (ICA) which divides the BOLD signal into different temporal and spatial independent components (ICs). The fluctuations of the BOLD signal of all voxels of one component are temporally correlated. Voxels of one component represent regions that are considered to be functionally connected. Thus, ICA allows analyzing the functional connectivity within the entire brain, making it an appropriate tool to investigate pathological influences on brain connectivity.

Methods: Pregnant rats were administered with LPS (100□g/kg) at gestational day 15 and 16 while control dams received saline injections. The offspring was then tested in a variety of behavioral paradigms at different developmental stages. RsfMRI was performed with adult male rats (control group (mothers received saline): n=3; LPS-group: n=4) on a 7T MR scanner (Bruker BioSpec USR 70/20, Ettlingen, Germany) using a volume coil for excitation and a 4-channel array surface coil for signal reception. Initially, rats were anesthetized with 2-3% isoflurane administered in 100%O_2. During the experiment, animals were sedated using medetomidine which was first injected as a bolus of 0.05mg/kg followed by continuous infusion (0.05mg/kg/h) [2]. Isoflurane was discontinued 15min after the bolus injection of medetomidine. In order to assess whole-brain BOLD signal fluctuations at a wide range of frequencies, data acquisition was performed using a conventional EPI sequence (TE=12 or 30ms, TR=2000ms, nvol=400or800, in-plane resolution=280-300µm, slice thickness=1mm, nsl=17or21 to cover the whole brain). Data preprocessing was done with SPM12 [3] for slice timing and post-hoc motion correction. Data were decomposed into spatial and temporal components using ICA (MELODIC / FSL5 [4]) after spatial smoothing with a 2mm kernel. The power spectra of all estimated independent components (ICs) of one run were averaged to a characteristic spectrum. In order to accentuate the difference between both treatment groups, the spectra from individuals were averaged over the members of the respective groups.

Results: Following these preprocessing steps, the ICA reveals about 90-100 ICs. The vast majority of them comprises separated single, well known morphological areas such as S1 left, S1 right, etc. but not coherent parts of the default mode network (DMN). The power spectra of all estimated ICs of one run are averaged to give a representative spectrum of the frequencies of the individual brain. As depicted in the figure below, the average of these averaged power spectra of individuals are characteristic for the different treatment groups: Healthy, well performing animals of the control group (*green*) exhibit spectra with two separated frequency bands: (i) the well known fluctuations of up to 0.1Hz and (ii) a range between 0.18-0.22 Hz, but no signal around 0.15 and above 0.22. The spectra of animals from LPS-treated mothers (*red*) also have clearly separated bands: (i) one with low frequencies below 0.1Hz, (ii) a second with frequencies of 0.15-0.18 Hz and (iii) a third above 0.22 Hz - but no signals around 0.2 Hz. Thus, both treatment groups are clearly distinguishable simply by the average power spectrum of all ICs. Interestingly, the spectrum of one control animal differed strongly from the normal control pattern (*gray*) and showed significant overlap with the spectrum chracteristic for the LPS group. This individual showed a very bad performance in behavioral tests, especially those testing PPI and working memory.

Discussion and conclusion: In this neurodevelopmental rat model of schizophrenia, we observed that the exposure to bacterial infection during the prenatal phase results in condition specific frequency differences of the BOLD signal obtained from the adult offspring in the absence of any stimulations. These signals are collected from the entire brain and may reflect altered network connectivities in the offspring. Our study supports the notion that rsfMRI provides an attractive tool for defining biomarkers of neuropsychiatric disorders in preclinical animal models as it is non-invasive, undemanding and limited in scanning time.

References: [1] Baharnoori, M. et al. (2013) PLoS One 8:e54439 [2] Weber, R. et al. (2006) Neuroimage 29:1303 [3] SPM12: http://www.fil.ion.ucl.ac.uk/spm/software/ [4] FSL5: http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/