Local intrinsic connectivity measures relate to GABA/Glx levels

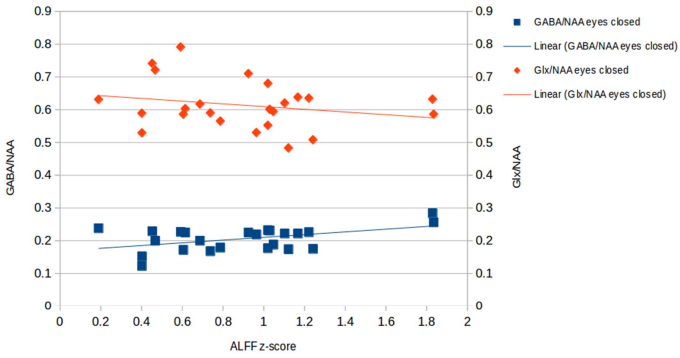
Katarzyna Bienkowska[1] and Valentin Riedl[1]
[1]*Neuroradiology, Technische Universitat Munchen, Munich, Germany*

Target audience: basic scientists, neuroscientists interested in multimodal imaging, MR spectroscopists.

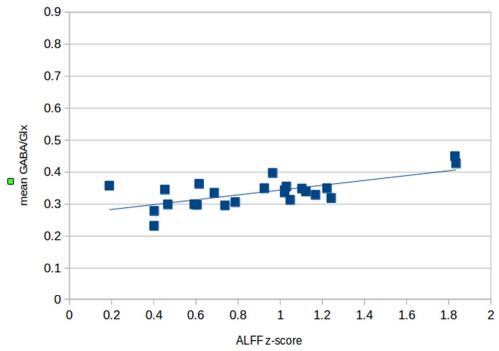
Purpose: Recently there has been considerable progress done in investigating interactions between GABA level and BOLD signal change during visual stimulation (task) [1, 2, 3]. What has not been carefully studied yet is the relationship between resting state coherent BOLD signal change (functional connectivity) and excitatory/inhibitory neurotransmitter balance. In order to examine interaction between GABA/Glx levels and local intrinsic brain activity (iFC), a combined fMRI-MRS study was performed. GABA and Glx concentration in the occipital cortex were correlated with local functional connectivity (lFC) and amplitude of low frequency fluctuations (ALFF) of the resting brain in eyes-open and eyes-closed condition.

Methods: Study was performed in 3T PET/MR Siemens Biograph mMR scanner. 25 healthy participants (12m/13f, M=27.7yrs) underwent consecutive magnetic resonance spectroscopy (MRS) and resting state-fMRI (rs-fMRI) measurement in one day. J-difference-edited MEGA-PRESS spectroscopy sequences of 7 min eyes open and 7 min eyes closed were acquired (TR/TE=2000/68ms, 128 averages, voxel size 25x25x25mm^3, placed in occipital cortex). 360 acquisitions of rs-fMRI were collected in blocks comprising of 6 min eyes open and 6 min eyes closed (T2*-weighted echo-planar-imaging (EPI) of TR/TE=2.000ms/30ms; 35 slices, voxel size 3.0×3.0×3.0mm3). **MRS processing:** 256 transients of 1024 data points were collected and analyzed with LCModel. Results are given as ratio of GABA and Glx (Glu+Gln) to total NAA. **MRI processing:** rs-fMRI data was analyzed with spm8 and DPARSF/REST tool. Data from eyes open and eyes closed blocks were collated into one data set. Mean white matter and CSF signal was regressed out from the main signal. Filtering (not for ALFF) and smoothing with 4 mm Gaussian kernel was performed. For the local functional connectivity (lFC) brain-wise functional analysis was performed from the ROI placed in the primary visual cortex and corresponding to the spectroscopy voxel. Mean from the MRS ROI was than extracted from the spm map. Analysis of amplitude of low frequency fluctuations (ALFF) was performed within the primary visual cortex voxel, corresponding to the MRS voxel. All extracted mean signals were represented on the z-scale. Pearson's correlation coefficients between different iFC measures and GABA as well as Glx were calculated.

Results: ALFF was positively correlated with GABA level in eyes closed (r=0.48, p=0.0152), eyes open condition (r=0.39, p=0.0539) as well as mean GABA level (r=0.45, p=0.0240). A negative, but not significant correlation was found between Glx and ALFF level in eyes closed (r=-0.23, p=0.2687). GABA/Glx ratio was correlated positively with the ALFF (r=0.68, p=0.0002). Similar, although not significant trend is found in correlation between lFC and GABA/NAA in eyes closed (r=0.2, p=0.2281) as well as Glx/NAA in eyes closed (r=-0.25, p=0.3378). GABA/Glx ratio was correlated positively with the lFC (r=0.32, p=0.1189).



Correlation between ALFF z-score in eyes closed and GABA/NAA and Glx/NAA



Correlation between ALFF z-score and mean GABA/Glx

Discussion and Conclusions: Our results demonstrate a relation between local intrinsic connectivity measures and inhibitory/excitatory neurotransmitters levels in the occipital cortex. A positive significant correlation has been found between the amplitude of low frequency fluctuations (ALFF) and GABA/Glx ratio. ALFF levels in several brain regions have been recently found to be distorted in neurodegenerative diseases (multiple sclerosis, Alzheimer Disease), psychiatric diseases and personality disorders (schizophrenia, antisocial personality disorder) as well as in the early stage of spinal cord injury [4, 5]. ALFF correlation with microstructural brain damage and slow cognitive processing has been suggested. Presented in this study associations might suggest a biological role of rest GABA/Glx ratio in local intrinsic brain activity modulations, more prominently for ALFF than for lFC. Further studies on the role of GABA/Glx ratio in the modulation of intrinsic functional connectivity should be considered in order to investigate a possible role of amplitude of low frequency fluctuations and other measures as a powerful marker indicating inhibition/excitation dysregulation processes in the brain.

References: **[1]** Bednarik P., Tkac I., Giove F., Deelchand D.K. and Mangia S. (2014). 'Correlations between BOLD and neurochemical responses measured in the human visual cortex at 7T', Proc. Intl. Soc. Magn. Reson. Med. 22. **[2]** Donahue, M.J., Near, J., Blicher, J.U. and Jezzard, P. (2010). 'Baseline GABA concentration and fMRI response', NeuroImage, vol. 53, no. 2, pp. 392–398. **[3]** Muthukumaraswamy, S.D., Edden, R.E., Jones, D.K., Swettenham, J.B. and Singh, K.D. (2009). 'Resting GABA concentration predicts peak gamma frequency and fMRI amplitude in response to visual stimulation in humans', Proceedings of the National Academy of Sciences of the United States of America, vol. 106, no. 20, pp. 8356–8361. **[4]** Zhou F., Zhuang Y., Wu L., Zhang N., Zeng X., Gong H., Zee Ch. (2014). 'Increased thalamic intrinsic oscillation amplitude in relapsing-remitting multiple sclerosis associated with the slowed cognitive processing', Clinical imaging, vol. 38, no. 5, pp. 605-610. **[5]** Weiler M., Teixeira C.V.L., Nogueira M.H., Machado B. (2014). 'Differences and the relationship in default mode network intrinsic activity and functional connectivity in mild Alzheimer's disease and amnestic mild cognitive impairment', Brain connectivity, vol. 4, no. 8, pp. 567-574.