# Interregional associations between excitatory and inhibitory neurotransmitters in the resting human brain

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**Target audience:** Researchers and members of the Psychiatric MR Spectroscopy Study Group and of the Magnetic Resonance Spectroscopy Community.

**Purpose:** As reported in recent studies, several psychiatric and neurologic disorders like schizophrenia, major depression or chronic pain are often associated with metabolic changes in specific regions of the human brain[1,2]. Of particular interest are changes of the main excitatory and inhibitory neurotransmitters glutamate (Glu) and GABA as they are key constituents of the neurochemical processes regulating neuronal activity. Metabolite concentrations reveal, however, large inter-individual variations, which may be ascribed to interregional relations within the network of brain regions known from resting state functional connectivity studies. Therefore, compared to an isolated description of local metabolic changes, taking these metabolic associations into account might be more specific to explore the neurochemical origins of neurological disorders. In the present study, Glu and GABA concentrations were quantified in the left insula (Ins), anterior cingulate cortex (ACC) and posterior cortex (PC) of healthy subjects to explore interregional differences of neurotransmitters as well as potential metabolic associations between these three regions known to be functionally connected in the resting state[3,4].

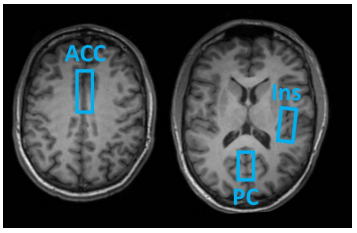


**Fig. 1** Location of the MRS voxels in ACC, Ins and PC.

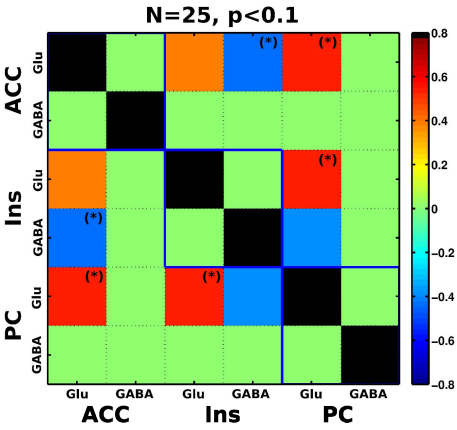


**Fig. 2** Pearson correlation matrix of Glu and GABA concentrations in ACC, Ins and PC. All correlation coefficients with $p \geq 0.1$ are set to zero, coefficients with $p < 0.05$ are labelled with (*).

**Methods:** In this study 25 healthy volunteers (18f/7m, 53 ± 7 years) were measured on a clinical whole-body 3 T MR scanner (Magnetom TIM Trio, Siemens, Erlangen, Germany) with a vendor supplied 12-channel head matrix coil. Conventional and edited $^1$H MR spectra were collected from ACC, Ins and PC with PRESS (TR/TE: 1800/30 ms, TA = 1 min) and MEGA-PRESS sequence (TR/TE: 1800/68 ms, TA = 11 – 13 min), respectively (Fig. 1). The intensities of Glu were quantified from conventional spectra with LCModel[5], whereas the GABA intensities were determined in edited spectra with jMRUI package[6]. Furthermore, absolute metabolite concentrations were calculated with respect to heterogeneous tissue composition by using the unsuppressed water signal as an internal reference. Regional and interregional neurotransmitter interrelations were determined by using Pearson correlation between GABA and Glu within as well as between the examined brain regions. Additionally, gray matter fractions (GM', CSF fraction excluded) in spectroscopic voxels were determined from tissue segmented $T_1$-weighted whole brain MRI data (*Freesurfer* toolbox, V 4.5.0, http://surfer.nmr.mgh.harvard.edu/) and used to calculate GM' normalized metabolite concentrations in order to consider GM' differences between voxels for interregional comparison of GABA and Glu concentrations (*t*-test).

**Results:** Fig. 2 shows the correlation matrix between the regional and interregional dependencies of the neurotransmitters in the investigated volunteers ($p < 0.1$, $p < 0.05$ marked with (*)). Selected examples of significant associations ($p < 0.05$) are shown in Fig. 3. Overall, significant positive correlations of Glu levels were observed between PC and ACC and between PC and Ins as well as a trend towards positive correlation ($p < 0.1$) between Ins and ACC. A significant negative association of Glu and GABA levels were identified between ACC and Ins. A similar trend was seen for Glu in PC and GABA in Ins. Averaged overall subjects, the Glu/GM' ratios (Tab. 1) revealed significant interregional differences between ACC, Ins and PC ($p < 0.05$), respectively. Moreover, GABA/GM' showed significant higher values in Ins compared to ACC and PC while the GM' fractions was lower compared to the other regions.

**Discussion and Conclusion:** Our findings suggest interrelations between GABA and Glu concentrations in brain regions, which are known to reveal resting state functional connectivity under healthy conditions. In particular, the positive Glu associations between ACC, Ins and PC may indicate small scale synchrony of glutamatergic microcircuits regulating the interactions within the functional neuronal network. Interestingly, the observed negative correlations between Glu and GABA may reflect inhibitory insular regulation of glutamatergic inputs from ACC and PC, underlining the subtle interaction between inhibitory and excitatory neurotransmitters, also described as excitation-inhibition balance. Additionally, we detected significant differing Glu/GM' and GABA/GM' ratios in the examined brain regions, which may be ascribed to varying densities of excitatory and inhibitory neurons.

**Tab. 1** Mean and standard deviation values of GM', Glu/GM' and GABA/GM' in each brain region.

| | GM' | Glu/GM' | GABA/GM' |
|---|---|---|---|
| **ACC** | 0.67 ± 0.05 | 10.5 ± 1.5 | 1.2 ± 0.2 |
| **Ins** | 0.53 ± 0.05 | 11.8 ± 1.3 | 1.7 ± 0.2 |
| **PC** | 0.70 ± 0.04 | 8.9 ± 1.0 | 1.3 ± 0.2 |

**References:** 1. Harris RE, et al. Neurosci. Lett. 2012; 520:192–196. 2. Maddock R, et al. Curr. Top. Behav. Neurosci. 2012. 3. Gorka SM, et al. J Psychopharmacol. 2014; 1-10 4. Taylor KS, et al. Hum. Brain Mapp. 2009; 30:2731–2745. 5. Provencher SW. NMR Biomed. 2001; 14 (4):260–264. 6. Stefan D, et al. Meas. Sci. Technol. 2009; 20 (10):104035.

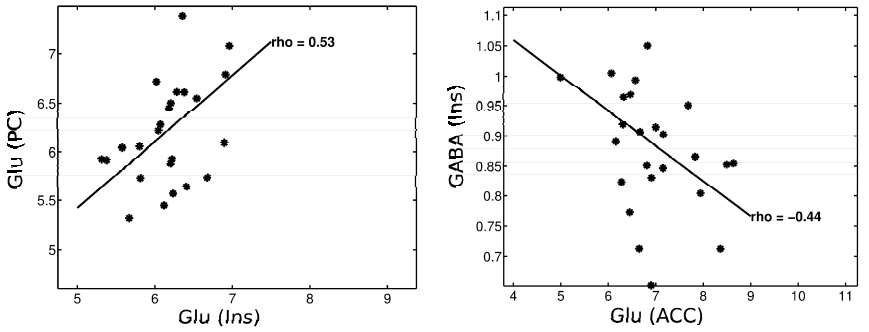


**Fig. 3** Representative Glu and GABA distributions showing a significant positive correlation between Glu in PC and Glu in Ins (left) and negative correlation between GABA in Ins and Glu in ACC (right).