Towards metabolic profiling of the neurocircuitry of mood: small-voxel, non-water-suppressed ^{1}H-MRS in the nucleus accumbens, amygdala and cingulate cortex at 3T

Andreas Hock[1,2], Niklaus Zoelch[1], Milan Scheidegger[1,2], Marcus Herdener[2], Erich Seifritz[2], and Anke Henning[1,3]

[1]*Institute for Biomedical Engineering, University and ETH Zurich, Zurich, Zurich, Switzerland,* [2]*Department of Psychiatry, Psychotherapy and Psychosomatics Hospital of Psychiatry, University of Zurich, Zurich, Zurich, Switzerland,* [3]*Institute for Biological Cybernetics, Max Planck Institute, Tuebingen, Baden Württemberg, Germany*

Introduction: Proton magnetic resonance spectroscopy (^{1}H-MRS) provides non-invasive insight into brain metabolism to better understand brain function and related pathological processes. However, because of the intrinsic low sensitivity of the method (about 10 000 times lower than MR imaging) the spatial sensitivity is restricted; therefore large volumes of interest (typically 3-30 ml) are needed to obtain a sufficient signal to noise ratio (SNR). Especially in neuropsychiatric disorders, findings obtained with complementary methods (e.g. positron emission tomography (PET), fMRI, animal models) revealed considerable region specific alterations of brain function and metabolism which cannot be investigated with expansive voxels. Thus, MRS methods allowing high quality measurements of small but clinically relevant brain regions such as the nucleus accumbens or the amygdala are needed.

The aim of this investigation was to enable MRS measurements in small (about 1.3 ml), specific human brain regions. For this purpose, non-water suppressed MRS via the metabolite cycling technique (1,2) was used enabling frequency and phase alignment of individual FIDs prior to averaging using the high SNR of the water peak. This allows for constructive averaging which increases the resulting SNR and reduces the line width of the spectra.

Methods: With the approval of the local ethics committee, non-water suppressed PRESS (1,2) localization combined with inner-volume saturation (3 T Achieva, Philips Healthcare, Best, TE/TR = 33/2500 ms, 512 averages/volunteer, 2000 Hz band width) was performed in 16 healthy volunteers (11 female; average weight: 67.8±11 kg, average age: 29.6±7 years). MRS spectra were obtained from three specific regions of interest with high clinical relevance for neuropsychiatric disorders such as the bilateral dorsal anterior cingulate cortex (dACC; voxel size = 23.6x11.2x8.6 mm), the left nucleus accumbens (NAcc; voxel size = 10.2x19.0x8.6 mm), and the left amygdala (AMG; voxel size = 10.0x11.6x8.6 mm) as well as an additional control region in the left occipital cortex (OCC; voxel size = 17.8x11.2x8.6 mm). Individual and averaged group spectra were quantified similar to ref. (2). Metabolite concentrations ratios to Cr based on fitting results (LC Model (3)) with Cramer-Rao lower bounds (CRLBs) lower than 25% were considered as reliable. To further explore the potential of the method metabolites with CRLBs between 25% and 50% are also considered for the quantitative analysis.

Results: Group average spectra (n = 16), LCModel fit, and the fit-residual of the four brain regions (Fig. 1) indicate good spectral quality (mean SNR: OCC = 44, NAcc = 43, AMG = 29, dACC = 69, mean line width: OCC = 2.9 Hz, NAcc = 5.8 Hz, AMG = 3.9 Hz, dACC = 3.9 Hz). In addition, mean metabolite concentration ratios and standard deviations over creatine derived from quantitative analysis of spectra from all individual volunteers are compared to the concentration ratios of the group average spectra for all four brain regions as shown in Fig 2. Creatine (Cr), N-acetyl-aspartate (NAA), glutamate (Glu) and the combination of Glu and glutamine (Glx), choline (Cho) and myo-inositol (mI) could be quantified reliably in all group average spectra and in the vast majority of the individual data sets. Mean metabolite concentrations obtained from individual spectra are in good accordance with those obtained from group average spectra. Depending on the specific brain region, the group analysis enables quantification of additional metabolites such as glutathione (GSH), aspartate (Asp) and scyllo-inositol (sI).

Discussion: Considering the small voxel size, the proposed method allows the detection of metabolite markers in specific brain areas with high data quality. In particular, the narrow line width is a consequence of the small voxel size in combination with phase correction and frequency alignment prior to averaging. Hence metabolic profiling of small brain regions with high relevance for neuropsychiatric disorders at 3T becomes feasible and complements already established molecular imaging methods. For instance, specific regional differences in metabolite concentrations such as higher glutamate (Glu/Glx) levels in the dACC compared to AMG, NAcc and OCC converge with complementary evidence from PET studies highlighting regional differences in glutamatergic receptor densities (4). Such region-specific metabolic indices could promote better understanding of the role of possible dysfunctions of brain metabolism and neurotransmission in neuropsychiatric disorders.

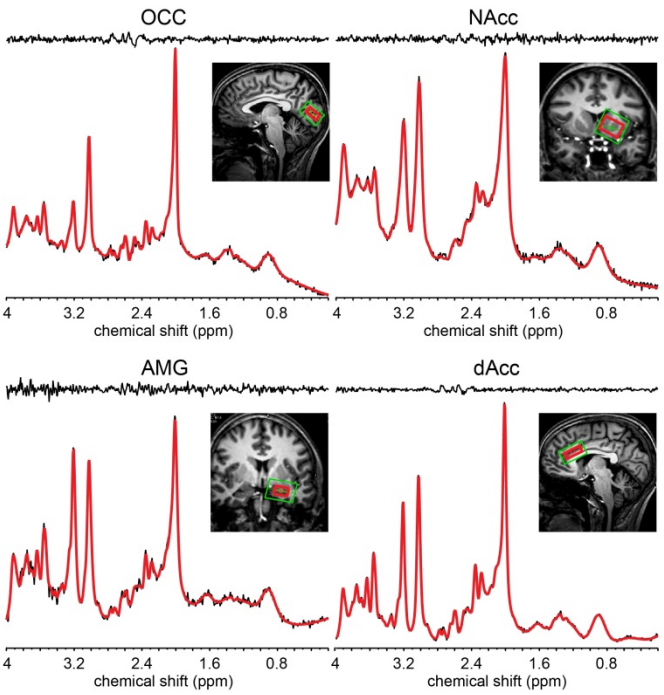

Fig. 1: Group average spectra, LCModel fit, and the fit-residual of the four brain regions.

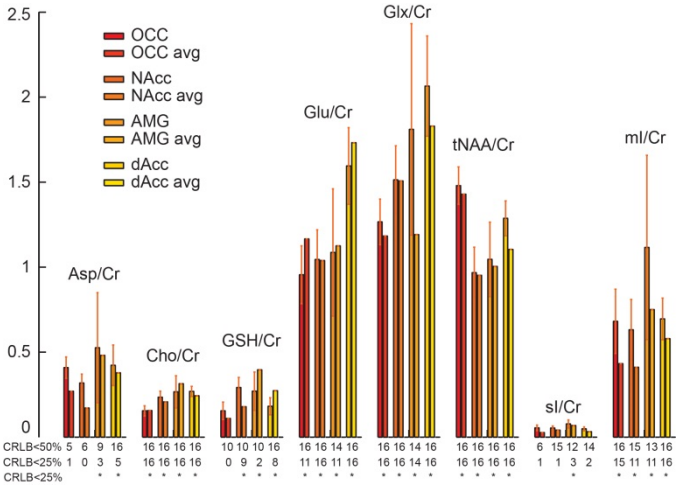

Fig. 2: Mean metabolite concentration ratios and standard deviations over creatine derived from quantitative analysis of spectra from all individual volunteers are compared to the concentration ratios of the group average spectra for all four brain regions. Numbers below each bar indicate the number of valid fitted data sets (CRLBs<25% and CRLBs < 50%) for the specific metabolite in the individual spectra and asterisks indicate reliable quantification in the group average spectra.

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