NMR-BASED METABOLIC PHENOTYPING OF A RODENT ALZHEIMER´S DISEASE MODEL

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BACKGROUND

- Alzheimer's Disease (AD) is a severe neurodegenerative disorder which currently affects more than 27 million people worldwide.
- To investigate Alzheimer-related pathophysiology, several transgenic mouse and rat lines have been established in recent years.
- Despite their general applicability in basic and applied research, quantitative tools to monitor pathophysiology as well as associated rewiring of metabolic pathways on a systemic level are lacking.

AIM

- Use nuclear magnetic resonance (NMR) spectroscopy-based metabolic phenotyping to provide a quantitative basis for investigation of Alzheimer-related pathophysiology.

MATERIALS AND METHODS

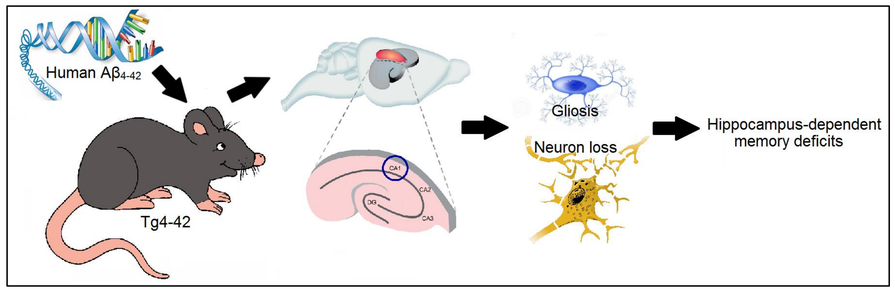


Figure 1: TBA83 transgenic, male mice which overexpress human amyloid beta 4-42 were investigated at the age of 6 months in this study. This model shows neuron loss and gliosis mainly in the CA1 (Cornu Ammonis) region of the hippocampus.

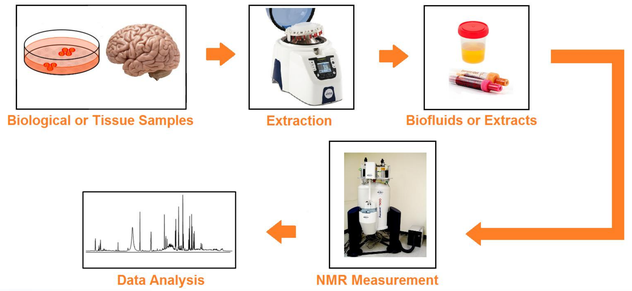
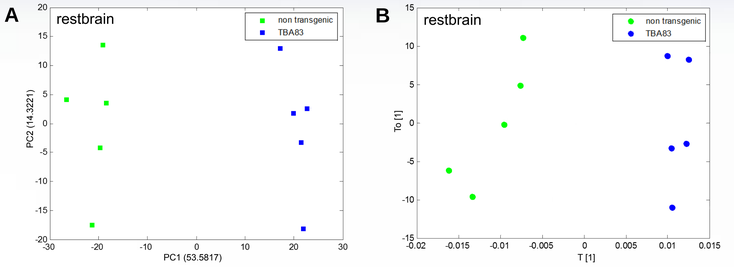


Figure 2: To define a metabolite biomarker panel, metabolites were extracted from brain tissues like cortex, hippocampus and restbrain. For the tissues a soft homogenisation with a Precellys system was performed. Serum or other biofluids can be used directly. The measurement was done with a 500MHz NMR spectrometer using an untargeted approach. As the last step, data analysis was prepared using statistical tools (PCA, OPLS-DA).

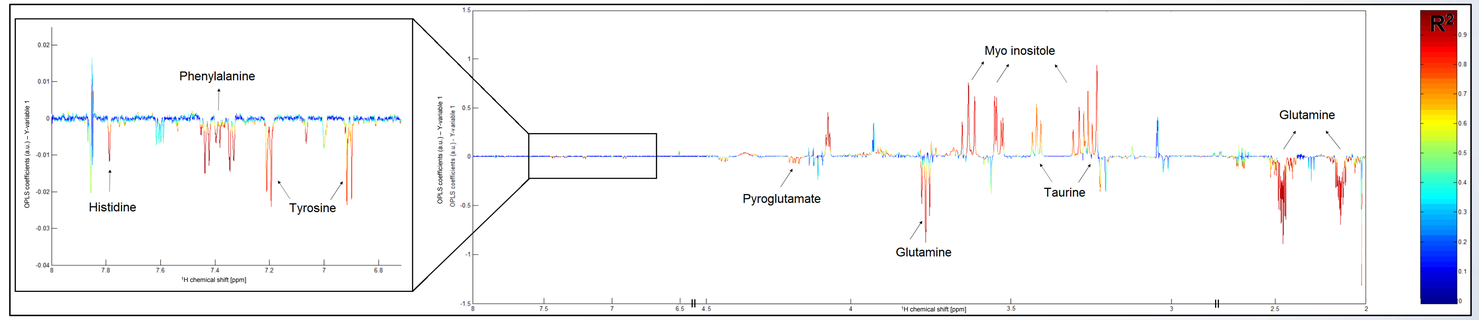
RESULTS

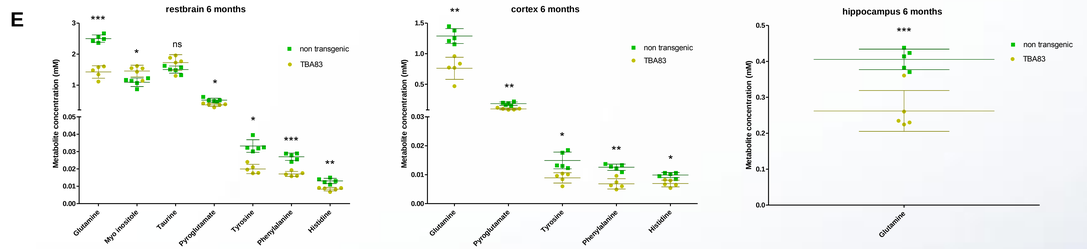
- A biomarker panel with significantly altered metabolites was determined in different brain tissue regions (restbrain, cortex, hippocampus).



C

restbrain	Glutamine	**decreased**
	Tyrosine	**decreased**
	Phenylalanine	**decreased**
	Histidine	**decreased**
	Pyroglutamate	**decreased**
	Myo inositole	**increased**
	Taurine	**increased**
cortex	Glutamine	**decreased**
	Tyrosine	**decreased**
	Phenylalanine	**decreased**
	Histidine	**decreased**
	Pyroglutamate	**decreased**
hippocampus	Glutamine	**decreased**





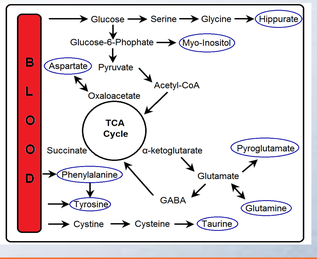


Figure 3: **(A)** PCA scores plot. **(B)** OPLS-DA cross-validated scores. **(C)** Overview of changed metabolites in different tissue regions. **(D)** Reduced spectra shows different significant altered metabolites in the restbrain of five TBA83 mice compared to non-transgenic controls. **(E)** The absolute concentration of each metabolite was determined and corrected to tissue weights. Statistical analyses (Unpaired t-test) revealed significant differences of metabolites between the TBA83 homozygous and the non transgenic animal groups. Adjusting the false discovery rate for multiple comparisons, Benjamini-Hochberg procedure was used for p-value correction. The false discovery rate was set to 0.05. * p-value <0.05, ** p-value <0.01, *** p-value <0.001. **(F)** Overview of the metabolic pathways.

CONCLUSION

- Using NMR-based metabolic phenotyping we defined a quantitative readout of transgenic animal models in the form of a biomarker panel.
- These biomarkers not only contribute to the understanding of this devastating neurodegenerative disease and the related pathophysiological processes on a systemic level, but set the base for a wide range of biomedical applications.
- This approach can be easily extended to other tissues, matrices, or disease models and translated across species.

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AAIC 2017, P2-07-229, Poster: #16959