BACKGROUND
- Alzheimer’s Disease (AD) is a severe neurodegenerative disorder with progressive loss of memory and cognitive functions.
- 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 an integrative approach – behavioral tests, immunofluorescence and untargeted nuclear magnetic resonance (NMR) based metabolic phenotyping to get a better understanding of (patho-)physiological alterations in complex biological networks involved in AD.

MATERIALS AND METHODS
- Tg4-42 and Wild-type mice of different ages were tested in the Morris water maze test to receive read-outs of the disease related to spatial learning and memory.
- Neuroinflammation and plaque load were analyzed by immunofluorescent labeling with GFAP, Iba-1 and Aβ1-42 antibodies, respectively.
- Untargeted NMR spectroscopy to monitor perturbations in a large pool of metabolites related to spatial learning and memory.

RESULTS
- Behavioral test
  - Escape latency

- NMR-based metabolic phenotyping

CONCLUSION
- The combination of different methods is important to link change in biomarkers and the associated dysregulation of metabolic pathways with changes in neuropathology and behavior.

This integrative approach (behavioral studies, immunofluorescence, NMR-based metabolic phenotyping) not only contributes to the understanding of this devastating neurodegenerative disease and the related pathophysiological processes on a systemic level, but sets the base for a wide range of biomedical applications. It can be easily extended to other tissues, matrices, or disease models and translated across species.

Figure 1: NMR-based metabolic phenotyping

Figure 2: Morris water maze test

Figure 3: Immunofluorescent labeling

Figure 4: NMR-based metabolic phenotyping

Brain tissue was labeled with amyloid beta 1-42, GFAP to determine astroglia, Iba-1 for microgliosis and DAPI nuclear staining in non transgenic (NTG) and Tg4-42 transgenic mouse (TG). Astroglia was found in this region of the Tg4-42 transgenic animals. Furthermore the CA1 cell layer is thinner in Tg4-42 transgenic mice compared to non-transgenic controls.

Statistics
- Statistical analyses (Unpaired t-test) revealed significant differences of metabolites between the Tg4-42 homozygous and the non transgenic animal groups. Adjusting the false discovery rate for multiple comparisons, Bonferroni-corrected p values were used for pairwise comparisons. The false discovery rate was set to 0.05.
- p <0.05, **p<0.01, ***p<0.001.

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