**INTRODUCTION**

- PET-MRI benefits from the complementary information provided by the two modalities, setting the stage for truly novel imaging approaches that are currently being explored, such as the use of dual-modality tracers, the concept of motion effects in PET based on real-time MR information, and advanced MRI techniques that complement PET.1
- Krabbe Disease is a rare genetic disorder leading to demyelination and death of affected child within years of birth. Hematopoietic stem cell transplantation (HCST), the only treatment available, leaves us with very limited opportunities to diagnose the disease at an early stage.
- Preclinical PET-MRI is only gradually leaving the proof-of-concept stage, which may be explained by technical difficulties due to the size-constraints (bore diameter of often <30 cm) and the particularly high magnetic field strength needed for preclinical MRI (>7T).
- In this study, we present initial results of a first in vivo application of 18F-Fluorodeoxyglucose (FDG). PET-MRI at 9.4 Tesla in the Twitch mouse model of Krabbe disease, in which an altered pre-symptomatic glucose metabolism had been suggested by metabolomics.2

**PET-MRI SETUP**

The employed prototype PET detector ring was provided by SynchroPET, Inc. (Stony Brook, NY).3 It is comprised of 12 radially oriented scintillator crystals (LYSO, 18.5x9.6x9mm3, 4x8 pixels) and avalanche photodiodes (APD, 415V) resulting in 44cm/39mm inner/outer shell diameters and a depth of 25mm. We used a 20 cm diameter horizontal-core 9.4 Tesla magnet (Biopac 9420 USR, Bruker Biospin) equipped with a standard imaging gradient coil (inner diameter 11.4cm), and a quadrature volume transceiver coil (inner/outer diameter 23/44mm). An in-house built modular holder was used for the PET camera, RF coil, and anesthesia/monitoring equipment as shown in Fig. 1.

**EXPERIMENTAL DESIGN**

- The local radiation safety committee approved the experimental setup. In this study, we present initial results of a first in vivo application of 18F-Fluorodeoxyglucose (FDG). PET-MRI at 9.4 Tesla in the Twitch mouse model of Krabbe disease, in which an altered pre-symptomatic glucose metabolism had been suggested by metabolomics.2
- We injected the mice at postnatal (P) day 15 (P15; pre-symptomatic), P21 (just prior to first symptoms), and P28 (symptomatic and with moderate symptoms) with 100mg of 18F-FDG, 250±59μCi. After 20 minutes of awake uptake time under a heat lamp, mice were anesthetized with isoflurane and positioned on the animal bed in the magnet room.
- PET scanning started 30 minutes after the injection and continued for up to 60 minutes. Simultaneously, we acquired axial T2-RARE and T1-RARE images with MRI.

**RESULTS**

Two mice and one wild type did not survive the experiments or their data did not pass quality control at P21 and P28, respectively. Figure 4 shows the group average whole-brain FDG uptake. Both wt (p<0.01) and Twi (p<0.02) showed significantly decreasing FDG uptake from P15 to P21, which then stabilized (p>0.2). Whole brain uptake was similar between groups at all time points (p>0.2).

Figure 5 summarizes the regional analyses. The highest uptake was seen in both groups at P15 in the Thalamus and in the olfactory lobes in P21 and P28. Uptake was not significantly different in any of the regions between groups at P15 and P28 (p>0.12). Differences reached significance at P21 in the cortex (p<0.02), where it was reduced in Twi compared to wt.

**IMAGE RECONSTRUCTION AND CO-REGISTRATION**

We reconstructed PET images every 60 seconds on a 0.245x0.245x0.293mm3 grid using an iterative 3D maximum likelihood-expectation maximization (MLEM) algorithm with 3D spline-based spatial filtering. PET image intensities were decay-corrected to the injection time, augmented with animal body weight, and normalized relative to the injected dose.

Corrected PET images were fully automatically registered to the T2-RARE images based on a separate coordinate-system calibration experiment (Fig. 2a).

**SPATIAL NORMALIZATION**

We normalized the T2 images to a custom template (Fig. 2b) calculated from all T2 scans with ANTs, and applied the resulting deformation fields to the T2-registered PET images. A subsequent iterative rigid-body registration of all PET images to the cohort-average mitigated the impact of detector positioning inaccuracies.

**ATLAS-BASED ANALYSIS**

We registered the Brookhaven National Laboratory (BNI) C57BL Mouse Atlas to the custom T2 template using ANTs (Fig. 3) and assessed the average regional FDG uptake in major brain regions and in the whole brain.

**DISCUSSION AND CONCLUSION**

- We have demonstrated the feasibility of in vivo longitudinal PET-MRI at 9.4T to quantify regional glucose metabolism in mouse pups and during maturation. MRI enabled non-invasive analysis of brain PET images via spatial normalization.
- The highly similar glucose uptake patterns at P15 for both groups demonstrated the reproducibility and stability of the experimental setup. Twi animals showed decreased uptake at P21 but differences reached significance only in the cortex. These results are in line with a previously suggested disturbance of glucose metabolism in Krabbe disease.3
- Limitation of our study is the small number of animals and differences in body weight between groups (in particular at P28) that render the commonly-used mass-based normalization of uptake values problematic. Twi and wt animals did not differ significantly in weight at P15 (p=0.05; Twi: 5.61±0.38g, wt: 5.61±0.40g), but at P21 (p>0.018; Twi: 7.62±0.79g, wt: 8.49±1.47g) and P28 (p=0.001; Twi: 9.00±0.70g, wt: 13.6±2.2g).
- The effect of body weight differences will have to be studied in more detail. A more detailed statistical analysis may exploit the longitudinal nature of the data and account for differences in baseline blood glucose levels.

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