Longitudinal [^{18}F]FDG PET-MRI at 9.4 Tesla in Twitcher mice using spatial normalization

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***Abstract*— This study presents preliminary results on the feasibility of truly simultaneous PET-MRI in live mice on a conventional 9.4T MRI system retrofitted with a miniature-PET ring. Wild-type and Twitcher mice, a model of Krabbe disease, were anaesthetized and imaged longitudinally at four time points. Simultaneously acquired MRI images allowed the generation of a model-specific brain template for voxel and atlas based analyses of the PET scans. Preliminary findings were in line with previous results from metabolomics suggestive of alterations in brain glucose metabolism in Twitcher mice. A brain region-specific analyses based on segmented MRI scans will allow the quantification and statistical analysis of the glucose uptake.**

***Index Terms*—MRI, PET, small animal**

I. INTRODUCTION

The prospective of the simultaneous imaging with Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) lies in the ability to enrich the molecular PET information with MR imaging metrics that cannot be obtained merely by serial PET and MR imaging. This capability of PET-MRI is increasingly being recognized in the *clinical* setting. Preclinical PET-MRI, on the other hand, is only slowly leaving the proof-of-concept stage, which may be explained by technical difficulties due to the size-constraints (bore diameter of often <20 cm) and the magnetic field strength needed for preclinical MRI. Ultra-high magnetic field (>7T) PET-MRI in rodents with advanced MRI techniques such as MR spectroscopy or diffusion tracking (DTI) bears the potential to have a high impact on translational research because it would set the stage for entirely new approaches to drug development and disease mechanism elucidation.

We have previously presented an integration setup for retrofitting a micro-PET detector into a commercial 9.4T magnet with a 20cm bore. In the present work, we present initial results of a first *in vivo* application of ^{18}F-Fludeoxyglucose (FDG) PET-MRI at 9.4T in the Twitcher mouse model of Krabbe disease, in which an altered pre-symptomatic glucose metabolism had been suggested by metabolomics [1].

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II. METHODS

A. PET-MRI setup:

The employed prototype PET detector ring (SynchroPET, Inc.; Stony Brook, NY) has been presented at the PSMR in 2016 [2]. In brief, it comprised of 12 radially oriented scintillator crystals (LYSO, 18.5x9.6x6mm^3, 4x8 pixels) and avalanche photodiodes (APD, 415V) resulting in 44mm/80mm inner/outer shell diameters and a depth of 25mm (Fig. 1b). We used a 20 cm diameter horizontal-bore 9.4 Tesla magnet (Biospec 94/20 USR, Bruker Biospin) equipped with a standard imaging gradient coil (Fig. 1a). A custom modular holder was used for the PETcamera, RF coil, and anesthesia/monitoring equipment (Fig. 1c)

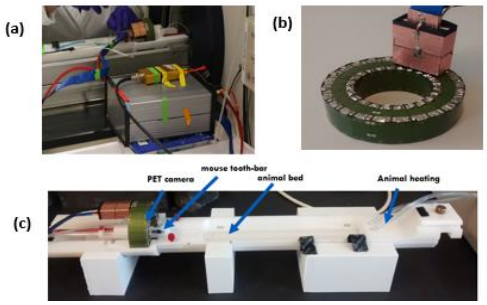

Figure 1: Overview of the modular experimental setup for simultaneous PET-MRI at 9.4 Tesla. (a) Animal bed with installed miniature PET detector in front of the magnet bore during animal positioning. (b) PET detector with the electromagnetic shield in green. (c) Custom 3D printed modular integration set up of the PET ring.

B. Experiments:

The local radiation safety committee approved the experimental procedures, and all procedures involving animals were performed according to the guidelines of Institutional Animal Care and Use Committee (IACUC). Twitcher mice (Twi) were maintained on the background of C57BL/6N purchased from Charles River Laboratories (Kingston, PA). We injected the mice at postnatal (P) day 15 (P15; pre-symptomatic), P21 (first symptoms), P28 (structural and behavioral changes), and P41 (full signs of disease) with 100µCi to 200µCi of ^{18}F-FDG, depending on body weight. 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 was 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. We enrolled 10 Twi and 10 wild-type (wt) animals at P15 and performed

serial imaging on 7 animals of each group longitudinally through P28. 3 Twi and 2 wt were imaged at P40.

C. PET-MRI co-registration:

We reconstructed PET images every 60 seconds on a 0.24x0.24x0.29mm^3 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.

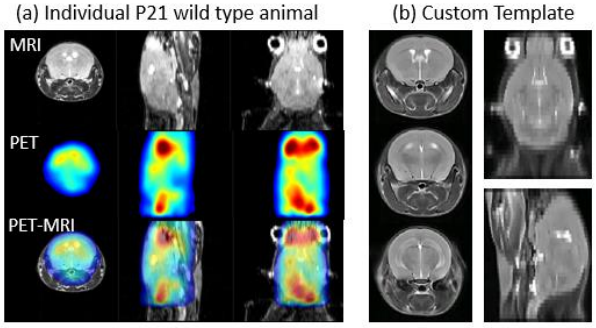

Fig. 2 (a) T2 weighted MRI, PET, PET overlayed on MRI. (b) Sagittal, coronal and three axial views of a common template generated iteratively using T2 weighted images.

D. Spatial Normalization:

Using the T2-MRI (Fig. 2(a)). scans, we iteratively computed a common template with ANTS. Individual T2-images were normalized to the template (Fig. 2(b)). and resulting deformation fields were applied to the MRI-registered PET images. Also, shown in the (Fig. 2(a)). is individual PET and PET image overlayed on MRI.

III. RESULTS

Spatially normalized group-average FDG uptake of wt animals showed highest glucose uptake at P15 and decreasing uptake with increasing age (Fig. 3). Between groups (Fig. 4). uptake was most similar at P15, and decreased faster in Twi animals compared to wt in different localized regions of the brain with disease progression.

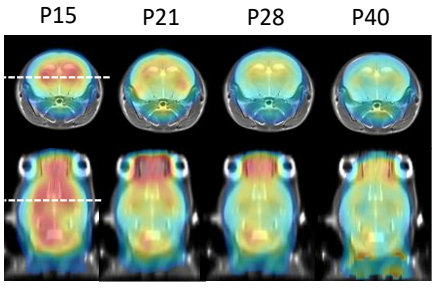

Fig. 3. Axial and coronal views of the group average of wt animals at the four time points, P15, P21, P28, and P40. Same color bar range used in all panels. The dashed white lines indicate the anatomical locations of the shown slices.

IV. DISCUSSION AND CONCLUSION

We have demonstrated the feasibility of *in vivo* longitudinal PET-MRI at 9.4T to quantify regional glucose metabolism in the Twitcher mouse model. MRI enabled a voxel based analysis (VBA) of PET images via brain normalization. The highly similar glucose uptake patterns at P15 for both groups demonstrated the reproducibility and stability of the experimental setup.

Decreasing glucose uptake with age in wt animals is consistent with previous reports of decreasing uptake during the transition from adolescence to adulthood [4]. Differences between the groups showed a high spatial and temporal variability in the symptomatic disease stage (>P15) with overall decreased uptake in Twi at P28 and increased uptake at P40. A voxel based general linear model analysis will quantify the differences between groups and time points.

Overall, our observations are in line with a previously suggested disturbance of glucose metabolism in Krabbe disease [1].

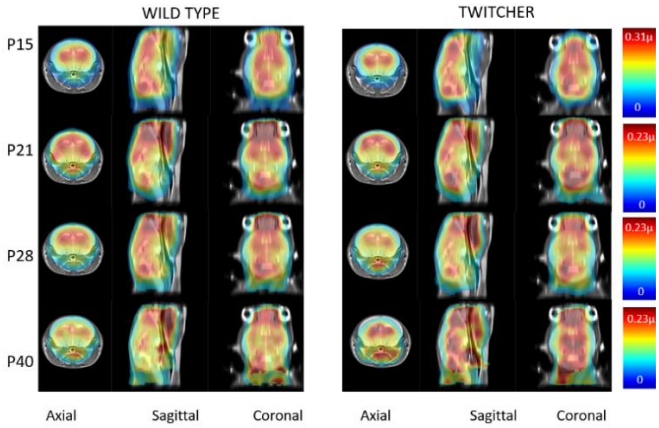

Fig. 4. Axial, sagittal and coronal views of the group average FDG uptake in wt and Twi animals at the four time points. Note the different color bar ranges at each time point!

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