DYT1 Dystonia of Mice and Men
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Introduction
Dystonia is a neurological disease characterized by sustained involuntary muscle contractions [1]. Previous studies using positron emission tomography (PET) and magnetic resonance diffusion tensor imaging (DTI) showed metabolic abnormalities in the cerebellum and basal ganglia dystonia patients with DYT1 mutation [2] and implicated the cerebello-thalamo-cortical pathway [3,4]. Here, we studied genetically engineered mice in which human DYT1 mutation has been “knocked in” to endogeneous mouse allele [5], and report metabolic and diffusion abnormalities that are similar to the published human studies. Our study can be considered a reverse translation study from human to mice that explores changes linked to genetic nature of dystonia.

Subjects and Methods
We studied 8 DYT1 heterozygous mice and 6 littermate controls (12 weeks of age) using in vivo 3Tesla MRI, FDG microPET and ex vivo 9.4 Tesla MR DTI. In vivo MRI protocol included T1 and T2w imaging. In T2w imaging image resolution was 0.125mm x 0.125mm x 1mm, TR 4.8 s, TE 100ms, 8 NEX; in T1w imaging, image resolution was 0.156mm x 0.156mm x 0.2mm, TE 2ms, TR 7.8 ms, 6 NEX. The microPET image acquisition parameters included a matrix size of 128x128x95 with a voxel size of 0.949mm x 0.949mm x 0.796mm. After in vivo imaging the mice brains were perfusion fixed and later scanned ex vivo. 3D volumetric image sets of ex vivo diffusion weighted images were acquired in 6 directions. The minimum b-value was 210 s/mm² and the maximum b-value was 2138 s/mm². The DTI matrix was 136x84x64 which was zerofilled to 272x168x128. The FOV was 17mm x 10.5mm x 8mm. The nominal resolution was 62.5µm x 62.5µm x 62.5µm with a total imaging time of approximately 20 hours. After data acquisition, FA and ADC maps were calculated. A 9-parameter affine registration was applied to each mouse brain to bring it to a common space using SPM Mouse [6]. Micro PET images were processed as in [7].

Results
Metabolic group differences in DYT1 mice when compared to normal littermates with microPET images are shown in Fig. 1 top row. Bottom row shows published metabolic abnormalities from human subjects [2]. In figure 2, left column shows the FA decreases in DYT1 mice group when compared to controls. In the right column published FA decreases in human DYT1 subjects [3] are shown. The correlation between striatal and cerebellar metabolic abnormalities in DYT1 mice are plotted in Fig. 3 below.

Discussion/Conclusions
In this translational study, we compared changes in mouse “genecopy” of DYT1 dystonia with their wild type littermate controls using microPET and MR DTI images. Notably these mice express the disease protein at normal levels and with normal profile unlike classical transgenic mice. Our results show that there are significant group differences between DYT1 mice and controls. We found that DYT1 mice exhibit metabolic and FA abnormalities that resemble the DYT1 patients. The correlation between striatum and cerebellum metabolic activity and the correlation between the metabolic activity and the FA abnormalities are also shown.

References: