# A Parkinson's disease $^{31}$P-MRSI study at 7T

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**TARGET AUDIENCE–**Clinicians interested in neurodegenerative disorders, spectroscopy physicists, neuroscientists.

**PURPOSE–**One of the pathological changes in Parkinson's Disease (PD) is the loss of dopaminergic neurons in the substantia nigra (SN), believed to be related to impaired mitochondrial function. Phosphorus spectroscopy imaging ($^{31}$P-MRSI) allows *in-vivo* measurement of energy and phospholipid metabolism with signals from phosphocreatine (PCr), inorganic phosphate (Pi), and gammaATP (γATP) among other metabolites, thus offering a marker of mitochondrial activity. Published reports on these measures are limited to putamen (PUT) differences [1] (but not SN) and sex differences (but not group) [2,3]. Here we aim to revisit the mitochondrial metabolism by exploring the stability of the data, and the effects of age and sex on these measures. This is the first step towards the use of 7T $^{31}$P-MRSI as a biomarker for Parkinson's disease.

**METHODS–** Twenty-two subjects (8 healthy volunteers (HV), 8 sporadic PD patients, 4 patients with early parkinsonism presentation (ePP) -not meeting diagnostic criteria for PD-, 1 patient with scan without evidence of dopaminergic deficit -SWEDD- and 1 young onset PD) participated in a $^{31}$P MRSI study conducted in an active-shielded 7T whole body MR system (Magnetom 7T, Siemens Healthcare, Erlangen) using a dual-transmit-receive coil assembly of a $^{1}$H and $^{31}$P birdcage coil (Quality Electrodynamic LLC, Mayfield Village, Ohio, USA). Thirteen of them repeated the exam one year later (±1.5 months). After a quick localizer, anatomical imaging was performed using MPRAGE with 1mm isotropic resolution. After shimming, the $^{31}$P RF power level was calibrated for each volunteer as previously described by Scheenen et al [4]. 3D $^{31}$P-MRSI with a spatial resolution of 17.28 cc (FOV=200 x 180 x 180 mm$^3$, matrix=12 x 12 x 12) was acquired with Nuclear Overhanser Enhancement (NOE) (rectangular, count 10, duration 98 ms, pause 2000ms, flip angle 90, hard pulse excitation 300ms) and TR 1550ms, TE 0.1ms, flip angle 45, avg time 4, for a total scan time of ~21 min. Data processing was performed using JMRUI software [5]. After apodization (20 Hz Gaussian), seven peaks (PE, PC, GPE, GPC, Pi, PCr and gamma ATP) were estimated using the AMARES algorithm. PCr line width was determined by the AMARES algorithm; line widths for low energy peaks were matched to PCr. All peak shapes were set as Gaussian. Zero order phase was estimated from -180.0 to -90.0 deg with a starting value of -156.0 deg. The output file from AMARES was then converted to a nifti volume using custom Matlab scripts. Using header information from the MRSI and MPRAGE, AMARES data were overlaid with MPRAGE volume and up-sampled to 1mm. AFNI [6] was used to define four regions-of-interest in bilateral SN and PUT, based on Freesurfer segmentation [7]. Statistical tests were performed in R [8]. First, we correlated right and left results for each area, and averaged them if highly correlated. Second, we evaluated the two measures for each subject to find the metabolite with higher correlation. Third, for each area, we performed an ANOVA for group, using sex and age as covariates. Lastly, we compared the values of the SWEDD and young onset PD with the PD population.

**RESULTS –** Inter-hemispheric values where highly correlated for all metabolites (r>0.72) therefore, right and left hemisphere data were averaged for subsequent analyses. γATP showed a correlation >0.8 for both SN and PUT, PCr correlations were >0.6, while Pi showed the larger variability (SN: -0.03, PUT: 0.5). SN-γATP data showed an effect of group (p=0.013) (fig a), sex (p=0.049), age (p=0.015) (fig b), and a strong interaction of group-by-age (p=0.007). Values in putamen only showed a significant effect of sex (p=0.014) and a trend for age (p=0.08). These results hold when performing the analysis including only HVs and PDs. Note that the SWEED and young onset PD patient can be distinguished in the figure. The younger subject has a low SN-γATP value for age. The SWEDD patient has a large value for age.

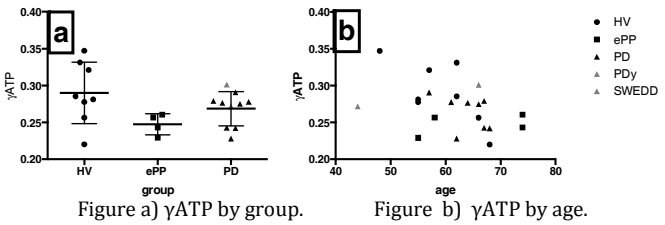


Figure a) γATP by group. Figure b) γATP by age.

**DISCUSSION–**

Our results explain the discrepancies observed in the literature. Taking into account sex and age, we found group differences. Previously reported negative results might be explained by heterogeneity of the PD population. Here, we were able to test two single cases, a young onset, and a SWEDD. It became apparent that those cases do not fit the distribution of the data. The low values seen in the early onset case might shed light into the different pathophysiology of these cases in comparison with sporadic PDs. The high value seen in the SWEDD needs to be validated on a larger sample, but suggest a non-invasive test for identifying these cases. Follow-up measures from this cohort and a larger number of subjects are underway to further establish the relationship between mitochondrial dysfunction and PD.

**CONCLUSION–**$^{31}$P MRSI measurement at 7T has the potential to become a relevant marker for the differential diagnosis of PD. In this pilot study, we were able to detect changes limited to the areas where histopathological abnormalities have been demonstrated. Larger populations and longitudinal studies will be needed to confirm this measure as a reliable biomarker.

**REFERENCES –**[1] Hattingen et al. Brain, 2009.[2] Weiduschat et al. J.Neuroimaging, 2013. [3] Weiduschat et al., Parkinsonism and Rel Dis, 2014. [4] Scheenen et al. ISMRM 2013. 4489. [5] Stefan, D., et al. Quantitation of magnetic resonance spectroscopy signals: the jMRUI software package. Measurement Science and Technology 20:104035, 2009. [6] Cox et al 1996. http://afni.nimh.nih.gov. [7] Freesurfer.net. [8] http://www.r-project.org.