Assessment of iron distribution in Hallevorden-Spatz Syndrome using phase imaging and relaxation rate measurements.

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Introduction:
Pantothenate kinase-associated neurodegeneration (PKAN), also called Hallervorden-Spatz Syndrome is an autosomal recessive disorder characterized by dystonia, parkinsonism and an excessive iron accumulation in basal ganglia. No therapy for PKAN is available at this time, however it is believed that characterization of iron deposition will help to explicate pathogenesis, track disease progression and monitor treatment effects. The typical MRI appearance in patients with PKAN is a bilaterally symmetrical hyperintense signal in anterior medial globus pallidus (GP) with surrounding hypointensity on T2w images. These imaging features are characteristic of PKAN and have been termed the "eye-of-the-tiger" (EoT) sign [1,2].
The presence of iron in the brain produces changes to the magnitude as well as the phase of MRI images . The methods based on magnitude changes include measurements of R1, R2, R2' and R2* relaxation times. The measurements of relaxation rate parameters demonstrate a degree of correlation with iron content in a healthy brain but their application as biomarkers of neurodegenerative disease state has not been supported by current data [3].
The aim of this study was to investigate iron accumulation and distribution within the GP in patients with PKAN using phase imaging and to compare sensitivity of phase imaging technique to relaxation rate measurements.

Methods and Results:
Brain MR images were acquired on a 3T Philips scanner. Eight PKAN patients and one healthy volunteer were imaged. Following localizer images, standard T1 and T2 scans in the axial and coronal planes with 256 x 192 resolution matrix, FOV = 20 cm and slice thickness 4 mm were collected. Relaxation parameters R1 and R2 have been extracted from the MIX sequence, provided by the vendor, that automatically generates T1 and T2 maps. R2* rates have been calculated using FFE double-echo gradient echo sequence with TE1=5ms and the TE2=25ms. Example images are presented in Fig.1. A,B. All images were acquired with the same spatial resolution.
The FFE image phase variations are affected by numerous background factors such as global magnetic field inhomogeneities, non-uniform RF penetration, magnetic field gradients from air-tissue interfaces and eddy currents. These effects must be eliminated or at least minimized before iron-related effects on phase images could be assessed. Our phase processing involved two steps. First, gradient-echo phase data was preprocessed using a region growing phase unwrapping algorithm [4]. Then, the remaining variations of the phase across an image were removed with the use of Hann filter with a 32 pixels window size. (Fig.1. C,D,E). As a metrics for iron accumulation we measured averaged phase gaps across left and right GP in all subjects [5]. Examples are shown in Fig1. E,F.
For relaxation rates analysis, GP structure has been divided into two segments: an Eye and a Rim. For calculation purposes the areas of interest have been manually traced on images and the relaxation rate distributions have been measured from data histograms in an Eye and a Rim segments of GP (Fig. 2.A-E)

A B C D E F

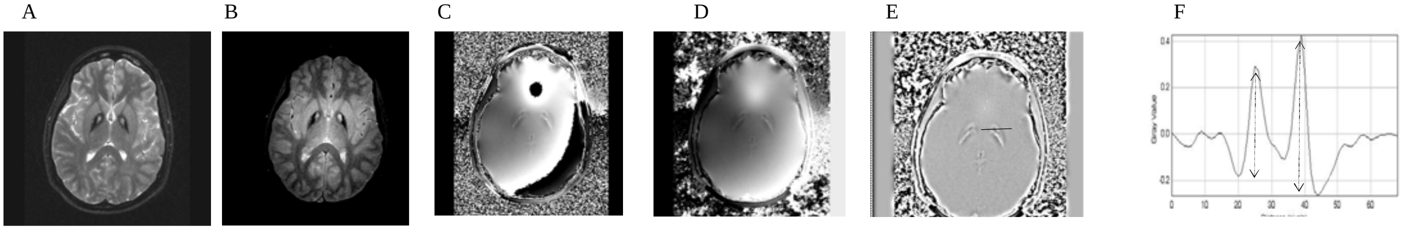

Fig.1. A representative set of axial brain images at a GP level of a patient with PKAN. (A) T2w image with "eye-of-a-tiger" sign. (B) Gradient-echo image (TE 5ms) and its corresponding phase image (C). Phase image after phase unwrapping (D) and Hann window filtering (E). Profile of phase changes (in radians) across a GP region (black line in E) are shown in F. Measured phase gaps are indicated by arrows in (F).

A B C D E F

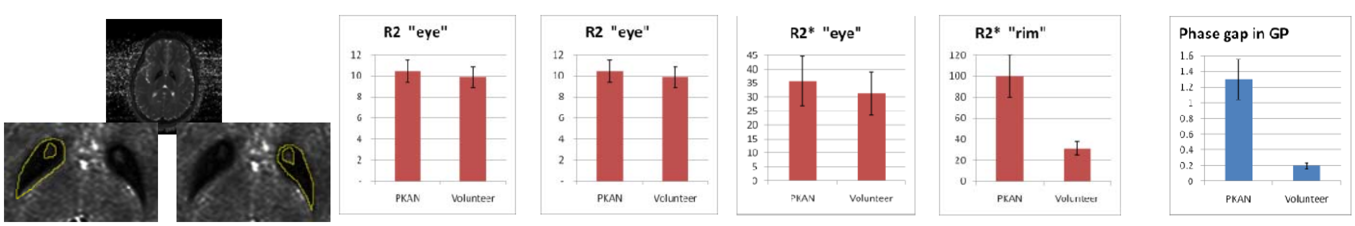

Fig. 2. GP segmentation (A) together with averaged R2 and R2* relaxation rates (in s^{-1}) (B-E) and averaged phase gap differences (in radians) (F) for PKAN patients (PKAN)) and a healthy volunteer (Volunteer). Note significantly increased sensitivity of phase gap measurements for iron detection compared to relaxation rates measurements (compare B through E versus F).

Conclusions and Discussion:
Our results of phase gaps and relaxation rate measurements in globus pallidus of PKAN patients indicate the following:
1. Iron accumulates non-uniformly in GP structure of PKAN patients with much higher concentration in the "rim" then in the "eye" of the GP.
2. Phase gap measurements have significantly higher sensitivity to iron accumulation then relaxation rates R1, R2 and R2* measurements. Among magnitude methods the R2* rate measurements (not surprisingly) are the most sensitive to iron accumulation. A ratio of R2* and a ratio of phase gaps between PKAN patients and a healthy volunteer were on average 3.1 : 1 and 6.5 : 1, respectively.
3. Up to an order of magnitude phase gap changes were measured between one PKAN patient and an age-matched healthy volunteer. Assuming that phase gap differences scale linearly with iron concentration we estimate that up to 2 mg Fe/g ww accumulates in globus pallidus of PKAN patients [6].

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