Introduction
Restless legs syndrome (RLS) is the most common disorder of movement and quiet wakefulness, with a prevalence in the general population between 3% and 9% (1). The pathophysiology of idiopathic RLS is poorly understood. Clinical and pharmacological observations point towards a central role for the dopaminergic system and iron metabolism (2). The potential role of iron metabolism involvement in RLS is indicated primarily by those secondary causes of RLS in which iron insufficiency is clear, but also from some limited pharmacological studies. Several studies showed a relation between low ferritin concentrations and symptoms of the syndrome, especially when ferritin was measured in the cerebrospinal fluid (CSF). Studies on CSF showed decreased ferritin, elevated transferrin and decreased pro-hepcidin (that interacts with the iron transport protein ferroportin on the surface of cells) in patients with RLS. Neuropathological data showed alterations of iron regulatory proteins in neuromelanin cells from brains of patients (2). Reduced brain iron in RLS patients is also suggested by the data of some MR studies that exploit the effect of iron on T2, T2* and T2', although with discrepant results (3-5). A recent technique that measures the phase shifts in gradient-echo images may be a sensitive tool to quantify the iron content of the brain (6). Tissue containing (paramagnetic) iron exhibits a negative phase in complex images compared to immediately adjacent tissue, which will have an increased phase. Our aim was to use phase imaging to study patients with idiopathic RLS.

Methods
11 RLS patients (age 54±11, mean ± SD) and 11 healthy volunteers (age 51±18) were studied in a 1.5 T General Electrics Medical Systems (Milwaukee, Wisconsin) Signa Horizon LX whole-body scanner equipped with a quadrature birdcage head coil. Diagnostic criteria of the International Restless Legs Syndrome Study Group (IRLSSG) were applied. The severity of RLS was assessed using the revised IRLSSG rating scale. Anatomical imaging was performed by a T2-weighted (T2W) FSE sequence in an axial oblique plane, using acquisition parameters: α=90º; echo time (TE): 107 ms; repetition time (TR): 5080 ms; square FOV: 24 cm; acq. matrix 320×256; reconstructed in-plane resolution: 0.938 mm; slice thickness; 4 mm w/o gap. # slices variable to cover whole head. NEX: 2. Phase-sensitized images were acquired using a gradient echo sequence, and preserving both real and imaginary channels. Slice locations matched those of the anatomical scan, excluding slices above the central corpus callosum, and below the dentate nucleus. Acquisition parameters: TE/TR: 40/60 ms; acq. matrix 512×256; reconstructed in-plane resolution: 0.938 mm; NEX: 2; bandwidth 15.6 kHz; maximum acq. time 7‘06”.

In the whole brain analysis, RLS patients showed lower phase dispersion, characterized by 10th and 90th percentile values of significantly smaller magnitude than in controls (p<0.01), while the median was no different (Figure 2). In the localized ROIs, differences were not significant although there was a clear trend, prevalently in red nucleus and substantia nigra. The 10th percentile of RLS patients correlated with disease duration (r=0.60, p<0.05), but not with IRLSSG rating scale or other clinical/demographic parameters. No correlations were found for the healthy control group.

Discussion
These data indicate that global brain iron content is reduced in RLS patients compared to healthy subjects of a similar age. As paramagnetic tissue causes a dipolar effect (6), alterations were seen in both the 10th and the 90th percentile of the whole brain histogram where the extremes of image phase variation were reduced, due to reduced paramagnetic tissue content in RLS subjects. The whole brain analysis appears to be more sensitive than the local ROI analysis in these cases, and is also far less operator dependent. This suggests that this imaging protocol may also be useful in all types of neurological disease characterized by a pathological increase of iron accumulation (neurodegeneration with brain iron accumulation), as a biomarker of disease progression and for assessment of pharmacological interventions with chelating drugs.

References

Figure 1. A-F. Example GE image at level of basal ganglia. A. Absolute value. B. Real channel. C. Imaginary channel. D. Filtered phase image. E. Automatically selected whole brain ROI. F. Histogram of phase under whole brain ROI, showing 10th and 90th percentile values.

Figure 2. Group distribution of 10th, 50th and 90th percentile phase values for RLS patients and controls, showing median, interquartile range and extreme values. ** = p<0.01