Nigral iron deposition in LRRK2 and Parkin mutation carriers using R2* relaxometry

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Target audience: Scientists and clinicians who are working in the field of neurodegerative diseases or relaxometry mapping

Introduction: Parkinson's disease (PD) is commonly sporadic but familial genetic forms of the disease are observed in less than 10%.[1] It is not known whether neurodegeneration mechanisms in mutation-related PD are similar to those in idiopathic PD (IPD). In IPD iron appears to play an important role in the neurodegenerative process.[2] Abnormal iron homeostatis with abnormal iron levels were reported in the substantia nigra (SN) in post-mortem studies.[2] Iron load can be estimated by using MR relaxometry based on the measurements of T2*/R2* relaxation rates[3]. In IPD, MRI relaxometry consistently showed decreased T2* and increased R2* in the SN.[3, 4] Few studies have examined subjects with genetic mutations associated with PD. MRI and positron emission tomography (PET) studies have demonstrated nigrostriatal damage in symptomatic and asymptomatic genetic PD.[5] Iron load in these patients was only investigated using transcranial sonography (TCS), which showed increased SN echogenicity indicating increased iron load.[6] The aim of the present study was thus to study iron load in symptomatic and asymptomatic PD-mutation carriers as compared with normal subjects and IPD using R2* measurements.

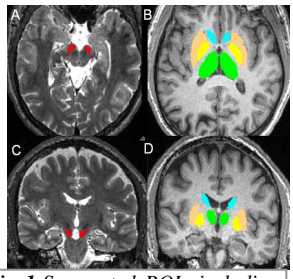

Fig 1:*Segmented ROIs including the SN (red), the putamen (orange), the caudate nucleus (blue), the globus pallidus (yellow) and the thalamus (green)*

Materials and Methods: **Subjects**: Nineteen subjects carried a mutation related to PD (Table 1)were compared with 20 age-matched subjects with IPD and 20 healthy volunteers. Clinical and neurological examination included the Unified Parkinson's disease Rating Scale (UPDRS III score) and the Hoehn and Yahr (HY) scale (Table 1). **MRI data acquisition** MRI acquisition was performed using a 3 Tesla TRIO TIM system (Siemens, Erlangen, Germany) using a 12-channel receive-only head coil. The protocol included three-dimensional (3D) T1-weighted (T1-w) images, 3D T2-weighted (T2-w) images, and T2 and T2* mapping. R2* mapping was performed using a gradient echo EPI sequence with 6 TEs (TE = 24 to 94 ms, TR/flip angle = 9000 ms/90°, voxel size = 2*2*2 mm3). **Image analysis** : Image processing and analysis were performed using in-house software written in MATLAB as well as SPM8 and FMRIB Software Library (FSL) v5.0 (FMRIB Analysis Group, Oxford, UK). Quantitative measures of R2 and R2* were obtained in selected regions of interest (ROIs, SN, caudate nucleus, putamen, globus pallidus, thalamus) (Fig 1). **Statistical analysis**: Statistical analysis of the ROI intensities and the clinical metrics was performed using Medical Calculator (MedCalc).

Results: **Substantia nigra.** ANOVA showed significant differences in R2* values between groups (F=18, p<0.0001) and no significant differences in R2 values (F=1.46, p=0.24). Compared with control subjects, IPD patients (p<0.0001), asymptomatic carriers (p = 0.021) and symptomatic mutation carriers (p<0.0001) showed significant increase in R2* values (Table 2, Fig. 2). Compared with IPD subjects, symptomatic carriers showed greater R2* values (p = 0.0023) whereas R2* values in asymptomatic carriers did not differ (p = 0.58). R2* values did not differ between symptomatic and asymptomatic mutation carriers (p = 0.179). **Other basal ganglia and thalamus.** There were no significant differences in R2 and R2* values in any other regions in mutation-carriers or IPD. **Clinical correlations**. There was no significant correlation between clinical variables in IPD or symptomatic mutation carriers and R2*.

	N	Mutation	Age (years)	M/F	Disease duration	UPDRS III	HY score
Controls	20	-	55.8±7.4	6/14	-	-	-
IPD	20	-	54.3±10.9	11/9	5.2±4.2	18.6±9.1	1.6±0.6
Asymptomatic mutation carriers	7	2 Parkin 5 LRRK2	47.7±14.8	4/3	-	-	-
Symptomatic mutation carriers	12	4 Parkin 8 LRRK2	53.9±13.9	5/7	10.6±5.2	25.3±14.8	2.0±0.8

Table 1: *Clinical characteristics of the subjects included in the analyse (mean ± standard)*

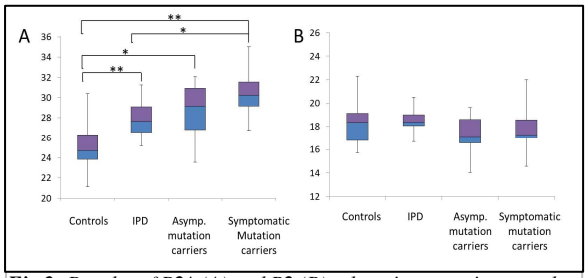

Fig 2: *Boxplot of R2* (A) and R2 (B) relaxation rates in control , IPD and genetic subjects. Significant differences are indicated using asterisks (*p<0.01, **p<0.001). Values are in S^{-1}.*

		Controls	IPD	Asymptomatic mutation carriers	Symptomatic mutation carriers
R2*	All mutations	25.05 ± 2.06	27.8 ± 1.53**	28.62 ± 3.07*	30.31 ± 2.15**,§
	Parkin	-	-	29.71 ± 0.87*	31.14 ± 2.96*,§
	LRRK2	-	-	28.18 ± 3.67*	29.89 ± 1.61*,§
R2	All mutations	18.33 ± 1.83	18.50 ± 1.30	17.29 ± 1.86	17.60 ± 2.01
	Parkin	-	-	18.97 ± 0.90	17.26 ± 1.18
	LRRK2	-	-	16.62 ± 1.72	18.26 ± 2.32

Table 2:*. Values of R2 and R2* in the SN (mean ± standard deviation (sec^{-1})). Significant differences with control subjects are indicated by *(p≤0.01) and **(p<0.001) and with IPD by § (p<0.01)*

Discussion: Patients with IPD showed increased R2* values in the SN in line with previous MRI studies.[3] Increased R2* is considered as an indicator of increased iron deposition.[7] Both symptomatic and asymptomatic mutation carriers had increased R2* values in the SN as compared with healthy subjects, suggesting increased iron load in line with TCS studies[5] and Parkin carriers[8] and with histological studies in Parkin patients.[9] R2* values in asymptomatic carriers were intermediate between those in patients with IPD and with mutation-related PD suggesting that iron load is increased in asymptomatic mutation-carriers . Whether increased R2* in the SN especially in asymptomatic LRRK2 carriers is predictive of conversion to PD remains to be determined. The lack of correlation with disease duration suggests that iron load may not be a reliable marker of disease progression in line with the absence of correlation between R2* values and disease duration in most of previous studies.[3, 4] Overall, results suggest that R2* may not be a reliable marker of disease severity.

Conclusion: The increased R2* observed in LRRK2- and Parkin-mutation carriers, including asymptomatic carriers, suggests increased iron load and that R2* measurements are promising biomarker of nigrostriatal damage in patients carrying a mutation. Its causal relationship and its prognostic value in the PD remain to be investigated in longitudinal studies.

References

1. Trinh J, Farrer M. Nature reviews Neurology 2013;9:445-454. 2. Sian-Hulsmann J, Mandel S, Youdim MB, Riederer P. Journal of neurochemistry 2011;118:939-957. 3. Peran P, Cherubini A, Assogna F, et al. Brain 2010;133:3423-3433. 4. Martin WR, Wieler M, Gee M. Neurology 2008;70:1411-1417. 5. Brockmann K, Groger A, Di Santo A, et al. Movement disorders 2011;26:2335-2342. 6. Berg D, Roggendorf W, Schroder U, et al. Archives of neurology 2002;59:999-1005. 7. Langkammer C, Krebs N, Goessler W, et al. Radiology 2010;257:455-462. 8. Hagenah JM, Konig IR, Becker B, et al. Journal of neurology 2007;254:1407-1413. 9. Takanashi M, Mochizuki H, Yokomizo K, et al. Parkinsonism & related disorders 2001;7:311-314.