Extended Abstract

T2* Relaxometry in Parkinson's Disease and Essential Tremor

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***Abstract* – Alterations in the Basal Ganglia and Motor Cortex have been described in Parkinson's Disease (PD) and Essential Tremor (ET). Previous studies suggested that T2* Relaxometry may detect differences in pathologic tissues, associated to increased iron deposits.**

The goal of this study was to assess the use of T2* as a biomarker for PD and ET. 43 subjects were imaged at 3.0T and two fitting algorithms were tested (Robust and Non-Robust). Regions of interest were drawn to estimate mean T2* in Motor Cortex and the Basal Ganglia. Intra- and Inter-Observer Reproducibility were studied. The difference between groups, the evolution of this parameter with the evolution of Parkinson's Disease were also investigated.

The only significant difference in T2* was found in the medial region of the SN between ET subjects and PD2-5 (p_{Robust}=0.036; $p_{Non-Robust}$=0.033). Intra-observer reproducibility tests show that both algorithms provide reproducible results (ICC_{robust}= 0.792, $ICC_{Non-robust}$=0.825) apart from the GP. The Robust algorithm provides improved measurement reproducibility between observers (K_{Robust}= 0.623, $K_{Non-robust}$=0.529). No significant changes were detected over one year (p>0.375).

***Keywords* –** Parkinson's Disease, Essential Tremor, Neuroimaging, MRI, T2* Relaxometry

Introduction

Parkinson's Disease and Essential Tremor are neurological disorders with unknown etiology. [1,2] PD affects more than 2% of the population over the age of 65, compared to 5% for Essential Tremor. [3,4]

PD is characterized by motor symptoms - tremor, bradykinesia, postural instability and gait disturbances. [5,6] In ET there is characteristic bilateral tremor of low amplitude, especially of the hand and forearm. [7,8]

It is also known that the development of these diseases is closely connected with alterations in the motor cortex and basal ganglia. [8,9]

MRI is a versatile technique that allows the evaluation of PD and the ET. Thus, it is possible to use Diffusion Tensor Imaging images, Susceptibility and T2/T2* relaxometry for the study of these pathologies. The latter of which allows analyzing local changes in the magnetic field. [2,10,11]

Methodology

Sample Characterization - 42 subjects were imaged: 10 Controls, 11 "de Novo" PD patients, initially untreated (PDN), 8 PD patients diagnosed 2 to 5 years before the start of the study (PD2-5), and 13 patients with ET – Table 1.

Group	No (M/F)	Age, years (mean±SD)	UPDRS Total
Controls	10 (6/4)	61.2±7.4	8.1± 21.4
PDN	11(5/6)	60.9 ±11.2	43.7± 28.3
PD2-5	8 (6/2)	67.1±7.2	43.3± 14.7
ET	13 (5/8)	74.2±7.3	-

UPDRS: Unified Parkinson's Disease Rating Scale;
SD: Standard Deviation

Table 1- Sample Characterization

Image Acquisition - Controls and PD patients underwent 2 MRI examinations separated by 1 year; ET patients were scanned once.

Gradient echo T2* Relaxometry images with 7 echo times were acquired (minimum TE=13.8ms, ΔTE=4.7ms).

Image Processing - The images were analyzed using a Matlab graphical user interface developed at IBEB [7], and two distinct algorithms were tested to fit to the equation *ln[S(TE)]=ln[S0]-TE/T2**: a Robust approach including iterative weighting to reduce the influence of outliers, and a Non-Robust algorithm that assigns the same weight to all signal intensities *S(*TE*)*.

The mean T2* was estimated in the following regions-of-interest (Fig.1): Substantia Nigra (SN), Caudate Nucleus (CN), Putamen (PM), Globus Pallidus (GP) and Motor Cortex (MC).

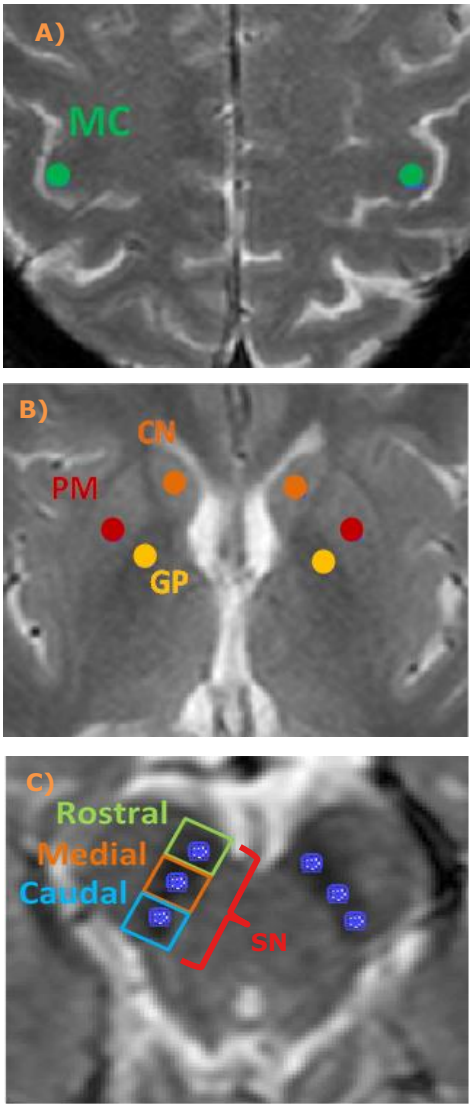

Fig. 1 - Segmentation of anatomical structures: A) ROI of Motor Cortex; B) ROI of Basal Ganglia; C) ROI of Substantia Nigra showing its three different portions.

The analysis of the first MRI examination was conducted twice, one week apart to evaluate the intra-observer reproducibility. The inter-observer reproducibility was also evaluated using SN measurements performed by two different observers.

Statistical Analysis - To assess differences between groups the Kruskal-Wallis test was employed with Bonferroni corrections (significance level of 0.05);

To evaluate intra- and inter-observer reproducibility, the appropriate Intraclass Correlation Coefficients and Cohen's Kappa were calculated, respectively (reproducibility was considered to be excellent if ICC>0.75 and K>0.80). The Wilcoxon test was used to compare samples acquired at different time points.

Results

Difference Between Groups

A statistical difference was found in the medial region of Substiantia Nigra when comparing between Essential Tremor and PD2-5 (p_{Robust}= 0.036; $p_{Non\text{-}Robust}$ =0.033) – Table 2.

		Controls	PDN	PD2-5	ET
SN All	**R**	24 (10)	26 (22)	24 (15)	31 (27)
	NR	24 (11)	25 (22)	23 (16)	31 (29)
SN Rostral	**R**	20 (15)	18 (19)	21 (12)	22 (22)
	NR	20 (17)	19 (20)	19 (11)	23 (22)
SN Medial	**R**	24 (17)	28 (22)	**20 (18)**	**31 (35)**
	NR	24 (20)	27 (22)	**18 (17)**	**31 (36)**
SN Caudal	**R**	29 (19)	30 (39)	27 (20)	38 (38)
	NR	29 (19)	30 (39)	27 (21)	35 (39)
CN	**R**	36 (24)	35 (30)	39 (34)	39 (19)
	NR	35 (26)	35 (28)	39 (33)	37 (18)
GP	**R**	22 (18)	22(8)	17 (21)	19 (16)
	NR	21 (16)	22 (12)	16 (20)	19 (16)
PM	**R**	26 (29)	29 (16)	28 (24)	29 (16)
	NR	29 (27)	29 (15)	28 (23)	29 (17)
MC	**R**	36 (21)	34 (21)	29 (25)	36 (25)
	NR	36 (22)	25 (20)	29 (24)	35 (24)

Table 2 – T2* (ms): median (range) for each subject group and ROI. R (Robust) NR (Non-Robust. **T2* values** showing a significant statistical difference between ET and PD2-5.

Evaluation of Parkinson's Disease

No significant changes were detected over the period of one year for either PD or control subjects. (p>0.375).

Intra-Observer Reproducibility

The intra-observer reproducibility tests show the correlation between two measurements made by the same observer. According to this criterion, it is possible to say that both algorithms provide reproducible results – Fig. 2.

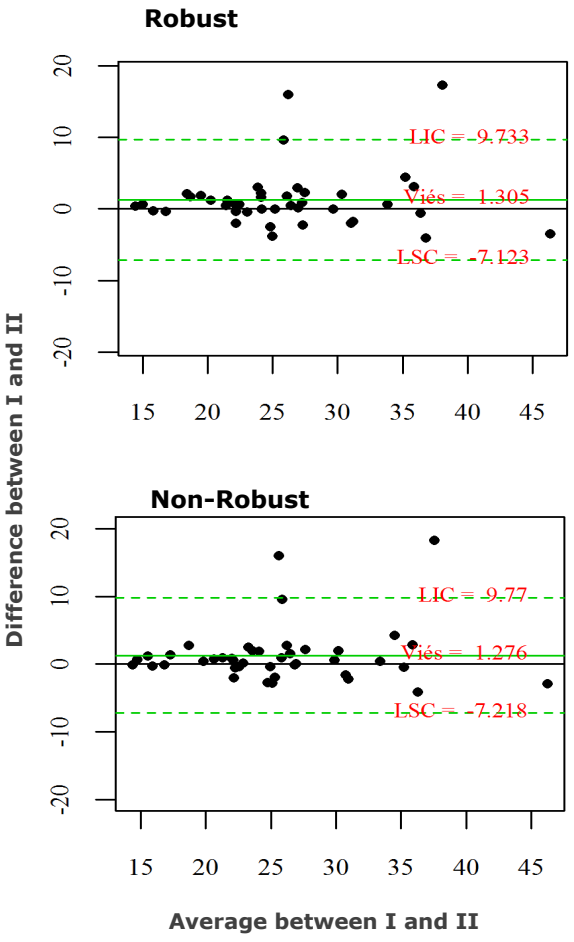

Fig. 2 –Intra-Observer reproducibility evaluated using the Bland-Altman method, demonstrating a very small bias.

Excellent Intra-Observer reproducibility (ICC_{robust}= 0.792, $ICC_{Non\text{-}robust}$=0.825) was observed in all regions apart from the GP – Table 3.

		ICC	95% CI	
SN All	R	0.897	0.804	0.945
	NR	0.898	0.806	0.945
CN All	R	0.935	0.880	0.965
	NR	0.922	0.855	0.958
GP All	R	**0.486**	0.063	0.720
	NR	**0.610**	0.282	0.789
PM All	R	0.848	0.710	0.919
	NR	0.871	0.758	0.931

Table 3 –Characterization of the Intra-Observer Reproducibility. **ICC** of the measures with the worst intra-observer agreement.

Inter-Observer Reproducibility

The Inter-Observer Reproducibility tests show that the Robust algorithm provides more reproducible results, with excellent reproducibility when outliers are eliminated (K_{Robust}= 0.832, $K_{Non\text{-}robust}$=0.689) – Fig. 3.

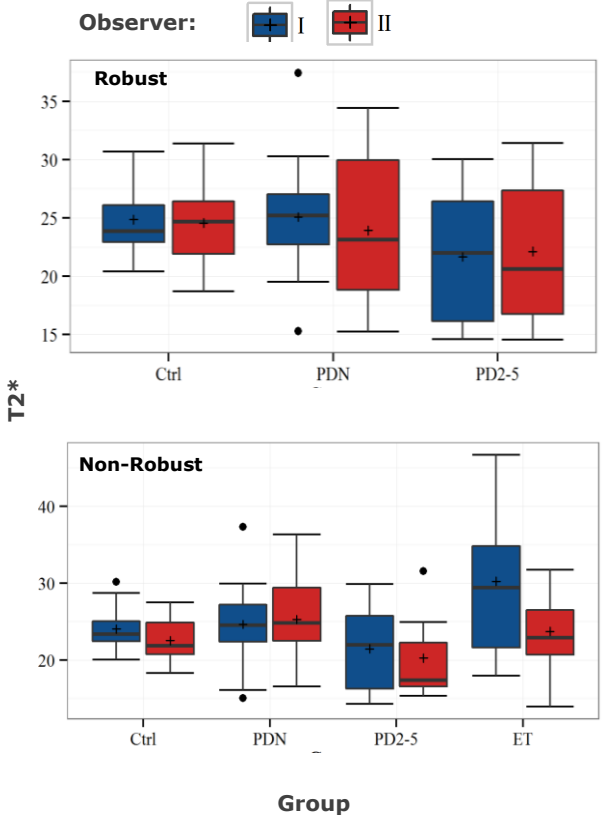

Fig. 3 - Inter-Observer Reproducibility accounting for subject group. The difference between measurements performed by two observers is illustrated for both the Robust (A)) and Non-Robust algorithms (B))

Discussion & Conclusions

Excellent intra-observer reproducibility was demonstrated for T2* estimates; the only region where this was not the case was the GP. This may be due to a high frequency of lacunae and enlarged perivascular spaces influencing ROI positioning.

The Robust algorithm provides better inter-observer reproducibility that the Non-Robust.

The fact that differences between groups could only be detected in one of the studied regions suggests that this type of measurement may not be sufficiently sensitive to be used as a biomarker for PD, at least at an early stage of the disease.

In the future we would also like to include patients at a more advanced stage of the disease and explore alternative pulse sequences, such as SWI and T2 mapping.

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