

# Increased Anisotropy in Subcortical Gray Matter Structures: a Neurodegeneration Marker in Multiple Sclerosis.

S. HANNOUN<sup>1,2</sup>, F. DURAND-DUBIEF<sup>1,3</sup>, D. IBARROLA<sup>2</sup>, J. COMTE<sup>2</sup>, C. CONFAVREUX<sup>3</sup>, and D. SAPPEY-MARINIER<sup>1,2</sup>

<sup>1</sup>CREATIS-LRMN, UMR5220 CNRS & U630 INSERM & Université de Lyon, Bron, France, <sup>2</sup>CERMEP-Imagerie du vivant, Bron, France, <sup>3</sup>Hopital Neurologique, Groupement Hospitalier Est, Bron, France

## Introduction

Multiple Sclerosis (MS) is not only a chronic inflammatory disease characterized by demyelination and gliosis, but the disease also implies neurodegenerative processes. MS exhibits clinically three different forms classified as relapsing-remitting (RR) phases of inflammation followed by a secondary progressive (SP) period, or directly as a primary progressive (PP) evolution which may constitute the clinical expression of neurodegenerative processes [1]. Conventional MRI allows the evaluation of lesion load revealing the inflammatory process of the disease. However, MRI suffers from a lack of specificity since it is unable to detect subtle changes in the normal-appearing white or gray matter [2]. Thus, MR spectroscopy and magnetization transfer as well as DTI have been developed to provide more sensitive markers to detect early pathological changes in MS [3]. While DTI studies in MS have been focused on white matter, we proposed in this study to apply DTI in different subcortical gray matter (SGM) structures such as thalamus, caudate and lenticular nuclei, in order to characterize the early neurodegenerative processes in correlation with the disease progression.

## Methods

Our study includes 62 patients of different clinical forms: 24 RR ( $36.4 \pm 7.9$  y), 24 SP ( $42.9 \pm 4.7$  y) and 14 PP ( $44.3 \pm 3.8$  y) patients and 19 control subjects ( $37.2 \pm 10.5$  y). All patients were diagnosed with definite MS according to McDonald's criteria and their expanded disability status scale ratings (EDSS) measured. MR exams have been performed on a 1.5 T Siemens Sonata system. DTI protocol included a spin-echo EPI sequence (TR = 3800 ms, TE = 96 ms) with 96 x 96 phases-encoding with a FOV of 240 x 240 mm and 51 axial slices of 2.5 mm thickness. DTI images have been obtained in 24 directions with b values of 0 and 1000 s/mm<sup>2</sup> and processed using MedINRIA software [4]. ROIs have been manually delimited on FA images for three SGM structures: the caudate nuclei (CN), the lenticular nuclei (LN) and the thalamus (T) (Fig.1). Diffusion parameters (FA, ADC,  $\lambda_a$  ( $\lambda_1$ ) and  $\lambda_r$  ( $(\lambda_2 + \lambda_3)/2$ )) have been measured from these ROIs and histograms statistically analyzed.

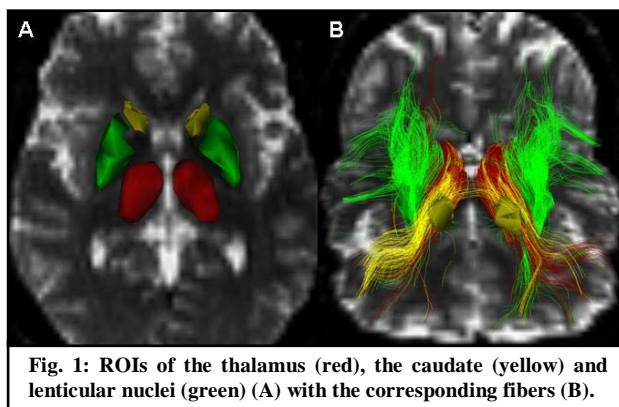


Fig. 1: ROIs of the thalamus (red), the caudate (yellow) and lenticular nuclei (green) (A) with the corresponding fibers (B).

## Results

As reported in Table 1, FA and  $\lambda_a$  values were significantly increased in all SGM structures of all MS patient forms compared to control subjects. In contrast, no significant changes were observed in ADC and  $\lambda_r$  values, except in the CN where  $\lambda_r$  decreased significantly in SP ( $0.646 \pm 0.021^*$ ) and PP forms ( $0.643 \pm 0.029^*$ ) compared to controls ( $0.670 \pm 0.026$ ). A significant increase in FA values was also observed in PP ( $p < 0.001$ ) and SP ( $p < 0.01$ ) patients compared to RR in the CN and in PP ( $p < 0.05$ ) patients compared to RR in the LN.

Subjects	N	FA			$\lambda_a$		
		CN	LN	T	CN	LN	T
Controls	19	0.192±0.013	0.192±0.015	0.302±0.014	0.886±0.040	0.866±0.035	0.940±0.020
RR	24	0.235±0.023#	0.238±0.015#	0.327±0.015#	0.922±0.039*	0.920±0.038#	0.977±0.024#
SP	24	0.262±0.020#	0.243±0.027#	0.335±0.022#	0.953±0.037#	0.900±0.042*	0.983±0.030#
PP	14	0.272±0.040#	0.261±0.035#	0.343±0.020#	0.954±0.047#	0.927±0.042#	0.979±0.041●

Table 1: Values (Mean ± SD) of FA and  $\lambda_a$  (mm<sup>2</sup>) in caudate nuclei (CN), lenticular nuclei (LN) and thalamus (T) regions (\* $p < 0.05$ , ● $p < 0.01$ , # $p < 0.001$ ).

## Discussion

This DTI study showed a highly significant increase in FA and in axial diffusivity ( $\lambda_a$ ) in all structures in contrast with a decrease in radial diffusivity ( $\lambda_r$ ). This pattern of diffusivity alterations observed in SGM contrast significantly with white matter measurements where FA is decreased along with an increase of axial and radial diffusivities [5]. While WM changes may result directly from axonal damage, the strong increase in anisotropy and the lack of change in radial diffusivity may suggest a reduced dendritic branching and connectivity in subcortical gray matter structures. These findings may demonstrate for the first time that SGM structures are involved in a neuronal degenerative process. Further, this hypothesis is enhanced by the observation of a stronger increase in FA values of the PP form which is believed to represent the clinical expression of a progressive and neurodegenerative model.

In conclusion, DTI provides new markers that could detect early and progressive pathological changes in SGM structures of MS patients. Therefore, the measurement of such diffusivity parameters in different cerebral tissue could characterize different pathological processes such as inflammation or neurodegenerative phases and guide the early differentiation of clinical forms.

## References

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