3T-PET/MRI analysis of cortical metabolism in MS patients discloses various patterns of association with white and grey matter pathology

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Background

The peculiar features of cortical pathology in MS, even in the very early disease phases, are microglia activation, loss of synapses and neuronal apoptosis with no significant evidence of blood-brain barrier damage.
The early and diffuse activation of microglia cells may first induce metabolic changes in the cortex and then determine synapsis and neuronal loss and atrophy.
If this hypothesis is correct, in MS we should be able to demonstrate **changes in cortical metabolism before the evidence of structural changes**.
Preliminary data in degenerative diseases of the CNS seem to further support this view. Indeed, longitudinal studies have explored cortical metabolism by means of ^{18}F-FDG PET in the aging brain and in Alzheimer's disease. A discrete percentage (7/26, 27%) of cognitively normal elderly controls were found to have cortical hypo-metabolism before having evidence of amyloid deposition.

Aims

This study is aimed to analyse cortical metabolism and its association with MRI parameters of white matter (WM) and grey matter (GM) damage in MS at clinical onset by means of a fully integrated 3T-Positron Emission Tomography/Magnetic Resonance Imaging (3T ^{18}F-PET/MRI) system.

Patients & Methods

Two groups of MS patients, whose diagnosis was achieved according to the McDonald/ Polman's diagnostic criteria [9], were enrolled in the study. The two groups were selected in order to avoid possible age-related bias.

	F/M	Age mean ± ds [range]	Disease duration (mean ± ds) [range]	EDSS (mean ± ds) [range]
CIS/ eRRMS	10/4	36.6 ± 9.64 [22-53]	1.7 ± 0.33 [0.25-1.67]	2.04 ± 0.9 [1-4]
RRMS	10/7	40.3 ± 8.99 [22-52]	19.1 ± 10.0 [1-33]	3.1 ± 1.3 [1-6]
Total	20/11	38.5 ± 9.49 [22-53]	10.7 ± 11.3 [0.25-33]	2.6 ± 1.2 [1-6]

Table 1. Demographic and clinical information about the two groups. eRRMS stands for RRMS with dis. duration <3 years.

The following set of images was obtained from each subject:

- MRI 3D T1-MPRAGE, used for segmentation and cortical thickness (CTh) evaluation with FreeSurfer 5.3
- MRI 3D FLAIR, used for manual WM lesion segmentation
- MRI 3D DIR, used for manual GM lesion segmentation
- ^{18}F-MDG PET images in list mode, used for evaluation of absolute glucose rate (aMRglu), via Patlak Plot method with Pmod 3.7.

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Results

1. RRMS differ from CIS/eRRMS in CTh and in WM and GM lesion load.
CTh of RRMS was significantly lower in left frontal ($p<0.01$), parietal ($p=0.03$) and occipital ($p=0.02$) lobes and in right frontal ($p=0.02$) and parietal ($p<0.01$) lobes. The regional analysis performed on 66 cortical areas (33 for each brain hemisphere) disclosed a significant difference in 13/33 areas in the right hemisphere and in 8/33 in the left hemisphere ($p=0.04$).
As expected, RRMS significantly differed from CIS/eRRMS in both T2WM lesion volume and number ($p=0.004$ and $p=0.002$, respectively) and the cortical lesion volume and number ($p=0.02$ and $p= 0.008$, respectively).

2. RRMS did not differ from CIS/eRRMS in global aMRGlu.
No difference in the global cortical aMRGlu was observed between RRMS and CIS/eRRMS.

3. No correlation was demonstrated between CTh and WM and GM lesion load.

4. No correlation was found between global and regional aMRglu and CTh.

5. aMRglu correlated with lesion load
Inverse correlation was found between the total number of focal lesions (WM+GM lesions) and the global cortical aMRglu ($R=-0.36$ e $p=0.04$), and between WM lesion volume and number and cortical global aMRglu ($R=-0.4$ and $p=0.02$ for both). Moreover, the total number of GM lesions mildly and inversely correlated with global aMRglu ($R=-0.36$, $p=0.046$).

6. Non-clinical subgroup divisions shown in Table 2.

Groups	Composition	Results			
A. # Lesions < 70	**A.** 12 CIS, 5 RR		mean A.	mean B.	p-val
B. # Lesion > 70	**B.** 5 CIS, 10 RR	aMRglu	22.18	19.04	0.03
		CTh	2.57	2.44	0.02
A. aMRglu > 18.5	**A.** 11 CIS, 3 RR		mean A.	mean B.	p-val
B. aMRglu < 18.5	**B.** 3 CIS, 14 RR	CTh	2.52	2.50	0.64
		LN	55	109	0.03
		LV	832	1001	0.17
A. aMRglu>18.5, CIS	**A.** 11 CIS, 0 RR		mean A.	mean B.	p-val
B. aMRglu<18.5, RR	**B.** 0 CIS, 14 RR	CTh	2.54	2.50	0.39
		LN	39	138	0.0007
		LV	278	1051	0.003

Table 2. Stratification by non-clinical subgroups and statistical results. By "CIS" we indicate CIS/eRRMS, by "RR" RRMS. Units of measure: aMRglu [g cm^{-3} s^{-1}]; CTh [mm]; (grey and white) Lesion Volume=LV [mm^3]; (grey and white) Lesion Number=LN [].

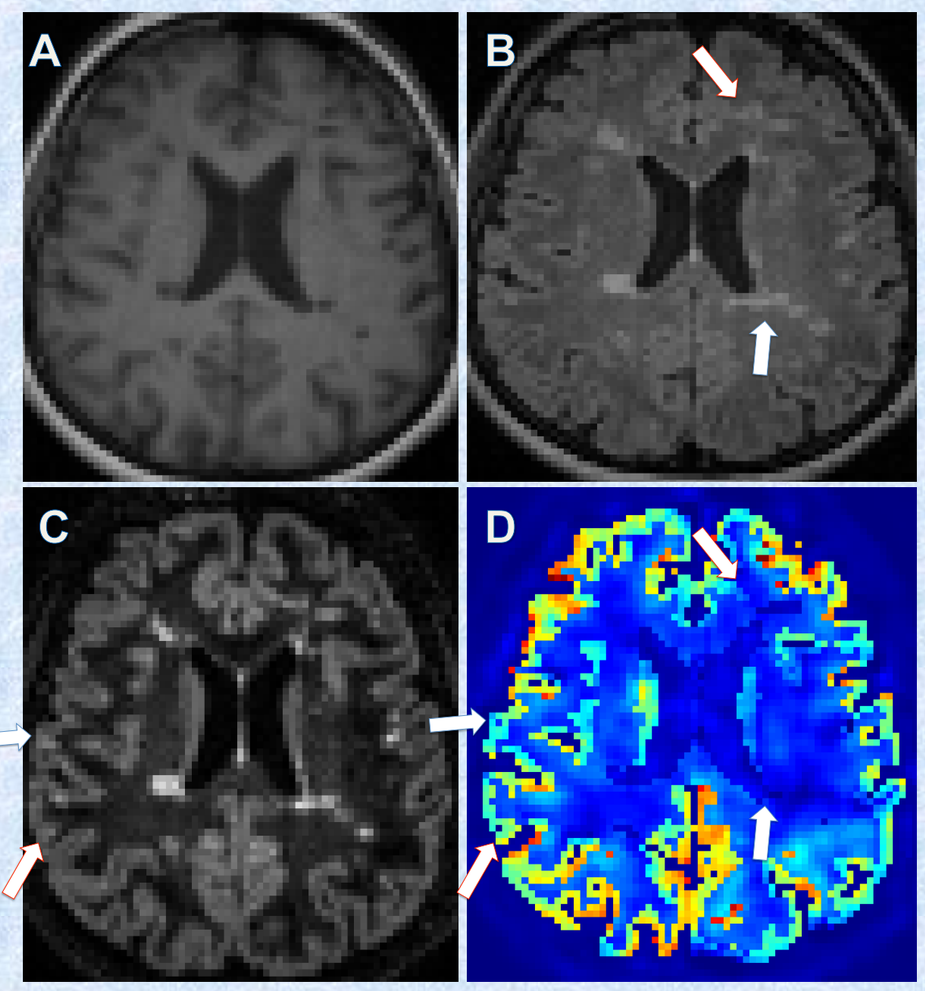

Figure 1. A: T1-w axial slice of a patient; B: FLAIR; C: DIR; D: Voxel-wise map of Mrglu sampled at 2x2x2 mm resolution. All images were registered to D.
Blue arrows: lesions with corresponding hypo-metabolism; red arrows: lesions with corresponding high MRglu values.

Discussion

These findings indicate that aMRGlu does not necessarily associate with changes in CTh. In other words, the cortex of MS in early disease phases may go through different states of metabolic activity.
We may hypothesize that:

- In a **first phase** pro-inflammatory cytokines released by activated microglia lead to an increase of the synaptic metabolic rate.
- In a **second phase**, the excitotoxic damage determines a progressive decrease in synaptic activity with a consequent decrease of metabolism, but still normal CTh.
- Finally, in a **third phase**, the progressive loss of synapsis and the neuronal death determine the appearance of cortical atrophy. In MS cortex, all these conditions may take place in different areas at the same time.

Conclusions

Various patterns of association between aMRglu and WM and GM pathology were observed in CIS/eRRMS and RRMS. Our findings indicate that cortical metabolism is a dynamic parameter especially in the early disease phases, probably linked to variable state of activation of both neurons and glial cells.