Analysis of cortical metabolism in multiple sclerosis: a 3T 18F-FDG PET/MRI study

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Background

The cortex is severely damaged in multiple sclerosis (MS). Cortical atrophy can be demonstrated in some patients at clinical onset and its progression associates with physical and cognitive disability. Once established, atrophy is irreversible. Whether a cortical metabolic dysfunction may precede atrophy in very early disease phases has not been investigated yet. Recently, a fully integrated Positron Emission Tomography/Magnetic Resonance Imaging (PET/MRI) system that allows the measurement of the absolute glucose metabolic rate in the cortex has become available.

Objectives

In this pilot, explorative study we investigated cortical metabolism in MS patients and its possible association with structural measurements, as cortical thickness, by means of a fully integrated 3T-PET/MRI system. Our aim was to find possible differences in cortical metabolism between MS patients at clinical onset and Relapsing-remitting multiple sclerosis (RRMS) patients with long disease duration and clinical evidence of cortical dysfunction.

Methods

Patient population

28 patients were enrolled in the study: 13 Clinically isolated syndromes/early relapsing-remitting multiple sclerosis (CIS/eRRMS) with a very short disease duration and no sing of cognitive impairment, and 15 RRMS patients with a long disease duration and clinical evidence of cognitive dysfunction (table 1). The two groups were selected in order to avoid possible age-related bias (no significant differences in mean age).

All patients underwent neurological examination with Expanded Disability Status Scale (EDSS) and neuropsychological assessment with Rao's Brief Repeatable Battery of Neuropsychological Tests (BRB-NT). Patients were considered cognitively impaired if their neuropsychological assessment showed at least 1 test with z-score < -2 or 2 tests with z-score < -1,5.

	F/M	Age	Disease duration	EDSS
CIS/eRRMS	8/5	36.2±9.8 [22–53]	1.0±0.4 [0.1–1.3]	2.2±0.9 [1–4]
RRMS	10/5	40.3±9.3 [22–52]	18.3±10.4 [6–36.4]	3.1±1.3 [1–6]
TOT	18/10	38.4±9.6	10.3±11.5	2.7±1.2

Table 1. Demographic and clinical characteristics of the patients included in the study. Data are expressed as mean ± SD and range (into brackets). Age and disease duration are expressed in years. EDSS= expanded disability status scale.

Image acquisition and analysis

3T ^{18}F-FDG-PET/MRI (Siemens Biograph mMR PET System) images were obtained from all patients. Image-derived Input Function (IDIF) was obtained with a new methodology using PMOD 3.6 software: the tracer was injected while acquiring PET dynamic images of the thoracic aorta for 10 minutes and, after resting for 40 minutes out of the scanner, for 5 minutes on the same region. Then, early and late data were interpolated to obtain a complete IDIF and fitted using Patlak plot to PET brain curves obtained by segmentation on simultaneously acquired 3D-T1 images. The so obtained absolute metabolic rate of glucose (aMRglu) is an accurate way of describing cortical kinetics. Regional cortical thickness was obtained from a anatomical 3D-T1 (magnetization-prepared rapid gradient echo -MPRAGE- with resolution 1x1x1 mm, FoV 250x250 mm, TR 1900 ms, TE 2.44 ms, TI 900 ms, flip angle 9°, slices 192, duration 5 min) by Freesurfer suite in cortical areas according to Desikan Killiany protocol. Given the difference in spatial resolution between MRI and PET, MRI areas were dilated with “dilation” algorithm of PMOD, and applied to PET data (figure 1).

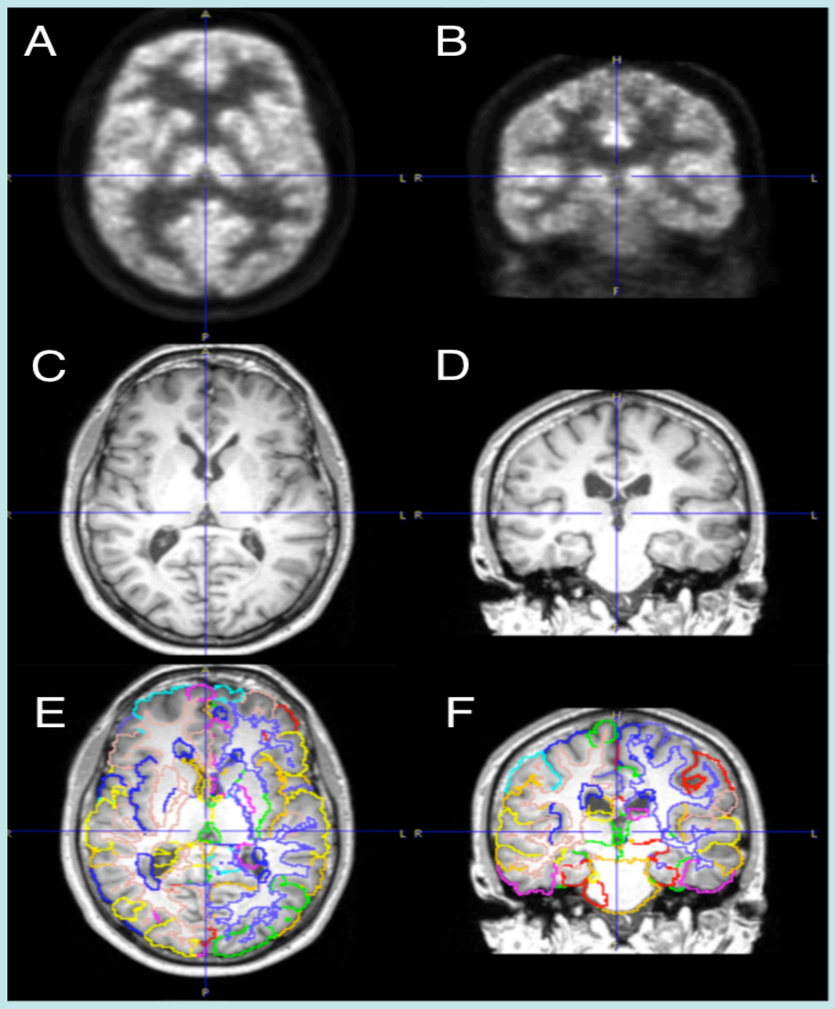

Figure 1. PET (A, B) and MRI (C, D) axial and coronal images acquired with fully integrated 3T PET/MRI system. Desikan Killiany atlas was applied on MRI dilated images overlapped on PET to analyse regional cortical thickness and metabolism (E, F).

Results

As expected, the structural analysis of cortex by means of Freesurfer showed a significant difference between RRMS and CIS/eRRMS patients. Considering macro-anatomical areas, cortical thickness was significantly lower in RRMS compared to CIS/eRRMS in left frontal (p=0.16), parietal (p=0.03) and occipital (p=0.02) lobes and in right frontal (p=0.019) and parietal (p=0.01) lobes. A more detailed regional analysis performed on 66 cortical areas (33 for each brain hemisphere) found a significant difference in 13/33 cortical areas in the right hemisphere and in 8/33 in the left one (p<0.04), with CIS/eRRMS showing higher thickness than RRMS patients. Surprisingly, no significant difference in cortical aMRglu was found between RRMS and CIS/eRRMS groups except for the right paracentral area (p=0.04) and the left parietal lobe (p=0.05). These results disclose an unexpected homogeneity in cortical metabolism between the two patients subgroups, despite their important differences in cortical thickness and clinical profile (figure 2).

To investigate the association between cortical metabolism and thickness we performed a correlation analysis on all cortical areas of Desikan Killiany atlas. Only in RRMS group significant positive correlations were found in some cortical areas between cortical thickness and aMRglu, whereas no correlation was found in CIS/eRRMS group (figure 3).

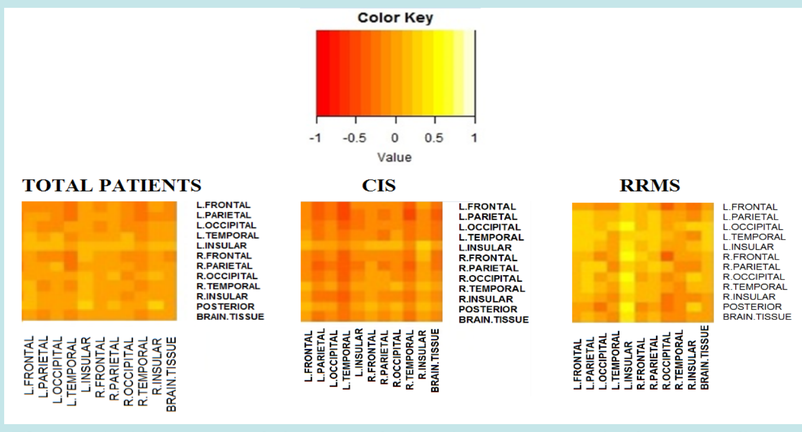

Figure 3. Heatmap of the correlation between cortical metabolism and thickness of the macro-anatomical areas in CIS/eRRMS and RRMS groups.

Conclusions

This study shows that CIS/eRRMS and RRMS have similar values of cortical metabolism despite they significantly differ in cortical thickness. This suggests that a metabolic dysfunction probably precedes MRI detectable structural damage in the cortex of MS. Whether this metabolic abnormality is secondary to local inflammation or precede the immunopathological process occurring in MS cortex deserves further investigation. The identification of morphologically normal but hypometabolic areas in very early disease phases may have important pathological and clinical consequences.

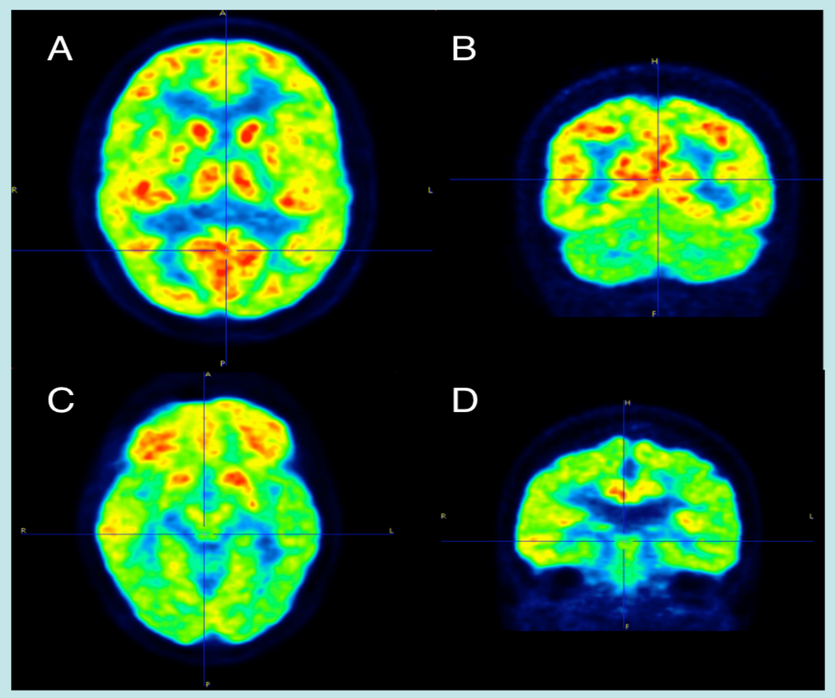

Figure 2. Axial and coronal 18F-FDG PET images of a CIS (A, B) and a RRMS patient with cognitive decline (C, D) . In both cases areas of hypometabolism can be observed. The similarity of the images in these two different patients shows the complexity in distinguishing CIS from RRMS.

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