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The relationship between MRI and PET changes and cognitive disturbances in MS

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Abstract

Cognitive dysfunction in multiple sclerosis (MS) is present in approximately 50% of the patients. Only moderate correlations have been found between cognitive dysfunction and T_2 lesion load, black holes or atrophy. Cognitive dysfunction in MS is probably related to the overall disease burden of the brain including abnormalities in normal appearing white matter (NAWM) and cortical grey matter, which is undetected with conventional magnetic resonance imaging (MRI). Hence, imaging techniques that embrace such abnormalities are needed to achieve better correlation with cognitive dysfunction. MR spectroscopy (MRS) performed with multi-slice echo planar spectroscopic imaging (EPSI) and PET measurements of brain metabolism as the cortical cerebral metabolic rate of glucose are imaging methods that are able to provide information on axonal loss or dysfunction in both MS lesions and in NAWM and cortical grey matter. Measurements of global NAA using multi-slice EPSI is a new promising method for measurement of the global neuron capacity and can be repeated with only little discomfort and without any risk for the patient.

Keywords: Multiple sclerosis; PET; MRI; MR spectroscopy; *N*-acetyl aspartate; Cognitive dysfunction; Disability

1. Introduction

Magnetic resonance imaging (MRI) shows structural changes with high resolution in multiple sclerosis (MS) but contains little information regarding the associated changes in brain function, whereas MR spectroscopy (MRS) with measurements of *N*-acetyl-aspartate (NAA) provide information of neuronal loss or dysfunction [1–4]. The use of positron emission tomography (PET) has made it possible to measure in vivo physiological processes in the brain reflected by blood flow or glucose metabolism. A coupling between cerebral metabolic rates and neural activity has been shown in humans, which allowed PET measurements to be used as an indirect estimate of brain function [5].

Cognitive dysfunction occurs in approximately 50% of MS patients increasing with later stages of the disease [6–11]. The pathophysiology of the cognitive deficits is not clear but white matter lesions affecting tracks connecting cortical areas seem to be important factors although undetected pathological changes in normal appearing brain might also be involved. The association between the total lesion area (TLA) on T_2-weighted MRI images and physical disability is weak and T_2-weighted lesion load has only been reported to show moderate correlations to neuropsychological measures [6–18]. This is partly caused by the lack of pathological specificity of T_2 lesions that do not discriminate between edema, demyelination and axonal loss and partly because

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pathological changes in normal appearing white matter may be of importance.

At Copenhagen University Hospital, we have applied multi-slice echo planar spectroscopic imaging (EPSI) of whole-brain NAA and performed PET to improve the correlation between imaging techniques and cognitive dysfunction in MS [19–21].

1.1. Multi-slice echo planar spectroscopic imaging (EPSI)

Multi-slice EPSI is a promising alternative to non-localized spectroscopy for obtaining whole-brain NAA estimates. The multi-slice EPSI sequences and analyses have been described in details elsewhere [19]. Eight 10-mm axial slices cover most of the cerebrum with 1 ml isotropic voxels. Global NAA was calculated as a ratio relative to Cr to correct for cerebrospinal fluid content, coil sensitivity variations and edema. The adapted brain mask covers approximately 60% of the brain parenchyma. Mathiesen et al. [22] studied 20 patients, 16 females and 4 males, with newly diagnosed clinically definite relapsing remitting MS and disease duration less than 5 years. Fifteen of the patients received immunomodulatory therapy. All patients underwent traditional brain scans with T_2-weighted images obtained using fluid attenuated inversion recovery (FLAIR) to assess the total lesion volume and the total intracranial volume. To determine the amount of grey and white matter a magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence was performed. The brain parenchymal fraction (BPF) was calculated by dividing the volume of grey and white matter with the total intracranial volume.

Table 1
Cognitive impairment measured by sixteen neuropsychological measures constituting the Cognitive Dysfunction Factor

Neuropsychological measures	Mean residual scores	Significance, 2-tailed
Digits Backward	−6.47	$p=0.02$
Serial Seven Subtraction Test	−1.67	n.s.
Stroop (simplified version)	−1.68	n.s.
List Learning	−2.18	n.s.
7/24 Spatial Recall Test		
Part B	−5.17	$p=0.014$
Part A, delayed recall	−3.02	n.s.
Boston Naming Test	−12.54	$p<0.000$
Naming of Famous Faces (naming %)	−4.12	n.s.
Controlled Oral Word Association Test (COWAT)		
Animals	−7.46	$p=0.008$
Words with “s”	−5.45	n.s.
Symbol Digit Modalities Test (SDMT)	−6.91	$p<0.000$
Tower of London		
Rule breaks	−5.19	n.s.
Design Fluency		
Errors	−6.19	$p=0.049$
Rey Complex Figure		
Copy	−9.15	$p=0.045$
Recall	−0.37	n.s.
Mesulam Cancellation Test, random shapes		
Errors	−4.87	n.s.
Cognitive Dysfunction Factor	−9.744	0.002

Mean residual scores (difference between obtained *T* scores and expected *T* scores).

Table 2
Global NAA/Cr (reduced NAA/Cr<1.5) in patients with and without cognitive impairment measured by CDF (Cognitive Dysfunction Factor)

	Global NAA/Cr<1.55	Global NAA/Cr>1.55	Total
CDF residual score>−15	2	9	11
CDF residual score<−15	7	2	9
Total	9	11	20

CDF residual score <−15 indicates cognitive impairment. 2×2 contingency table ($p=0.036$).

All patients underwent a neuropsychological test battery of 18 tests resulting in 29 measures covering a broad range of cognitive functions. A Cognitive Dysfunction Factor (CDF) was constructed by taking the mean *Z*-scores of the 16 test variables that discriminated best between a normal control group and the patient group. The normalized *Z* scores were standardized to *T* scores with a mean of 50 and a standard deviation (SD) of 10 in the control group ($N=75$). In order to estimate the difference (residual scores) between obtained *T* scores and expected premorbid *T* scores a multiple regression analysis based on the control group with gender, age, age squared, and educational index as predictors was performed (Table 1). A significant correlation was found between global NAA/Cr and the Cognitive Dysfunction Factor ($r=0.62$; $p=0.045$). The patients were divided into 2 groups using a residual score of −1.5 SD as cut-off point to classify cognitive impairment. Thus, 9 patients were cognitively impaired and 11 patients were found to be cognitively unimpaired. (Table 2). Cognitively impaired patients had significantly lower global NAA/Cr than unimpaired patients ($p=0.036$). In contrast to this result the conventional MRI such as T_2 lesion volume and brain parenchymal fraction did not show significant correlation with the Cognitive Dysfunction Factor.

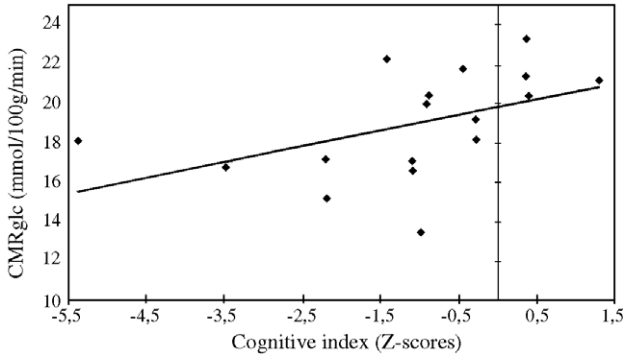

Fig. 1. Relationship between global cortical cerebral metabolic rate of glucose (CMRglc) and general cognitive function (*Z*-scores of composite of 19 neuropsychological tests). From Blinkenberg et al. [20].