Comparison of MR Perfusion and FDG-PET Brain Studies in Patients With Alzheimer's Disease and Amnestic Mild Cognitive Impairment

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Research Article

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Abstract

Background: The aim of this study was to compare Dynamic Susceptibility Contrast Enhanced MRI (DSC-MRI) and PET with fluorodeoxyglucose (FDG-PET) in the diagnosis of Alzheimer's Disease (AD) and amnesic Mild Cognitive Impairment (aMCI).

Methods: Age and sex matched 27 patients with AD, 39 with aMCI and 16 controls underwent brain DSC-MRI followed by FDG-PET. Values of relative Cerebral Blood Volume (rCBV) and rCBV z-scores from frontal, temporal, parietal and PCG cortices were correlated with the rate of glucose metabolism from PET. Sensitivity, specificity and accuracy of DSC-MRI and FDG-PET in the diagnosis of AD and aMCI were assessed and compared.

Results: In AD hypoperfusion was found within all examined locations, while in aMCI in both parietal and temporal cortices and left PCG. FDG-PET showed the greatest hypometabolism in parietal, temporal and left PCG regions in both AD and aMCI. FDG-PET was more accurate in distinguishing aMCI from controls than DSC-MRI. In AD and combined group (AD + aMCI) there were numerous correlations between DSC-MRI and FDG-PET results.

Conclusions: In AD the patterns of hypoperfusion and glucose hypometabolism are similar thus DSC-MRI may be a competitive method to FDG-PET. FDG-PET is a more accurate method in the diagnosis of aMCI.

1. Introduction

Due to aging of the population early diagnosis of dementia is an important problem in modern medicine. The most common cause of dementia is Alzheimer's disease (AD), while amnesic mild cognitive impairment (aMCI) is considered a prodromal condition with a high risk of conversion to AD [1]. Many studies show that brain alterations in AD occur many years before the first clinical manifestations [2].

Structural magnetic resonance imaging (MRI) plays an important role in the diagnosis of dementia firstly in excluding secondary causes of cognitive impairment such as for example vascular lesions, brain tumors or hydrocephalus, secondly in the assessment of a distribution of brain atrophy. A typical pattern of brain atrophy in the course of AD degeneration involves medial temporal lobes and temporo-parietal areas including posterior cingulate gyrus (PCG), followed by frontal lobe atrophy in advanced cases [3, 4]. Moreover, modern advanced MR techniques allow for the assessment of not only brain structure but also its function or metabolism. One of such methods is Dynamic Susceptibility Contrast Enhanced MRI (DSC MRI) enabling insight into the cerebral microcirculation on the basis of evaluation of the first pass of a contrast material through the brain microvasculature. Dynamic Susceptibility Contrast Enhanced MRI requires administration of contrast material and its results are parametric maps for several perfusion parameters among which Cerebral Blood Volume (CBV) is the most important. Perfusion is the fundamental biological function whereby blood flow is responsible for supplying cells with oxygen and nutrients, for this reason perfusion parameters may anticipate in time structural changes seen later on conventional MRI. Reports on DSC MRI studies in AD patients have shown a significant reduction in bilateral CBV values in the temporal-parietal cortex including PCG with a relative sparing of the sensorimotor cortex [5, 6, 7, 8, 9] while in aMCI hypoperfusion was reported mainly in PCG [10, 11]. Some studies have shown a significant correlation of perfusion results with neuropsychological tests in AD and MCI [9, 10].

It has to be stressed that in the pathogenesis of AD degeneration, in addition to the amyloid cascade hypothesis, the vascular hypothesis has been postulated recently. On one hand, it is assumed that amyloid itself shows both neuronal and endothelial toxicity (ABSEN hypothesis) leading to brain degeneration and hypoperfusion [12]. On the other hand, cerebrovascular risk factors including higher level of high-sensitivity C-Reactive Protein (hsCRP) and lower level of high-density lipoprotein (HDL) may cause disturbances of macro- or microvasculature circulation and endothelial damage which contributes to amyloid accumulation and to neuronal death [13, 14]. In line with the new concept of the neurovascular unit, not only amyloid is angiotoxic, but chronic hypoperfusion and vascular damage further accumulate beta amyloid and exacerbate brain degeneration [15].

Fluorodeoxyglucose positron emission tomography (FDG-PET) is a nuclear medicine technique which looks at the cerebral metabolic rate of glucose (CMR glc) and it has been widely used in the diagnosis of dementia. In AD this examination shows glucose hypometabolism in very specific locations called "AD metabolic pattern" including temporo-parietal associative cortex, PCG, precuneus, medial temporal lobes, especially in the entorhinal cortex and the hippocampus [16, 17, 18, 19, 20, 21]. In the advanced course of the disease changes occur in the frontal cortex, with saving primary sensorimotor cortex. However, in MCI, decreased metabolism is mainly found in PCG, and to a lesser extent in the temporo-parietal area, which may be a sensitive prognostic indicator of conversion to AD [20, 22, 23, 24, 25]. Even though FDG-PET is a great method of evaluation of early changes in the brain of AD patients or even in predementia states such as aMCI, its use in everyday clinical practice is limited due to high cost and worse availability. Moreover, it requires injection of radionuclide tracer and uses ionizing radiation since it is performed in conjunction with CT (PET/CT scanner).

Looking at previous studies, structural, perfusion and metabolic changes in AD or aMCI seem to follow the same pattern but there are not many reports comparing them on the same groups of patients. Perfusion and metabolic changes have been reported to proceed structural atrophy but there have been only few reports focusing on direct comparison of MR perfusion with the results of FDG-PET studies in AD and aMCI [5, 8, 9, 11]. Recently, more and more reports are comparing FDG-PET with Arterial Spin Labelling (ASL) MR perfusion which is a technique that does not require injection of any contrast material [26, 27, 28, 29, 30]. The ASL results have been found to correlate with SPECT and PET studies [13, 26, 27, 31, 32]. Despite the great advantage of the lack of contrast agent, prolonged acquisition time in ASL makes it impossible to use in non-cooperative patients (e.g. with advanced dementia). Next disadvantage of ASL is a low signal-to-noise ratio (SNR) and necessity of scanning with 3 Tesla MR machines [33, 34].

Due to low availability of FDG-PET and ASL perfusion we believe that DSC MRI could still play an important role in the diagnosis of dementia as an alternative to those studies. During all the performed MR studies we have not encountered any problems in cooperation with the elderly patients nor any post-contrast side-effects have been reported. It has to be emphasized that modern gadolinium-based contrast materials used in MRI are safe and may cause health problems mainly in patients with severe renal insufficiency.

The major aim of our study was to establish the role of DCS perfusion in relation to FDG-PET imaging based on a detailed comparison of these two techniques. The main assumption of our research was that DSC MR perfusion results should be similar to FDG-PET studies because glucose metabolism is partially dependent on cerebral perfusion. The comparison of DSC MR perfusion and FDG-PET was performed based on: 1) the assessment of hypoperfusion and hypometabolism patterns in the selected brain areas in AD and aMCI, 2) the rate of correlation between the results of these two techniques and their accuracy in diagnosis of AD and aMCI, 3) the assessment of correlation between the results of DSC perfusion or FDG-PET and the severity of cognitive impairment in AD and aMCI. Our study comparing DSC MR perfusion with FDG-PET results in AD and aMCI fills the gap in the existing scientific literature.

2. Methods

2.1. Subjects

The research material consisted of 66 patients: 27 with AD (mean age 70.33 years, mean MMSE 18.67 points), 39 diagnosed with aMCI (mean age 66.6 years, mean MMSE 26.2 points). In addition, a control group of 16 subjects (mean age 65 years, mean MMSE 27.1 points) was recruited. All subjects underwent detailed psychiatric examination, as well as laboratory and neuropsychological tests including Mini-Mental State Examination (MMSE) adjusted for age and education level, Clinical Dementia Rating (CDR), Clock Drawing Test, Test Your Memory, Dementia Toolkit for Effective Communication, verbal fluency FAS test, Instrumental Activity of Daily Living, and Geriatric Depression Scale. The distribution of age, gender as well as MMSE scores for each group are presented in Table 1. The study was conducted in accordance with the guidelines of the University Ethics Committee for conducting research involving humans. Each patient provided his/her signed consent to participate in the study.

Table 1
The distribution of age, gender, MMSE scores within the subject groups
(mean±standard deviation)

	AD	aMCI	CG
Patients (n)	27	39	16
Age (years)	70.33 ± 8.68	66.59 ± 10.2	65 ± 8.38
Gender (male/female)	10/17	20/19	4/12
MMSE (points)	18.67 ± 5	26.2 ± 1.87	27.1 ± 1.2

AD – Alzheimer’s Disease; aMCI - amnesic mild cognitive impairment; CG – Control Group, MMSE - Mini-Mental State Examination (severe dementia 0–10 points, moderate dementia 11–18 points, mild dementia 19–23 points, mild cognitive impairment without dementia 24–26 points, normal 27–30 points)

2.2. Magnetic resonance examination

All MR examinations of the brain were performed with a 1.5 Tesla MR scanner (Signa Hdx, GE Medical Systems) using a 16-channel HNS (head-neck-spine) coil. Standard structural protocol was followed by DSC MR perfusion using fast echo planar (EPI) gradient T2*-weighted sequences with the parameters: TR = 1.900 ms, TE = 80 ms, FOV= 30 cm, matrix = 192×128, slice thickness = 8mm without spacing, NEX – 1.0. Ten seconds after the start of image acquisition, a bolus of 1.0 mol/l gadobutrol formula (Gadovist, Schering, Berlin, Germany) in a dose of 0.2 ml/kg of body weight was injected via a 20-gauge catheter placed in the antecubital vein. Contrast administration was performed using

an automatic injector (Medrad) at a rate of 5 ml/s and was followed by a saline bolus (20 ml at 5 ml/s). The whole perfusion imaging lasted 1 min 26 s in which sets of images from 13 axial slices were obtained before, during, and after contrast injection. The dynamic images were postprocessed into parametric perfusion maps using Functool software (GE, ADW 4.6). Maps of Cerebral Blood Volume (CBV) were computed on a pixel-wise basis from the first-pass data from the capillary bed. Values of CBV were obtained using manually drawn Regions of Interest (ROIs) within the frontal, temporal and parietal cerebral cortex (500 and 900 mm² in size), and the cingulate gyrus (100-200 mm² in size). The CBV values obtained from several ROIs were mathematically averaged to one frontal, temporal or parietal cortical value, separately for the right and left hemisphere. All CBV values were normalized to the mean CBV value of the cerebellar cortex in order to obtain the relative CBV (rCBV). The cerebellar cortex was chosen as the reference area because it is the region less affected in AD compared to other cortical measures [20]. The ROI in the cerebellum was approximately 300-400 mm² in size (Fig. 1). The location of the ROIs was chosen to best correspond with the glucose metabolism measurements in the FDG-PET study (Tab. 2).

Table 2
Nomenclature of the analyzed brain areas.

Names of the analyzed cortical regions	ROIs analyzed in DSC-MRI	Cortical regions in FDG-PET
R frontal (right frontal cortex)	mean of the three ROIs from the right frontal cortex	Frontal Association Right
L frontal (left frontal cortex)	mean of the three ROIs from the left frontal cortex	Frontal Association Left
R temporal (right temporal cortex)	mean of the two ROIs from the right temporal cortex	Temporal Association Right
L temporal (left temporal cortex)	mean of the two ROIs from the left temporal cortex	Temporal Association Left
R parietal (right parietal cortex)	mean of the two ROIs from the right parietal cortex	Parietal Association Right
L parietal (left parietal cortex)	mean of the two ROIs from the left parietal cortex	Parietal Association Left
R PCG (right posterior cingulate gyrus)	one ROI in the posterior part of the right cingulate gyrus	Posterior Cingulate Right
L PCG (left posterior cingulate gyrus)	one ROI in the posterior part of the left cingulate gyrus	Posterior Cingulate Left

ROI - Region of Interest, DSC-MRI - Dynamic Susceptibility Contrast Enhanced Magnetic Resonance Imaging, FDG-PET - Fluorodeoxyglucose Positron Emission Tomography

2.3. PET examination

PET studies were performed within 3 weeks after the MR examination. The PET images were obtained using a GE Discovery STE16 PET/CT scanner with [¹⁸F] Fluorodeoxyglucose (FDG) as a radiotracer. All participants fasted at least 6 h before examination. Data acquisition lasted 8 min and was performed 30 min after intravenous injection of 5 MBq/kg of FDG. Detector spatial resolution was 5.6 mm and data were displayed on a 128×128 pixel matrix. To avoid external stimulation during FDG uptake patients stayed in a resting condition in a darkened room. The acquired data were processed using iterative reconstructions. Attenuation and scatter corrections were made simultaneously by transmission measurements using CT. Next, PET/CT images were transferred to a workstation (GE Healthcare) and processed using commercial CORTEX ID application. Scans were spatially normalized to a stereotactic space based on the Talairach and Tournoux atlas [35]. Then brain images underwent size correction to standard dimensions of 3D-atlas and a regional anatomic variants correction to decrease individual variations. All data were normalized to the mean FDG uptake value of the cerebellum, where glucose utilization is comparatively preserved in dementia [36]. Realigned FDG-PET scans of all subjects were compared with a normative, age stratified reference database included in the CORTEX ID program. Metabolic activity was automatically determined in 14 cerebral regions and z-scores [(mean subject – mean database)/SD database] were calculated. Z-scores data were exhibited as 3D-SSP (Three Dimensional Stereotactic Surface Projection) images [37] to visualize abnormalities with high z-score values pointing out reduction of FDG uptake and glucose hypometabolism (Fig. 2).

Color-coded maps of absolute glucose metabolism - top two rows; color-coded maps of glucose metabolism in z-scores - bottom two rows; parametric values of z-scores of glucose metabolism normalized to the cerebellum - table on the right.

2.4. Statistical analysis

To compare DSC MRI with the FDG-PET studies, two types of perfusion parameters were used such as rCBV values and rCBV z-score. The rCBV z-score was used to make the MR results as similar as possible to the FDG-PET results, in which the level of glucose metabolism is automatically presented in the form of z-score that indicates the number of standard deviations of a given parameter from a population norm. A typical formula was used to calculate the rCBV z-score such as $(\mu - x) / \sigma$ with μ representing mean rCBV value for CG, x meaning the mean rCBV value for a given patient and σ standing for standard deviation of CG. In both DSC MRI and FDG-PET higher z-scores meant higher rate

of perfusion or metabolic impairment. The comparison of mean age and the results of DSC MRI and FDG-PET between the AD, MCI and CG groups was carried out using the ANOVA method followed by a Scheffe's post hoc test to compare the results in pairs between MCI and CG, AD and CG as well as AD and MCI. In turn, analyzes of correlation between MR perfusion and FDG-PET results as well as between the results of MR perfusion or FDG-PET and the results of psychological tests were performed using the Pearson correlation coefficient. Additionally, the sensitivity and specificity of MR and PET parameters in differentiating between AD, MCI and CG were calculated using the Receiver-Operating Characteristic (ROC) method, in which the accuracy of the test is indicated by the area under the ROC curve. In all statistical analyzes, p value of <0.05 was considered statistically significant. In the case of the rCBV z-score and PET z-score parameters, z-scores ≥ 1 were considered to be significantly different from the CG.

3. Results

In AD patients compared to CG, DSC-MRI results showed significantly decreased rCBV values ($p \leq 0.05$) and significantly higher z-core rCBV values (z-score ≥ 1) in all examined cortical locations.

Compared to healthy controls, MCI patients showed a significant decrease of rCBV values within the cortex of both parietal and temporal lobes and left PCG, while using the rCBV z-score significant hypoperfusion was found within the right parietal lobe.

The AD group compared to the MCI group, showed significantly lower rCBV values and higher rCBV z-scores within all examined areas of the brain cortex (Table 3).

Table 3
Comparison of MR perfusion and FDG-PET results from different cortical locations between AD, MCI and control groups.

Comparison of AD, MCI, and CG groups													
mean rCBV				rCBV z-score				PET z-score					
Study groups				ANOVA	Scheffe's post hoc test			Study groups		Scheffe's post hoc test	Study groups		Scheffe's post hoc test
Cortical location	AD (SD)	MCI (SD)	CG (SD)	p value	AD vs CG p value	MCI vs CG p value	AD vs MCI p value	AD (SD)	MCI (SD)	AD vs MCI p value	AD (SD)	MCI (SD)	AD vs MCI p value
R frontal	0.90 (0.11)	1.09 (0.19)	1.18 (0.17)	< 0.001*	< 0.001*	0.22	< 0.001*	1.64 (0.66)	0.51 (1.55)	< 0.001*	1.55 (1)	0.9 (0.44)	< 0.001*
L frontal	0.86 (0.1)	1.09 (0.22)	1.18 (0.13)	< 0.001*	< 0.001*	0.26	< 0.001*	2.44 (0.83)	0.65 (1.66)	< 0.001*	1.93 (1.25)	0.97 (0.49)	< 0.001*
R temporal	0.85 (0.09)	1.11 (0.18)	1.29 (0.3)	< 0.001*	< 0.001*	0.013*	< 0.001*	1.4 (0.29)	0.57 (0.61)	< 0.001*	2.24 (0.86)	1.02 (0.4)	< 0.001*
L temporal	0.85 (0.1)	1.09 (0.17)	1.3 (0.4)	< 0.001*	< 0.001*	0.01*	< 0.001*	1.12 (0.24)	0.52 (0.43)	< 0.001*	2.52 (0.96)	1.01 (0.47)	< 0.001*
R parietal	0.83 (0.09)	1.08 (0.18)	1.23 (0.14)	< 0.001*	< 0.001*	0.005*	< 0.001*	2.9 (0.68)	1.08 (1.33)	< 0.001*	2.5 (1.1)	1.31 (0.58)	< 0.001*
L parietal	0.81 (0.10)	1.08 (0.20)	1.24 (0.16)	< 0.001*	< 0.001*	0.008*	< 0.001*	2.64 (0.6)	0.95 (1.2)	< 0.001*	2.73 (1.23)	1.29 (0.61)	< 0.001*
R PCG	0.8 (0.11)	1.06 (0.22)	1.2 (0.22)	< 0.001*	< 0.001*	0.056	< 0.001*	1.83 (0.53)	0.64 (1.02)	< 0.001*	1.84 (0.71)	0.94 (0.58)	< 0.001*
L PCG	0.79 (0.11)	1.09 (0.22)	1.24 (0.23)	< 0.001*	< 0.001*	0.040*	< 0.001*	1.96 (0.48)	0.64 (0.94)	< 0.001*	2.12 (0.73)	1.03 (0.55)	< 0.001*
SD - standard deviation, * - statistically significant values p < 0.05, R - right, L - left, PCG - posterior cingulate gyrus, AD – Alzheimer's Disease, MCI - Mild Cognitive Impairment, CG - Control Group, rCBV - relative Cerebral Blood Volume													

The FDG-PET study in the AD group showed significant glucose hypometabolism within all measured areas of the cerebral cortex, while in the MCI group within the cortex of both parietal and temporal regions and left PCG. The greatest impairment of glucose metabolism in patients with AD, as well as in patients with MCI, was demonstrated in the parietal, temporal and left PCG regions. The AD patients compared to MCI subjects showed significantly higher impairment of glucose metabolism in all evaluated locations (Table 3).

In AD patients statistically significant positive correlations between MR perfusion and FDG-PET results were found almost for all evaluated cortical regions apart from right parietal cortex. In the MCI group there was only one single correlation between these two techniques found within the left PCG ($r = 0.4$, $p = 0.01$). In the combined group (AD + MCI) the PET z-score and rCBV z-score analysis showed statistically significant positive correlations in all locations. These correlations were strongly positive in the area of PCG and in the temporal lobes ($r > 0.5$), moderately positive in the area of the parietal lobes, and weaker in other locations ($r < 0.5$) (Tab. 4).

Table 4
The results of correlation between rCBV z-score and FDG-PET z-score separately for AD and MCI groups and for all patients (AD + MCI).

Location	AD	MCI	AD + MCI
R front	$r = 0.47$ $p = 0.01^*$	$r = -0.12$ $p = 0.46$	$r = 0.30$ $p = 0.01^*$
L front	$r = 0.39$ $p = 0.04^*$	$r = -0.16$ $p = 0.31$	$r = 0.31$ $p = 0.01^*$
R temp	$r = 0.49$ $p = 0.01^*$	$r = 0.27$ $p = 1$	$r = 0.6$ $p < 0.001^*$
L temp	$r = 0.48$ $p = 0.01^*$	$r = 0.02$ $p = 0.88$	$r = 0.55$ $p < 0.001^*$
R pariet	$r = 0.25$ $p = 0.2$	$r = 0.15$ $p = 0.35$	$r = 0.46$ $p < 0.001^*$
L pariet	$r = 0.5$ $p = 0.007^*$	$r = -0.1$ $p = 0.55$	$r = 0.45$ $p < 0.001^*$
R PCG	$r = 0.45$ $p = 0.01^*$	$r = 0.28$ $p = 0.8$	$r = 0.53$ $p < 0.001^*$
L PCG	$r = 0.42$ $p = 0.03^*$	$r = 0.4$ $p = 0.01$	$r = 0.63$ $p < 0.001^*$

r - Pearson correlation coefficient, p - probability value, SD - standard deviation, * - statistically significant values $p < 0.05$, R - right, L - left, PCG - posterior cingulate gyrus, AD - Alzheimer's Disease, MCI - Mild Cognitive Impairment

The third figure shows exemplary graphs of correlation between rCBV z-score and PET z-score in the right and left PCG regions in AD, MCI and the combined group (Fig. 3).

L PCG - left posterior cingulate gyrus, R PCG - right posterior cingulate gyrus, AD - Alzheimer's Disease, MCI - Mild Cognitive Impairment, rCBV - relative Cerebral Blood Volume

In distinguishing MCI from CG the highest sensitivity, specificity and accuracy (0.95, 1.0 and 0.95, respectively) were found for PET z-score, followed by rCBV z-score and rCBV (Table 5). The highest sensitivity, specificity and accuracy (0.98, 1.0 and 0.98, respectively) in distinguishing AD from CG were revealed for rCBV z-score, followed by FDG-PET z-score and rCBV (Table 5). And lastly, in differentiating AD from MCI the same sensitivity, specificity and accuracy (0.66, 0.94 and 0.84, respectively) were found for both rCBV z-score and rCBV (Table 5).

Table 5
Average values of sensitivity, specificity and accuracy of DSC-MRI and FDG-PET studies in the diagnosis of AD and MCI.

Compared groups	Parameter	Sensitivity	Specificity	Accuracy
MCI vs CG	rCBV	0.57	0.80	0.68
	rCBV z-score	0.76	1.00	0.77
	PET z-score	0.95	1.00	0.95
AD vs CG	rCBV	0.94	0.93	0.95
	rCBV z-score	0.98	1.00	0.98
	PET z-score	0.97	1.00	0.97
AD vs MCI	rCBV	0.66	0.94	0.84
	rCBV z-score	0.66	0.94	0.84
	PET z-score	0.82	0.77	0.81
AD – Alzheimer's Disease, MCI - Mild Cognitive Impairment, rCBV - relative Cerebral Blood Volume				
<p>The results of the study did not reveal many statistically significant correlations between FDG-PET or MR perfusion parameters and the results of the MMSE test in the separate MCI and AD groups. In AD, statistically significant correlations ($r = 0.3-0.4$) were found with the results of MR perfusion from the left parietal and left temporal lobes. When analyzing patients with MCI, statistically significant correlations were shown ($r = 0.3-0.4$) for PCG and both parietal cortices. In turn, in the FDG-PET study, statistically significant correlations ($r = 0.47$) with MMSE were found only in AD patients with the results from the left frontal lobe. After combining all AD and MCI subject in one bigger group (AD + MCI), a statistically significant correlation between MR perfusion or FDG-PET results and MMSE test was found in all examined locations (Table 6).</p>				

Table 6
The results of correlation between MR perfusion, FDG-PET and Mini-Mental test (MMSE).

	AD			MCI			AD + MCI		
Cortical location	rCBV	rCBV z-score	PET z-score	rCBV	rCBV z-score	PET z-score	rCBV	rCBV z-score	PET z-score
R frontal	r = 0.16 p = 0.43	r = - 0.16 p = 0.43	r = - 0.28 p = 0.14	r = 0.22 p = 0.18	r = - 0.22 p = 0.18	r = 0.21 p = 0.198	r = 0.46 p < 0.001*	r = - 0.46 p < 0.001*	r = - 0.42 p < 0.001*
L frontal	r = 0.2 p = 0.29	r = - 0.2 p = 0.29	r = - 0.47 p = 0.014*	r = 0.29 p = 0.073	r = - 0.29 p = 0.073	r = 0.025 p = 0.12	r = 0.52 p < 0.001*	r = - 0.52 p < 0.001*	r = - 0.56 p < 0.001*
R temporal	r = 0.28 p = 0.16	r = - 0.28 p = 0.16	r = 0.16 p = 0.4	r = 0.18 p = 0.26	r = - 0.18 p = 0.26	r = - 0.03 p = 0.85	r = 0.57 p < 0.001*	r = - 0.57 p < 0.001*	r = - 0.47 p < 0.001*
L temporal	r = 0.4 p = 0.03*	r = - 0.4 p = 0.03*	r = - 0.25 p = 0.21	r = 0.07 p = 0.69	r = - 0.07 p = 0.69	r = - 0.04 p = 0.77	r = 0.57 p < 0.001*	r = - 0.57 p < 0.001*	r = - 0.65 p < 0.001*
R parietal	r = 0.11 p = 0.57	r = - 0.11 p = 0.57	r = - 0.01 p = 0.96	r = 0.34 p = 0.034*	r = - 0.34 p = 0.034*	r = 0.05 p = 0.74	r = 0.57 p < 0.001*	r = - 0.57 p < 0.001*	r = - 0.43 p < 0.001*
L parietal	r = 0.38 p = 0.048*	r = - 0.38 p = 0.048*	r = - 0.36 p = 0.06	r = 0.34 p = 0.035*	r = - 0.34 p = 0.035*	r = 0.52 p = 0.75	r = 0.62 p < 0.001*	r = - 0.62 p < 0.001*	r = - 0.61 p < 0.001*
R PCG	r = - 0.05 p = 0.8	r = - 0.05 p = 0.8	r = - 0.14 p = 0.49	r = 0.4 p = 0.009*	r = - 0.4 p = 0.009*	r = - 0.5 p = 0.74	r = 0.5 p < 0.001*	r = - 0.5 p < 0.001*	r = - 0.4 p = 0.001*
L PCG	r = 0.11 p = 0.56	r = - 0.11 p = 0.56	r = - 0.17 p = 0.38	r = 0.37 p = 0.024*	r = - 0.37 p = 0.024*	r = - 0.14 p = 0.49	r = 0.58 p < 0.001*	r = - 0.58 p < 0.001*	r = - 0.57 p < 0.001*
r - Pearson correlation coefficient, * - statistically significant values p < 0.05, R - right, L - left, PCG - posterior cingulate gyrus, AD - Alzheimer's Disease, MCI - Mild Cognitive Impairment, rCBV - relative Cerebral Blood Volume									

4. Discussion

The aim of our study was to compare DSC MR perfusion and FDG-PET studies based on 1) the assessment of hypoperfusion and hypometabolism patterns in the selected brain areas in AD and MCI, 2) the rate of correlation between the results of these two techniques and their accuracy in diagnosis of AD and MCI, and 3) the assessment of correlation between the results of DSC MRI and FDG-PET with the severity of cognitive impairment in AD and MCI.

In our study AD patients, compared to the control group, showed significant hypoperfusion in all examined cortical localizations. Our results are consistent with the typical pattern of Alzheimer's degeneration and hypoperfusion reported in numerous publications within PCG, temporo-parietal cortices, and in later stages also frontal cortices with relative sparing of sensorimotor cortex [5, 6, 9, 38, 39]. In the MCI group, compared to controls, we found significantly decreased rCBV values within the cortex of both parietal lobes, temporal lobes and left PCG, while using the rCBV z-scores significant hypoperfusion was detected in the right parietal cortex, which is also consistent with the pattern of very early alterations in the course of AD pathology [6, 10, 11, 39, 40]. In the MCI group perfusion alterations were less severe than in the AD group, which confirms the theory that hypoperfusion is a marker of neuronal damage and becomes more prominent in the later stages of AD.

In our study the FDG-PET results in AD showed the greatest impairment of glucose metabolism in the parietal, temporal and left PCG regions, followed by hypometabolism in the frontal cortices while MCI subjects showed less severe hypometabolism mainly in the parieto-temporal regions and left PCG. Both these results are in accordance with the commonly accepted metabolic pattern in the course of AD [18, 19, 20, 21].

In our study in the AD patients we found significant correlations between the results of DSC MRI and FDG-PET in almost all evaluated locations apart from the right parietal cortex while in the MCI group there was only single correlation within the left PCG. Single correlation in case of MCI was probably due to a small sample of subjects. After combining AD and MCI subjects in one group significant correlations between MR perfusion and FDG-PET studies were revealed in all evaluated locations, probably due to the strong influence of the AD group. The strongest correlations were revealed within temporal ($r = 0.55-0.6$) and PCG ($r = 0.53-0.63$) regions followed by parietal ($r = 0.45-0.46$) cortices which are the regions of the most pronounced and typical changes in the course of AD degeneration. To our knowledge in the literature there are only two reports comparing DSC MRI with FDG-PET in AD and MCI. In the first paper by Gonzales et al the authors performed their study only on 10 patients with dementia (6 with AD) using visual evaluation of rCBV and brain glucose metabolism maps [8]. They compared the results within 8 brain layers and demonstrated a significant correlation ($r = 0.62$) at the levels of the upper and supraventricular layers. The mean correlation from all layers was $r = 0.53$, with the temporal area and the posterior fossa showing the weakest correlations ($r = 0.24-0.33$) what was explained by artifacts related to the vessel pulsation. Our results do not fully agree with these findings but it has to be stressed that our analyses were carried out on a bigger number of subjects and were based on parametrical values of rCBV and glucose metabolism and thus seem to be more accurate than a visual assessment. In the second report Zimny et al showed a statistically significant correlation ($r = 0.44$) of rCBV measurements and FDG-PET results in PCG [11]. The results of this report are partially consistent with our findings in the left PCG ($r = 0.4$). However, the authors did not compare other regions of the brain and did not separate PCG into the right and left regions.

Recently more reports have focused on the comparison of FDG-PET with a non-contrast MR perfusion technique such as ASL. Fällmar et al demonstrated a positive predictive value of ASL MR in AD and FTLT patients using visually analyzed perfusion maps and high specificity (0.84) of diagnoses, despite lower sensitivity (0.53) compared to FDG-PET (0.96) [41]. Similarly, Musiek et al demonstrated, using visual inspection of perfusion and glucose metabolism maps, that both methods showed alterations in parieto-temporal areas, while the FDG-PET examination also depicted hypometabolism within the frontal lobes [27]. Johnson et al comparing ASL MR and FDG-PET techniques in AD group showed that in both techniques lower parts of the parietal lobes, PCG, superior and middle frontal gyrus were involved. However this study had a technical limitation, namely the spins were labeled at the level of the Willis arterial circle and thus the assessment of perfusion in temporal and inferior frontal gyri was not possible [26]. On the other hand, in MCI group Johnson et al showed a reduction in perfusion in the lower part of the right parietal lobe, which was slightly consistent with the pattern of glucose hypometabolism [26]. Riederer et al also using ASL MR method in MCI showed no statistically significant differences in ASL perfusion rCBF parameter between aMCI and CG, in contrast to FDG-PET studies, which showed hypometabolism on both sides of inferior parietal, superior temporal, right prefrontal dorsolateral cortex, precuneus, PCG and MTL [28]. All the above studies were performed using only visual inspection of ASL MRI and FDG-PET maps. Despite a growing interest in the ASL perfusion due to the lack of contrast material needed during the examination, this MR method has several drawbacks. One of them is a prolonged acquisition time which makes ASL impossible to be used in non-cooperative patients (e.g. with advanced dementia). Other disadvantages are the necessity of 3 Tesla MR scanners to obtain reliable data which are not widely available and a low signal-to-noise ratio (SNR).

In the next part of the study we evaluated sensitivity and specificity as well as accuracy of DSC-MRI and FDG-PET studies in distinguishing AD and MCI from healthy controls. We found very similar high accuracy of DSC-MR perfusion and FDG-PET in distinguishing AD from the control group (0.98 and 0.97, respectively), and markedly higher accuracy of FDG-PET than DSC-MR perfusion in differentiation of MCI from the control group (0.96 and 0.68-0.77, respectively). When distinguishing AD from MCI both methods showed intermediate accuracy around 0.84 for MR and 0.81 for PET studies. It has to be stressed that though there are many reports in the literature showing the results of sensitivity, specificity and accuracy of DSC-MRI or FDG-PET in the diagnosis of AD or MCI, none of them were performed on the same groups of patients.

There are several reports evaluating MR perfusion in differentiation of AD from CG based on temporo-parietal areas and results are slightly worse than in this study, for example Harris et al defined sensitivity as 0.95 in moderately affected patients with AD and 0.88 in mild cases of AD, whereas specificity as 0.96 [6]. In turn Bozzao et al in distinguishing AD from CG achieved sensitivity of 0.91 and specificity of 0.87, while Maas et al 0.8 and 0.88 for sensitivity and specificity, respectively [5, 9]. On the other hand, Zimny et al in the regions of PCG alone showed the accuracy of AD diagnosis as 0.87 [10], so lower than in our study (accuracy 1.0). Our results of FDG-PET in differentiating AD from CG (sensitivity 0.97, specificity 1.0, accuracy 0.97) are similar to other publications by Gambir et al (reported sensitivity of 0.9-0.96, specificity of 0.67-0.97 and accuracy of 0.89), Mosconi et al (reported sensitivity of 0.99, specificity of 0.98 accuracy of 0.98) or Gupta et al (reported sensitivity of 0.9, specificity of 0.9 and accuracy of 0.92) and much higher compared to other studies reporting their sensitivity, specificity and accuracy results below 0.9 [18, 42, 43, 44, 45]. It should be emphasized that in MCI subjects cognitive functions are impaired to intermediate degree between proper aging and dementia and there are so-called overlap periods, so distinguishing AD from MCI is a more difficult task than AD from CG [1]. To our knowledge there are no reports in the literature in which authors would provide the accuracy values of MR perfusion in differentiating AD from MCI. In the differentiation of AD from MCI using FDG-PET method our results are similar to literature. Gupta et al when distinguishing AD from converting MCI assessed sensitivity, specificity and accuracy as 0.67, 0.88, 0.81 respectively (our study 0.82, 0.77, 0.81 respectively) [43]. According to De Santi et al it is best to differentiate AD from MCI based on results of glucose metabolism in the temporal

lobes, which is consistent with the results of our study where accuracy from this cortical location was greater (0.9-0.92) than in other regions [46]. Regarding differentiation of MCI from CG using DSC-MRI our study showed better results to some previous reports for example by Zimny et al who based on evaluation of PCG determined sensitivity, specificity and accuracy 0.72, 0.8, 0.7 respectively and in the next study accuracy as 0.67. [10, 11]. In the differentiation of MCI from CG using FDG-PET method our results are similar to literature [18, 19, 43]. For example, Gupta et al analyzing MCI converting to AD from CG showed the sensitivity, specificity and accuracy as 0.98, 1, 0.8 respectively (our study 0.95, 1.0, 0.95 respectively).

In the last part of our study we evaluated correlations between the results of DSC-MRI or FDG-PET studies and the results of the MMSE test. In AD, statistically significant correlations were found with the results of MR perfusion from the left parietal and left temporal lobes while in MCI in PCG and both parietal cortices. In the FDG-PET study, statistically significant correlations with MMSE were found only in AD patients with the results from the left frontal cortex. However, it should be emphasized that after combining all AD and MCI subject in one bigger group a statistically significant correlation between MR perfusion or FDG-PET results and MMSE test was found in all examined locations. So summarizing, it should be stated that in a larger group the results of these correlations are very similar for DSC-MR perfusion and FDG-PET. In the literature the results of correlation of MMSE test with DSC-MRI are ambiguous. Some authors showed no correlation of rCBV parameter with the MMSE test in AD or MCI patients [6, 38, 39] and several other authors found such correlations [9, 10]. The lack of correlation of psychological tests in separate groups of AD and MCI with FDG-PET results is in contradiction with several literature reports [45, 47, 48, 49].

There are a few limitations of our study. Firstly, manual determination of ROIs is somewhat subjective and makes the method operator-dependent. Secondly, rather small groups of subjects may have had an impact on some results. We assessed more significant correlations after combining patients in a larger group of AD and MCI subjects. Another drawback is a cross-sectional character of the study. We have not evaluated longitudinal results regarding follow-up studies of aMCI subjects and a rate of their progression to dementia. It would be very interesting to check if DSC-MR perfusion has a similar strength as FDG-PET in predicting such a conversion.

Conclusion

In our study we proved that aMCI and AD patients show very similar patterns of hypoperfusion in DSC-MR and glucose hypometabolism in FDG-PET with a high rate of significant correlations between these two techniques. FDG-PET seems to be a better method in diagnosis of MCI while DSC-MR perfusion was found to be more accurate in diagnosis of AD.

We believe that DSC-MR may be a good alternative to FDG-PET studies in patients with dementia. FDG-PET studies are still not widely available and very expensive while MR examination is a routine study in the work-up of patients with dementia or MCI. A standard MR examination may be easily extended with DSC perfusion which is a fast and fairly easy sequence to be performed.

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Figures

Figure 1

Location of particular Regions of Interest on CBV maps.

(a, b, c) – right and left frontal cortices, (d, e) – right and left parietal cortices, (f) – right and left posterior aspects of the cingulate gyri (PCG), (g, h) – right and left temporal cortices, (i) – right and left cerebellar hemispheres.

Figure 2

An example of the FDG-PET study result of a single patient presented as color-coded maps.

Figure 3

Graphs of the most significant correlations between rCBV z-score and PET z-score in PCG regions.