

Association between Cognitive Performance and Cortical Glucose Metabolism in Patients with Mild Alzheimer's Disease

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Key Words

Brain atrophy · Partial volume effects · Alzheimer's disease · Metabolism · Brain imaging techniques

Abstract

Background: Neuronal and synaptic function in Alzheimer's disease (AD) is measured in vivo by glucose metabolism using positron emission tomography (PET). **Objective:** We hypothesized that neuronal activation as measured by PET is a more sensitive index of neuronal dysfunction than activity during rest. We investigated if the correlations between dementia severity as measured with the Mini Mental State Examination (MMSE) and glucose metabolism are an artifact of brain atrophy. **Method:** Glucose metabolism was measured using [¹⁸F]fluorodeoxyglucose PET during rest and activation due to audiovisual stimulation in 13 mild to moderate AD patients (MMSE score ≥ 17). PET data were corrected for brain atrophy. **Results:** In the rest condition, glucose metabolism was correlated with the MMSE score primarily within the posterior cingulate and parietal lobes. For the activation condition, additional correlations were within

the primary and association audiovisual areas. Most local maxima remained significant after correcting for brain atrophy. **Conclusion:** PET activity measured during audiovisual stimulation was more sensitive to functional alterations in glucose metabolism in AD patients compared to the resting PET. The association between glucose metabolism and MMSE score was not dependent on brain atrophy.

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Introduction

Alzheimer's disease (AD) leads to regional neuronal and synaptic dysfunction in the brain. A sensitive index of neuronal and synaptic dysfunction is the regional cerebral metabolism rate for glucose (rCMR_{glc}) measured with positron emission tomography (PET) [1, 2]. In the early stages of AD, hypometabolism has been found within the temporal and parietal lobes [3–7]. At the earliest clinical stages of the disease, compensatory mechanisms may lead to relatively stable resting metabolism levels [8] but neuronal activity may not be sufficient to respond

Table 1. Local maxima of the positive correlation coefficients between resting glucose metabolism and MMSE scores before PVE correction and after PVE correction

Region	Broadman area	Coordinates			Correlation	
					before PVE correction	after PVE correction
<i>Right hemisphere</i>						
Parietal lobe						
Inferior parietal lobule	40	54	-46	34	0.61	0.56
	40	34	-56	40	0.68	0.64
	40	64	-40	42	0.62	0.20
	40	44	-52	44	0.67	0.56
Occipital lobe						
Fusiform gyrus	18	16	-100	-20	0.69	0.54
<i>Left hemisphere</i>						
Parietal lobe						
Inferior parietal lobule	40	-48	-42	24	0.60	0.39
	7	-44	-66	50	0.57	0.53
Posterior cingulate	31	0	-38	38	0.67	0.58
Temporal lobe						
Inferior temporal gyrus	20	-42	12	-22	0.56	0.28
Occipital lobe						
Precuneus	7	-4	-64	68	0.55	0.73
Cerebellum						
		-38	-92	-20	0.61	0.69
		-4	-90	-22	0.70	0.55

fully to functional stimulation [9–11]. In a group of patients with mild to severe AD, it was shown that rCMRglc was more sensitive to neuronal and synaptic dysfunction during audiovisual stimulation compared to resting rCMRglc [12]. Thus, PET during stimulation could be a more sensitive index of neuronal and synaptic dysfunction compared to resting state PET [13].

Because of the low spatial resolution of the PET scanner relative to the thickness of the grey matter (GM) layer, the activity measured by PET is an average of activity of the GM and nearby tissue such as white matter and cerebrospinal fluid [14, 15]. This leads to an underestimation of the rCMRglc activity in the GM called partial volume effects (PVE). In addition, brain atrophy compromises the PET assessment of neuronal and synaptic dysfunction because brain atrophy artificially decreases the measured brain metabolism. In mild AD patients, brain atrophy was present in regions that showed decreased glucose metabolism [16, 17]. The matching pattern of glucose metabolism abnormalities and brain atrophy suggested that the pattern of metabolism abnormalities in mild AD patients may have been due in part to brain atrophy.

The objective of this study was to investigate if activation PET shows greater sensitivity to neural and synaptic dysfunction than resting PET in a group of patients with

mild to moderate AD. In addition, we investigated the effect of PVE on the correlation between regional cortical glucose metabolism and MMSE score. This is the first study that applies PVE correction to the analysis of resting and activation metabolism measurements based on GM volume.

Materials and Methods

Subjects

We studied 13 patients (male = 9) with AD [mean age = 66.9 years, standard deviation (SD) = 8.6]. The patients met the NINCDC-ADRDA criteria [18] for probable AD and had an average MMSE score of 23.4 (SD = 3.5, range 17–29). The clinical evaluation included medical, neurological, psychiatric, and neuropsychological examinations, laboratory testing, EEG, ECG and structural magnetic resonance imaging (MRI). The presence of ischemic lesions in the patient group was excluded on the basis of T₂-weighted MR scans. The patients gave their consent to the study after detailed information on the study had been given to them. The study was approved by the Ethics Committee of the Medical Faculty of the Ludwig-Maximilian University and the Radiation Protection Authority.

PET and Magnetic Resonance Acquisition

A high-resolution Siemens ECAT HR+ PET scanner (Siemens/CTI, Knoxville, Tenn., USA) was used to measure regional glucose metabolism. A transmission scan was done at the same level as the emission scans to correct for attenuation effects.

Table 2. Local maxima of the positive correlation coefficients between resting glucose metabolism and MMSE scores after PVE correction and before PVE correction

Region	Broadman area	Coordinates			Correlation	
					after PVE correction	before PVE correction
<i>Right hemisphere</i>						
Parietal lobe						
Supramarginal gyrus	40	54	-50	32	0.64	0.57
Inferior parietal lobule	40	48	-54	46	0.57	0.63
Paracentral lobule	31	2	24	46	0.53	0.46
Posterior cingulate	31	2	-40	40	0.60	0.63
Superior parietal lobule	7	32	-58	40	0.67	0.64
Occipital lobe						
Precuneus	7	4	-56	32	0.60	0.54
Cuneus	30	22	-72	12	0.67	0.35
Fusiform gyrus	18	20	-100	-22	0.54	0.68
<i>Left hemisphere</i>						
Parietal lobe						
Postcentral gyrus						
Inferior parietal lobule	40	-52	-42	38	0.63	0.45
	40	-48	-64	44	0.57	0.53
	7	-30	-52	44	0.62	0.49
Precuneus	7	-2	-62	68	0.74	0.54
Superior parietal lobule	7	-46	-64	52	0.54	0.57
	7	-26	-80	56	0.73	0.53
	7	-20	-64	70	0.60	0.50
Temporal lobe						
Middle temporal gyrus	38	-52	-34	-2	0.58	0.48
Superior temporal gyrus	22	-50	-54	18	0.56	0.50
Occipital Lobe						
Middle occipital lobule	18	-30	-94	6	0.58	0.48
Inferior occipital lobule	19	-38	-94	-18	0.70	0.59
Cuneus	18	-12	-76	16	0.68	0.41
	19	-2	-90	34	0.65	0.34
Fusiform gyrus	19	-48	-80	-18	0.56	0.46
Gyrus lingualis	17	-2	-92	-20	0.64	0.61
Cerebellum		-52	-68	-24	0.59	0.52

Each patient underwent one PET scan for the rest and one for the audiovisual stimulation condition, respectively, where [¹⁸F]2-fluoro-2-deoxyglucose was used as a tracer. For the resting condition, the patients remained on the scanner bed (eyes patched and ears plugged). The audiovisual stimulation consisted of an episode of the movie 'Wizard of Oz', which was commenced after tracer injection and continued until the end of the data acquisition. The order of the scans (rest vs. stimulation) was randomized across patients. The data from the second scan were corrected for the residual radioactivity from the first injection. Each condition was 45 min in length and two 10-min scan frames (static) for each condition were obtained.

The structural MR images were obtained on a Siemens Vision 1.5-tesla scanner (Erlangen, Germany), using MPRAGE images. The field of view was 28 cm with a voxel size of 0.5468 × 0.5468 × 1.25 mm. The MRI scans were acquired within 2 months of the acquisition of the PET scan.

Data Analysis

The PVE analyses were performed on a Linux computer (Red Hat version 6.0, Red Hat Inc., Raleigh, N.C., USA). The algorithm corrects for PVE due to low resolution of the PET scanner compared to the size of the GM thickness. The method uses each subject's MR image to correct for PVE [19].

Statistical Analysis

The glucose metabolism images and PVE-corrected glucose metabolism images were spatially normalized to the Montreal Neurological Institute stereotactic space [20, 21] and smoothed using a Gaussian filter with a full width at half-maximum of 12 × 12 × 12 mm using SPM99 (Wellcome Department of Cognitive Neurology, London, UK). The normalized images were proportionally scaled to a mean of 10.

The correlation between the glucose metabolism values and the MMSE score was calculated at each voxel using software written in Matlab 5.3 (Mathworks, Inc., Natick, Mass., USA). The signifi-

Table 3. Local maxima of the positive correlation coefficients between activation glucose metabolism and MMSE scores before PVE correction and after PVE correction

Region	Broadman area	Coordinates		before PVE correction	after PVE correction
<i>Right hemisphere</i>					
Parietal lobe					
Superior parietal lobule	7	12	-66 54	0.80	0.68
Inferior parietal lobule	40	44	-52 42	0.75	0.65
	40	44	-50 56	0.76	0.65
Cingulate gyrus	31	10	-46 40	0.57	0.57
Temporal lobe					
Middle temporal gyrus	39	54	-64 12	0.58	0.56
Superior temporal gyrus	22	52	-8 -2	0.55	0.51
Occipital lobe					
Precuneus	19	30	-84 40	0.58	0.58
<i>Left hemisphere</i>					
Parietal lobe					
Supramarginal gyrus	40	-56	-42 36	0.60	0.70
Postcentral gyrus	1	-52	-20 60	0.58	0.58
Inferior parietal lobule	7	-40	-66 46	0.80	0.79
Temporal lobe					
Superior temporal gyrus	22	-50	-54 16	0.74	0.76
Occipital lobe					
Cuneus					
	18	-22	-100 12	0.64	0.66
	19	-16	-88 40	0.79	0.82
	19	-8	-94 24	0.68	0.68
Precuneus	7	-4	-48 38	0.58	0.55

cance level was set at $p < 0.05$ with a minimum cluster size of 10 continuous voxels. It was decided before analysis was performed that we would focus on the occipital, temporal and parietal lobes because the temporal and parietal lobes are the first and most affected areas by AD and the audiovisual stimulation would have the greatest effects on the audiovisual system within the occipital and parietal lobes.

Results

The regions where the relative glucose metabolism during rest was significantly correlated with the MMSE score are detailed in table 1. Before PVE correction, the local maxima were found in the right fusiform gyrus, left inferior temporal gyrus, left posterior cingulate, in the right and left inferior parietal lobule and left cerebellum. After correcting for PVE, 9 out of 12 local maxima remained significant.

The locations of the local maxima of the correlation coefficient map between the relative resting glucose metabolism and the MMSE score after PVE correction are detailed in table 2. There were more regions of the brain that correlated with the MMSE score after PVE correction than before PVE correction. In particular, addition-

al regions of significant correlations were located bilaterally within the occipital and parietal lobes. Of the local maxima of correlations after PVE correction, 12/24 did not remain significant when no PVE was applied.

For passive audiovisual stimulation, the distributions of significant correlations are shown in table 3. The local maxima were located in the early and association audiovisual areas and in the parietal lobes. Most of the local maxima (15/17) remained significant after PVE correction.

The locations of the local maxima of the correlation coefficient map after PVE correction between the activation glucose metabolism and the MMSE scores are detailed in table 4. In the right hemisphere, there were additional local maxima located in the fusiform gyrus, inferior temporal gyrus, and precuneus. In contrast to the uncorrected data, there were no local maxima located in the cingulate gyrus. In the left hemisphere, additional local maxima were located in the fusiform gyrus, superior occipital gyrus, middle temporal gyrus, precuneus, cingulate gyrus, and superior parietal lobule. Of the local maxima significantly correlated after PVE correction, 11/27 were not significant before PVE correction.

Table 4. Local maxima of the positive correlation coefficients between activation glucose metabolism and MMSE scores after PVE correction and before PVE correction

Region	Broadman area	Coordinates			after PVE correction	before PVE correction
<i>Right hemisphere</i>						
Parietal lobe						
Superior parietal lobule	7	34	-60	44	0.69	0.66
Precuneus	7	10	-66	46	0.80	0.68
Superior parietal lobule	7	30	-66	54	0.67	0.54
Temporal lobe						
Superior temporal gyrus	39	52	-58	8	0.57	0.53
Middle temporal gyrus	19	40	-80	20	0.63	0.51
	21	62	-20	-6	0.60	0.33
Inferior temporal gyrus	37	50	-70	-2	0.59	0.47
Occipital lobe						
Cuneus	30	18	-68	10	0.67	0.20
	19	22	-84	36	0.63	0.46
	19	10	-84	28	0.57	0.19
Fusiform gyrus	19	46	-62	-16	0.58	0.48
<i>Left hemisphere</i>						
Parietal lobe						
Precuneus	19	-14	-86	40	0.86	0.77
Postcentral gyrus	5	-2	-38	72	0.73	0.45
	19	-34	-82	38	0.76	0.67
Cingulate gyrus	31	-6	-44	46	0.56	0.51
Inferior parietal lobule	40	-54	-42	34	0.72	0.60
	40	-44	-64	46	0.81	0.78
Superior parietal lobule	7	-16	-64	64	0.80	0.66
Temporal lobe						
Superior temporal lobe		-52	-26	6	0.57	0.51
		-48	-56	18	0.77	0.71
Middle temporal gyrus	22	-52	-40	6	0.58	0.43
		-46	-68	8	0.69	0.66
Occipital lobe						
Cuneus	19	-14	-86	40	0.86	0.77
	19	-10	-84	28	0.57	0.19
	18	-6	-92	22	0.74	0.62
Superior occipital gyrus	19	-32	-88	24	0.71	0.57
Fusiform gyrus	19	-40	-76	-10	0.56	0.45
Precuneus	19	-34	-82	38	0.75	0.67
	31	-4	-56	36	0.60	0.57
Cerebellum		-44	-52	-20	0.59	0.52

Discussion

The findings from our study suggest that activation PET scans are more sensitive to neuronal and synaptic dysfunction than resting state PET when examining patients with mild to moderate AD. In addition, the results show that the correlation between glucose metabolism and the MMSE score is not an artifact of PVE.

Without PVE correction, relative glucose metabolism during the resting state was correlated with the MMSE score in the inferior parietal lobe bilaterally. Additionally,

relative glucose metabolism during passive stimulation correlated with the MMSE score bilaterally in the inferior and superior parietal areas. The finding of correlations in the superior parietal lobule for the activation condition indicates that additional areas of neuronal and synaptic dysfunction were detected when compared to the resting condition.

In addition, for the activation paradigm, we found significant correlations in the primary and association audiovisual areas of the brain. These areas are typically spared by AD. This is consistent with the idea that a con-

dition that stimulates the brain would be more sensitive to neuronal and synaptic dysfunction than a resting condition [9, 11, 22].

The results obtained show that the association between MMSE score and glucose metabolism was for most local maxima robust to PVE correction. In addition, PVE correction revealed additional correlations in additional brain areas. For the resting condition, these additional areas were located in early visual and audiovisual association areas. For the passive stimulation state, PVE correction led to an increase in the number of local maxima, but the regional distribution did not change compared to the noncorrected data. These findings suggest that PVE correction enhances the sensitivity of PET to detect AD-related functional failure.

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In summary, activation PET was more sensitive to neuronal and synaptic dysfunction in a group of mild to moderate impaired AD patients compared to resting PET scans. The magnitude and distribution of the regional correlations were not an artifact of GM atrophy.

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