Original Research Article

Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord 2007;23:416–422
DOI: 10.1159/000101956

Accepted: February 5, 2007
Published online: April 23, 2007

Metabolic Correlates of Brain Reserve in Dementia with Lewy Bodies: An FDG PET Study

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Key Words
Brain reserve · Neuroimaging · FDG PET · Education · Dementia with Lewy bodies

Abstract
Background: Studies suggest that brain reserve allows patients with more years of schooling to cope better with brain damage. Research has been mainly focussed on Alzheimer's disease and no studies exist on patients with dementia with Lewy bodies (DLB). The aim of this study was to provide evidence for brain reserve in DLB. ***Methods:*** Twenty-one consecutive patients with DLB and 16 age-matched healthy controls were included. The participants underwent cerebral ^{18}F-FDG PET imaging at rest. A group comparison was conducted in SPM2 between the patient and control groups. A linear regression analysis with glucose metabolism as the dependent and years of schooling as the independent variable was performed. Age, gender and a total score of the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery were included as covariates into the analysis. ***Results:*** The patients showed a significant metabolic reduction in the frontal and posterior association cortices, the basal ganglia and the pulvinar of the thalami. Glucose metabolism and education showed an inverse relationship in an extensive cluster in the left temporo-parieto-occipital cortex. ***Conclusion:*** Similar findings were previously reported in Alzheimer's disease and are regarded as evidence for brain reserve. Therefore, we suggest that brain reserve is also present in DLB.

Introduction

The repeated observation that brain pathology and its clinical symptoms are not tightly linked led to the formulation of the brain reserve capacity (BRC) hypothesis [1], a concept which was extensively reviewed in a publication by Stern [2]. According to this concept, education and mental stimulation provide a buffer against brain damage, somehow attenuating clinical symptoms. Bennett et al. [3], for example, recently reported that the association between Alzheimer's disease (AD) pathology and cognitive symptoms shortly before death was attenuated by the number of years of school education. Better educated patients had more pathology than would have been predicted from their cognitive status. Clinical, epidemiological and neuroimaging studies also support the concept of

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BRC. Epidemiological studies for example show that the incidence of clinical AD is lower in individuals with more years of school education and that higher educated patients with AD experience faster cognitive decline [4, 5]. Considering reduced cerebral blood flow or glucose metabolism as in vivo markers of neuropathology, studies consistently show that deficits of perfusion or metabolism are more pronounced in brain regions typically affected by AD in patients with more years of schooling as compared with less educated patients at the same level of cognitive impairment [6, 7].

The finding of BRC in distinct neurodegenerative disorders would support the assumption that BRC is a universal phenomenon which is independent of the underlying neuropathology. Therefore, evidence for BRC in neurodegenerations other than AD would further underscore this presumption. To the best of our knowledge, no evidence for brain reserve in dementia with Lewy bodies (DLB) exists to date. Our study was therefore designed to use functional imaging techniques to clarify the modifying effect of education on the association between brain pathology and clinical symptoms in patients with DLB. According to the hypothesis described in detail by Scarmeas et al. [7], we expected an inverse association between schooling and glucose metabolism as a measure of neuronal function in brain areas primarily affected by the disorder, controlling for cognitive symptom severity. We therefore hypothesized that metabolic correlates of BRC in DLB should be found in posterior temporal and parietal association cortices and in the occipital association cortex [8].

Methods

Study Sample

The study refers to 21 consecutive patients with probable mild to moderate DLB who were all recruited in the neurological clinic of the Technical University of Munich between 2001 and 2003. To compare regional glucose metabolism, we used a pre-existing dataset of 16 age-matched healthy control subjects that had been collected in a collaborative effort of the departments of psychiatry and neurology of the Technical University of Munich for clinical and research purposes [9]. The diagnosis of DLB was established by consensus of 2 experienced neurologists according to current diagnostic guidelines [10]. The thorough diagnostic evaluation included neuropsychological testing, structural (magnetic resonance) and functional positron emission tomography (PET) with 18-fluoro-2-deoxy-glucose (^{18}F-FDG) brain imaging, routine blood sampling and physical examination by an experienced neurologist. The neuropsychological diagnostic set-up was based on the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery (CERAD-NAB) [11], which incorporates the Mini-Mental State Examination (MMSE) [12]. A total score of the CERAD-NAB was calculated for each patient according to recently published criteria (subtest addition method) [13] to control for cognitive status in the regression analysis of PET data. Briefly, total scores were obtained by summing the scores from the individual subtests (excluding the MMSE score) into a total composite score (maximum for verbal fluency set at 24 points, maximum total score 100 points). This score was preferred to the MMSE score and scores of other neuropsychological tests because it covers a wider spectrum of cognitive function and was already used in a similar study in patients with AD [6]. Neuropsychiatric symptoms, including frequency and severity of hallucinations within the past 4 weeks, were rated on the Neuropsychiatric Inventory [14]. Severity of parkinsonian signs was rated on the Unified Parkinson's Disease Rating Scale (UPDRS) motor section [15]. The clinical documentation also included information on age, gender and years of education (defined as years attending school plus years of apprenticeship, technical school, college and university), and a standardized assessment of recurrent falls and fluctuations of consciousness. Patients who fulfilled diagnostic criteria for AD, Parkinson's disease dementia, cerebrovascular disease or frontotemporal lobar degeneration were excluded. Patients with a history of stroke, cerebral tumour, traumatic brain injury, epilepsy or psychiatric illness including major depression were also excluded. Written informed consent according to the Declaration of Helsinki was obtained from the patients after the full explanation of the procedures. Ethical approval to scan patients and controls was granted by the local ethics committee and the radiation protection authorities.

PET Scan Acquisition and Data Processing

Following exactly the same protocol, all patients and controls underwent PET scanning after being administered with ^{18}F-FDG injection at rest. The detailed PET scanning procedure is described in a study by Drzezga et al. [16]. Statistical parametric mapping software (SPM2, http://www.fil.ion.ucl.ac.uk/spm/software/spm2) based on Matlab, version 6.5 (Mathworks Inc, Natwick, Mass., USA) was used for image realignment, transformation into standard stereotactic space, smoothing and statistical analyses. Images were smoothed using a gaussian kernel (12 mm full width at half maximum). Individual global counts were normalized by proportional scaling to a mean value of 50 mg/100 ml/min.

Statistical Evaluation

The statistical evaluation of the imaging data included 2 steps. In the first step, a group comparison of the regional cerebral metabolic rate of glucose (rCMRglc) was conducted between patients and controls in order to identify brain regions with significantly reduced metabolism in patients. To minimize false positive results, a significance threshold of $p < 0.05$ corrected for multiple comparisons according to random field theory (false discovery rate) was applied. Only clusters with at least 100 contiguous voxels were regarded significant. The second step of the statistical procedure included a voxel-based linear regression analysis of rCMRglc with years of schooling as the independent variable, controlling for the CERAD-NAB total score, age and gender (coding 1 for male and 0 for female patients) in the DLB group. The regression analysis was restricted to brain areas where patients with DLB were found to have significant reductions in rCMRglc compared with healthy controls. To this end, the SPM2 output of

Table 1. Characteristics of the study sample

Characteristic	DLB group (n = 21)	Control group (n = 16)	p value
Age, years	71.1 (4.4)	67.88 (10.0)	0.35
Men:women	11:10	7:9	0.62
Schooling, years	10.4 (2.3)	11.69 (4.0)	0.18
Age at onset, years	63.1 (8.3)	n.a.	n.a.
Duration of disease, years	3.4 (2.1)	n.a.	n.a.
CERAD total score	46.6 (14.4)	n.d.	n.a.
MMSE	20.8 (4.8)	30 (0.0)	<0.001
UPDRS III	30.4 (15.6)	n.a.	<0.001
Visual hallucinations (yes:no)	14:7	0:16	<0.001
Fluctuations of consciousness (yes:no)	20:1	0:16	<0.001
Recurrent falls	12:9	0:16	<0.001

Data reported as means (with SD in parentheses). n.d. = Not done; n.a. = not applicable.

the group comparison in step 1 was saved to a file and used as a predefined region of interest in the regression analysis in step 2. Findings meeting a height threshold of $p < 0.001$ uncorrected for multiple comparisons were considered significant for this type of analysis. The extension threshold was set at 100 contiguous voxels again. Additionally, scatterplots between years of schooling and rCMRglc were also generated in SPM2 at the cluster with the strongest statistical correlation, and a regression line was fitted into these plots. The correlation coefficient was calculated in Matlab. Coordinates in MNI space (http://www.bic.mni.mcgill.ca) were transformed to Talairach space [17] using the Matlab function mni2tal (http://www.mrc-cbu.cam.ac.uk/Imaging). Anatomical regions were identified using the Talairach Demon Client, version 2.0 (http://ric.uthscsa.edu/recources). Demographic data were also analyzed in Matlab.

Results

The characteristics of the DLB group are presented in table 1. The MMSE score range of 11–26 supported the diagnoses of mild to moderate dementia [18]. Years of school education ranged from 8 to 15 years. The onset of cognitive symptoms was prior to or within 12 months of the onset of parkinsonian symptoms in all of the patients. Parkinsonian symptoms were present and of mild severity in all patients at the point of the diagnostic assessment. Optical hallucinations were present in 67%, recurrent falls in 57% and fluctuation of cognition in 95% of the patients.

Group Comparison of rCMRglc between Patients and Controls

Compared with controls in a voxelwise fashion, patients showed extensive hypometabolic areas in the frontal and posterior association cortices, which where grouped in two contiguous clusters encompassing frontal and posterior association areas, the thalamus (pulvinar) and the basal ganglia (table 2, fig. 1).

Regression Analysis of rCMRglc with Education as Independent Variable

At the significance level of $p < 0.001$ uncorrected for multiple comparisons, the voxel-based regression analysis revealed a significant negative association between years of schooling and adjusted rCMRglc (corrected for cognitive status and demographic characteristics) in an extensive cluster in the left temporo-parieto-occipital (TPO) cortex, encompassing Brodmann areas 19, 37, 39 and 40 (table 3 and fig. 2). The fitted curve for the linear regression analysis has a negative slope and is displayed in figure 3. The additional correlation analysis between the adjusted rCMRglc and years of schooling at the localization of the most significant cluster revealed a negative correlation coefficient r of –0.57. There was no significant positive correlation in any brain region.

Discussion

We recently reported a negative correlation between schooling and rCMRglc in patients with AD [6]. This finding was located in regions of the cerebral cortex known to be affected in the early stages of AD and is thought to represent evidence for BRC [7]. In the present study, we found an inverse association between schooling and rCMRglc in the left TPO cortex [19], which is known

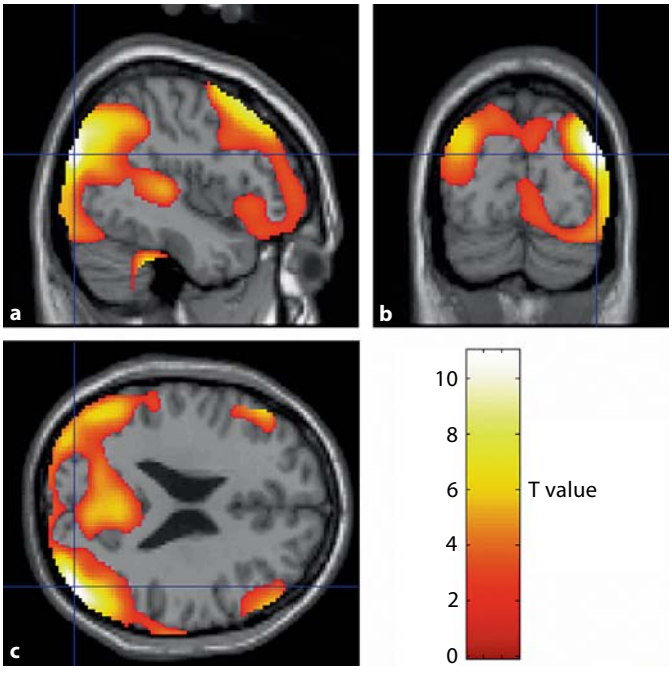

Fig. 1. Significant group differences of rCMRglc between the DLB and control groups. Anatomical localization (maximum in Talairach space at coordinates x/y/z = 46/–78/26, right superior occipital gyrus, $p < 0.05$, false discovery rate corrected for multiple comparisons), as projected on sagittal (**a**), coronal (**b**) and axial (**c**) sections of a normal MRI, spatially normalized into MNI template (crossbars located at the global maximum).

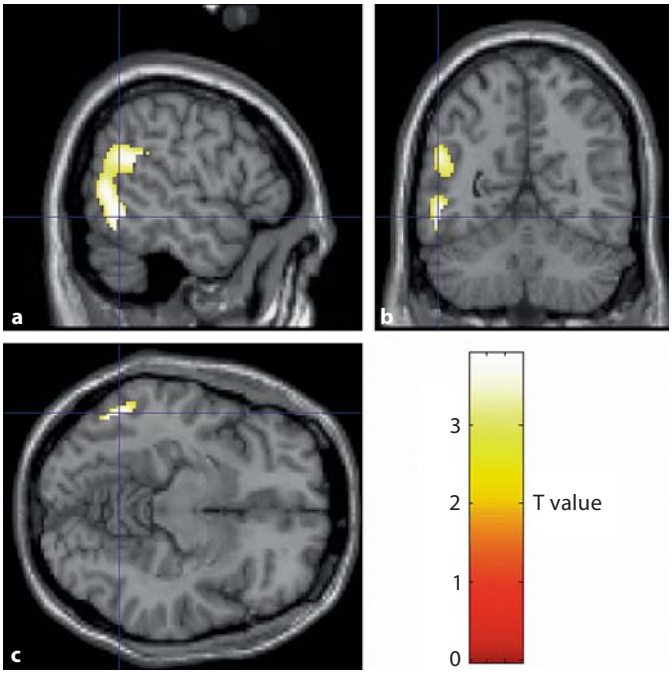

Fig. 2. Inverse association between rCMRglc and years of schooling. Anatomical localization of the significant cluster (maximum at Talairach coordinates x/y/z = –51/–55/–6, left inferior temporal gyrus, $p < 0.005$ uncorrected for multiple comparisons for display purposes), as projected on saggital (**a**), coronal (**b**) and axial (**c**) sections of a normal MRI, spatially normalized into MNI template (crossbars located at the global maximum).

Table 2. Peak metabolic reductions in patients with DLB compared with controls

Brain region	x	y	z	z-score	Cluster extension
Right superior occipital gyrus	**46**	**–78**	**26**	**7.75**	**34,535**
Left supramarginal gyrus	55	–45	35	6.15	
Right inferior temporal gyrus	57	–70	2	6.06	
Right caudate	**10**	**8**	**1**	**7.16**	**13,578**
Right middle frontal gyrus	48	18	49	6.37	
Right middle frontal gyrus	46	27	43	6.37	

Bold markings indicate the maximum within a cluster, subsequent non-bold markings delineate further submaxima within the same cluster; brain regions are indicated by Talairach and Tournoux coordinates x, y and z. x = medial to lateral distance relative to midline (positive: right hemisphere); y = anterior to posterior distance relative to the anterior commissure (positive: anterior); z = superior to inferior distance relative to the anterior-posterior commissure line (positive: superior).

to be closely associated with disturbances of understanding of complex spatial relations, a core neuropsychological deficit in DLB [20]. A role for school education in BRC would predict that, when controlling for cognitive status, patients with more years of school education would have more advanced pathological changes. Thus, using rCMRglc as an indirect indicator of pathology would show a negative correlation between the years of school-

Table 3. Peak negative correlations between rCMRglc and schooling in the DLB group

Brain region	x	y	z	z-score	Cluster extension
Left inferior temporal gyrus	**–51**	**–55**	**–6**	**3.28**	**734**
Left middle temporal gyrus	–50	–62	7	3.27	
Left supramarginal gyrus	–50	–47	23	3.12	

Bold markings indicate the maximum within a cluster, subsequent non-bold markings delineate further submaxima within the same cluster; brain regions are indicated by Talairach and Tournoux coordinates x, y and z. x = medial to lateral distance relative to midline (positive: right hemisphere); y = anterior to posterior distance relative to the anterior commissure (positive: anterior); z = superior to inferior distance relative to the anterior-posterior commissure line (positive: superior).

ing and rCMRglc in brain regions that typically show reductions of glucose metabolism. However, we do not claim that this compensatory effect is restricted to the TPO cortex in patients with DLB. We rather assume that similar effects can be found in most brain areas affected by neurodegeneration. This suggestion is supported by the fact that more extensive brain regions with an inverse association between schooling and rCMRglc were found once the significance threshold was lowered (results not shown). In analogy to findings in other neurodegenerative disorders, our results provide initial evidence for the existence of BRC in DLB. Furthermore, our results emphasize the independence of BRC from the particular type of neurodegenerative pathology. On no account do our results suggest that education protects against neurodegeneration. BRC merely provides some kind of counterbalance which allows individuals with more education to cope better with brain damage. Furthermore, pathological findings on ^{18}F-FDG PET scans of individual DLB patients show a wide variance. Therefore, group analyses do not always allow conclusions for individuals.

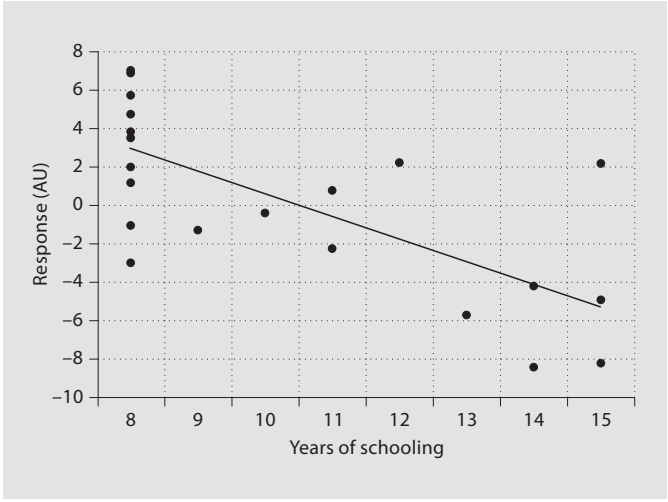

Fig. 3. Regression analysis of rCMRglc and years of schooling. Fitted and adjusted rCMRglc response in arbitrary units as dependent variable and years of school education as independent variable at the position of the most significant cluster (Talairach coordinates x/y/z = –51/–55/–6, left inferior temporal gyrus).

It is not likely that our finding of BRC in patients with DLB is attributable to the inclusion of patients with AD. Consensus diagnostic criteria which show a variable sensitivity (mean = 54%) but a very high specificity (mean = 90%) were applied. The accuracy of the clinical diagnosis of DLB is therefore comparable to the diagnosis of AD or Parkinson's disease [21]. Furthermore, the visual inspection of the ^{18}F-FDG PET scans showed the typical pattern of glucose hypometabolism in our patient group. The voxel-by-voxel comparison in SPM2 between the DLB group and an age-matched healthy control group also showed findings similar to previous studies in patients with DLB, which report a reduced glucose metabolism in most of the association cortices including the occipital association cortex with relative sparing of the sensorimotor cortex [22, 23]. The finding of reductions of rCMRglc in the occipital regions was reported to differentiate between patients with DLB and AD in particular [8, 23]. In our study, patients with DLB showed an extensive hypometabolism compared with controls in frontal and posterior association cortices with the statistical maximum located at the occipital association cortex. The SPM analysis furthermore revealed metabolic deficits in the basal ganglia, which may be linked to the motor features of Parkinsonism, and the pulvinar of the thalami, which is interconnected with parietal and occipital cortical areas

and therefore plays an important role in visual attention. The rate of recurrent visual hallucinations and severity of parkinsonian signs was also comparable to other study populations [24, 25]. Tiraboschi et al. [26] recently reported that recurrent visual hallucinations were the best positive predictor of DLB at autopsy (positive predictive value of 83%). However, this finding was not replicated in another autopsy-confirmed study [27]. Patients who developed dementia more than 12 months after the initial motor symptoms were excluded according to the recommendation by McKeith et al. [10]. Therefore, not only patients with AD but also those with Parkinson's disease dementia were reliably excluded. However, an inclusion of patients with AD cannot be entirely ruled out without a histopathological examination. Patients with DLB can have concomitant AD neuropathology even if clinical diagnostic criteria for DLB are strictly applied. Therefore, the contribution of AD pathology cannot be totally excluded in a clinical study. However, Merdes et al. [28] demonstrated that the degree of concomitant AD pathology, staged by a modification of the method of Braak and Braak, has an important influence on the clinical characteristics of DLB and, therefore, the clinical diagnostic accuracy of DLB. Consistent with previous studies, they report a higher prevalence of core symptoms in patients with 'pure' DLB than in those with superimposed AD pathology. Furthermore, del Ser et al. [29] reported that the early onset of core symptoms was crucial for a highly accurate clinical diagnosis of 'pure' DLB. In our study, approximately 70% of the included patients had dementia of a mild degree and the remaining 30% were moderately demented. Almost all of them had parkinsonian symptoms and fluctuations of cognition, and approximately two thirds had optical hallucinations and/or recurrent falls. But again, an autopsy would have been necessary to definitely exclude all patients with admixed AD neuropathology.

We conclude that BRC is also present in DLB. We therefore suggest that the hypothesized contribution of life experiences, styles and activities considered providing BRC in AD should also be explored in patients with DLB. This might allow further insight into the mechanisms of how pathology translates into clinical symptoms and facilitate interventions that may delay symptoms of dementia. We furthermore suggest testing the hypothesis of BRC in distinct neurodegenerative disorders to provide further evidence that reserve does not depend on the particular type of brain damage.

Acknowledgements

R.P. and A.K. received funding from the Federal Ministry of Research and Education as part of a national collaboration on dementia (Kompetenznetz Demenzen), grant No. 01GI0420. The sponsors played no role in the design and conduct of the study, the collection, management, analysis and interpretation of the data, and the preparation, review or approval of the manuscript. The authors wish to thank Dorottya Ruisz for proof reading.

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