Original Research Article

Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord 2008;26:475–481
DOI: 10.1159/000167791

Accepted: August 14, 2008
Published online: November 4, 2008

Activities of Daily Living, Cerebral Glucose Metabolism, and Cognitive Reserve in Lewy Body and Parkinson's Disease

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Key Words
^{18}F-fluorodeoxyglucose positron emission tomography · Dementia with Lewy bodies · Parkinson's disease · Cognitive reserve

Abstract
Aims: (1) To investigate the neural substrate of impaired activities of daily living (ADL) in Lewy body-associated disorders, such as dementia with Lewy bodies, classical Parkinson's disease, and Parkinson's disease dementia, and (2) to explore the effect of education on the relationship between cerebral metabolic changes and ADL performance. ***Methods:*** Fifty-four patients with Lewy body-associated disorders underwent an extensive clinical evaluation including cerebral positron emission tomography with ^{18}F-fluoro-2-deoxy-glucose scanning. First, those brain areas were identified where ADL performance and glucose metabolism were significantly correlated. Second, brain regions were detected where the association between metabolic changes and ADL performance differed significantly between patients with a low and a high educational background. ***Results:*** There was a significant association between glucose hypometabolism and impaired ADL performance in the prefrontal, temporoparietal, and occipital association cortices and the precuneus. However, there was a significantly stronger association between hypometabolism and impaired ADL in the low education group compared with the high education group in the right middle occipital gyrus. ***Conclusions:*** The study suggests (1) that brain metabolic alterations are significantly associated with the loss of everyday functioning in Lewy body-associated disorders and (2) that education modifies this association.

Introduction

Impaired activities of daily living (ADL) are an integral feature of dementing disorders. Therefore, instruments such as the Bayer ADL scale (B-ADL) [1], the Alzheimer's disease (AD) ADL international scale (ADL-IS) [2], and the AD cooperative study ADL scale (ADCS-ADL) [3] have been designed. These instruments have proven their sensitivity, simplicity of concept, international applicability, and relevance to patients coping with the demands of everyday life. Positron emission tomography with ^{18}F-fluoro-2-deoxy-glucose (^{18}F-FDG PET) provides reliable information on functional cerebral changes in AD [4] and other neurodegenerative disorders

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including frontotemporal dementia [5], dementia with Lewy bodies (DLB) [6], classical Parkinson's disease (PD), and PD dementia (PDD) [7], even at very mild stages [8]. However, to our knowledge, ADL performance and functional imaging findings have only been directly linked in one study before, although a better understanding of their interdependencies could help to understand the functional brain changes associated with impaired ADL. Salmon et al. [9] reported that four assessment scales reflecting the patient's global cognitive abilities, daily living functioning, and global dementia severity as well as the caregiver's evaluation of cognitive impairment were all related to brain metabolic deficits in the temporoparietal and frontal association cortices in AD.

Although neurodegeneration is undoubtedly the cause of clinical symptoms of dementia, repeated reports suggest that the association between pathology and clinical signs is not linear [10]. The concept of cognitive reserve (CR) [11] has been introduced to account for the phenomenon that school education and lifelong mental stimulation provide a buffer against brain damage, somehow attenuating the clinical expression of pathology. Bennett et al. [12] showed that the association between AD pathology and cognitive symptoms shortly before death was modified by years of school education. Better-educated patients had more pathology than would have been predicted from their cognitive status. In addition, neuroimaging experiments showed that, controlling for the overall severity of cognitive impairment, better-educated patients with AD [13, 14], DLB [15], frontotemporal dementia [16], and nonfluent progressive aphasia [17] had more pronounced metabolic or perfusion deficits in brain regions typically affected by their neurodegenerative disorders than less-educated individuals.

We pursued two main goals in the present study. First, we set out to investigate the neural substrate of impaired everyday functions in order to understand the role of ADL scales in the assessment of dementia severity in Lewy body (LB)-associated disorders including DLB, PD, and PDD. We expected a significant association between glucose hypometabolism and impaired ADL performance in regions typically affected in LB-associated disorders, such as prefrontal, temporoparietal, and occipital cortices [6]. Second, we aimed at exploring the effect of education on the relationship between cerebral metabolic alterations and ADL performance. Drawing on the predictions of CR [12], we anticipated a stronger association between metabolic deficits and everyday problems in less-educated than in better-educated individuals in brain regions affected in LB-associated disorders.

Materials and Methods

Sample

Fifty-four patients with LB-associated disorders (21 DLB, 19 PD, and 14 PDD) were recruited at the departments of neurology and psychiatry at the Technische Universität München. All patients were subjected to an identical clinical assessment protocol, and the diagnoses were established by consensus among two experienced clinicians according to the current diagnostic guidelines for DLB and PD [18, 19]. The diagnostic setup included neuropsychologic testing, routine blood sampling, physical examination, as well as structural (MRI) and functional (^{18}F-FDG PET) imaging of the brain. The neuropsychological assessment was based on the Consortium to Establish a Registry for AD Neuropsychological Assessment Battery, German version [20, 21], which incorporates the Mini-Mental State Examination (MMSE) [22]. The B-ADL scale was used to rate difficulties in everyday activities according to guidelines established by Hindmarch et al. [1]. The scale comprises 25 questions, which were completed by a caregiver or another informant sufficiently familiar with the patient (usually the patient's spouse or child). The B-ADL scale is used to rate the frequency of everyday problems on a 10-point scale, with '1' if problems never occur and '10' if the patient always has problems with the particular task. The B-ADL sum score is computed by summing the 25 individual item scores excluding those completed 'not applicable' or 'unknown. The frequency and severity of neuropsychiatric symptoms such as delusions, hallucinations, and depression was rated on the Neuropsychiatric Inventory (NPI) [23]. The severity of parkinsonian symptoms was assessed by the Unified PD Rating scale motor section (UPDRS III) [24]. The documentation also included standardized information on age, gender, years of schooling, recurrent falls, and fluctuations of consciousness. The data of all consecutive patients who met the inclusion criteria were used for the present analysis. Patients were also excluded if they had evidence for significant cerebrovascular disease on their MRI scans, relevant functional psychiatric disorders such as major depression or schizophrenia, or a history of traumatic brain injury, stroke, cerebral tumor, epilepsy, or alcohol abuse. The ethics committee of the Technische Universität München and the radiation protection authorities approved of the study protocol. Written informed consent was obtained from each study participant. In order to compare patients with low and high education, the sample was split in two groups at the median of the sample's years of school education, resulting in a low education group with less than or equal to 11 years of school education (low-EDU) and a group with more than 11 years of schooling (high-EDU).

Acquisition and Preprocessing of the Functional Imaging Data

Patients fasted for at least 6 h prior to the PET scanning. All patients were scanned in the medical 'off condition', i.e. dopaminergic medication was stopped at least 12 h prior to scanning, because dopaminergic medication had previously been related to alterations in the regional cerebral metabolic rate of glucose (rCMRglc) [25]. All patients were administered with an intravenous bolus of 185 MBq ^{18}F-FDG at rest 30 min prior to PET scanning. Scans were performed under standard resting conditions with the patient's eyes closed in dimmed ambient light. Exactly the same scanning protocol was applied to every patient. Imaging was performed on a Siemens ECAT/EXACT HR + PET scanner

(CTI, Knoxville, Tenn., USA). A sequence of three frames (10 min, 5 min, 5 min) was started (3-dimensional mode, total axial field of view of 15.52 cm) and later combined into a single frame. Attenuation correction was performed using a transmission scan. Data were corrected for random, dead time and scatter, and images were reconstructed by filtered back-projection with a Hamm filter (cutoff frequency 0.5 cycle/projection element) resulting in 63 slices in a 128 × 128 pixel matrix (pixel size 2.00 mm) and interplane separation of 2.425 mm. As published previously [13], individual PET scans were stereotactically normalized to the MNI PET template in SPM2, and smoothed with an isotropic gaussian kernel (12 mm FWHM) in the statistical parametric mapping software package SPM2 (Wellcome Functional Imaging Laboratory, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm2/), based on Matlab, v6.5 (The Mathworks Inc., Natick, Mass., USA) running on a standard personal computer. Individual global counts were normalized by proportional scaling to a mean value of 50 mg/100 ml/min.

Data Analyses

In addition to the exploration of the neural substrate of ADL impairment, the present study aimed at assessing whether there were brain regions with a stronger association between metabolic deficits and ADL impairment in less-educated than in well-educated subjects with LB-associated disorders. In other words, we wished to find out if the regression slope for the interaction between the rCMRglc and the B-ADL score was significantly different in the two educational groups. According to the General Linear Model, a factor by covariate analysis of variance was phrased in terms of a multiple regression, with each patient's educational group as condition and the B-ADL score as covariate, as described elsewhere [26]. The SPM2 single-subject condition and covariate option was used, coding the low-EDU and high-EDU groups as two different conditions, and the B-ADL score as the covariate of interest. A condition × covariate interaction was selected, and the covariate was centered around the condition mean. In the present analysis we were interested in three statistical effects: identifying brain regions with a significant rCMRglc difference between the two educational groups, i.e. the main effect of condition (model 1), identifying regions where rCMRglc significantly decreases with increasing B-ADL score, i.e. the main effect of covariate (model 2), and assessing significantly different effects of rCMRglc on B-ADL scores (different regression slopes) between the two educational groups, i.e. the interaction effect (model 3). The above effects of interest were assessed using linear t-contrasts [27]. To minimize the chance for false-positive findings, a conservative statistical significance threshold of $p < 0.05$ with a false discovery rate (FDR) correction for multiple comparisons was applied to the models 1 and 2, i.e. the main effects of condition and covariate. In model 3, i.e. the interaction effect, findings were considered significant above a level of $p < 0.001$, uncorrected for multiple comparisons, if they were located in brain regions with a significant association between rCMRglc and B-ADL score (model 2). This less stringent statistical threshold is usually accepted if an a priori hypothesis of involved brain regions is available [28]. All statistical procedures were selected according to previously published studies with similar approaches. Coordinates were converted from MNI (http://www.bic.mni.mcgill.ca) to Talairach space with the Matlab function *mni2tal* (http://www.mrc-cbu.cam.ac.uk/Imaging). Anatomical regions were indentified with the Talairach Daemon Client, v2.0 (http://www.talairach.org/). Clinical and demographic variables were analyzed in the Statistical Package for the Social Sciences (SPSS), v15 (The SPSS Inc., Chicago, Ill., USA). There were no significant differences in the most important sample characteristics between the two educational groups, except their years of schooling. Most importantly, the distribution of the diagnostic subgroups DLB, PD, and PDD did not significantly differ across the two groups (table 1).

Table 1. Sample characteristics

Characteristic	Low-EDU	High-EDU	p
DLB:PD:PDD	13:8:9	8:11:5	0.34
Age, years	69.43 (7.25)	70.29 (9.14)	0.70
Men:women	18:12	18:6	0.25
Schooling, years	8.93 (1.64)	13.81 (1.92)	<0.001
Duration of disease, years	7.59 (5.77)	7.54 (5.73)	0.98
MMSE score	22.53 (5.67)	24.25 (4.71)	0.24
B-ADL global score	130.10 (65.90)	107.40 (55.40)	0.18
Visual hallucinations, yes:no	13:17	14:10	0.27
UPDRS III score	36.17 (15.48)	31.17 (11.63)	0.18
NPI sum score	17.38 (3.04)	19.83 (2.52)	0.55
L-Dopa equivalent dose	491.67 (222.45)	538.89 (201.14)	0.51

Unless otherwise indicated, data are presented as mean (standard deviation).

MMSE = Mini-Mental State examination; UPDRS III = Unified Parkinson's Disease Rating scale motor section; NPI = Neuropsychiatric Inventory; low-EDU = low education group (less or equal to 11 years of schooling); high-EDU = high educational group (more than 11 years of schooling).

Results

Model 1: Comparison of rCMRglc between the Low-EDU and High-EDU Groups

No significant differences of rCMRglc were found between the two educational groups in either direction, i.e. low-EDU < high-EDU and high-EDU < low-EDU.

Model 2: Correlations between rCMRglc and B-ADL Score in the Entire Sample

At the stringent statistical threshold of $p < 0.05$, FDR corrected for multiple comparisons, significant inverse associations between the rCMRglc and the B-ADL scores were found in brain regions typically affected by pathology in LB-associated disorders, including the prefrontal, temporoparietal, and occipital association cortices and the precuneus. The statistical maximum was located at the left middle frontal gyrus (table 2;

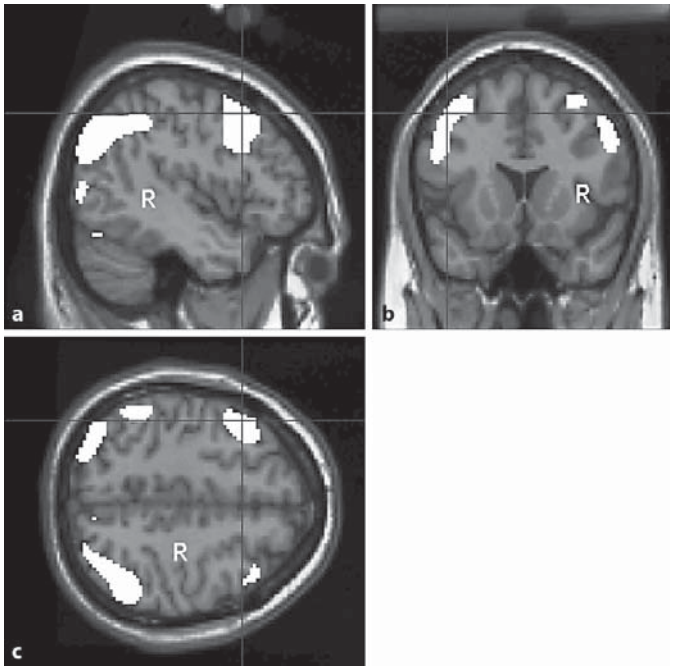

Fig. 1. Significant inverse association between the rCMRglc and the B-ADL score in the entire study sample. Anatomical localization as projected on sagittal (**a**), coronal (**b**), and axial (**c**) sections of a normal MRI, spatially normalized to the MNI template ($p < 0.05$ FDR corrected, maximum at Talairach coordinates x/y/z −44/18/43, left middle frontal gyrus), right side indicated (R), cross bars located at the global maximum; higher B-ADL scores indicate worse daily performance.

Table 2. Peak negative correlations between the rCMRglc and the B-ADL score

Anatomical region	Coordinates			Z score	Cluster extension
	x	y	z		
Right hemisphere					
Precuneus	**38**	**−68**	**38**	**3.87**	**2,116**
Inferior parietal lobule	51	−50	43	3.84	
Precuneus	8	−61	21	3.47	
Inferior frontal gyrus	**57**	**24**	**21**	**3.49**	**614**
Middle frontal gyrus	51	21	34	3.39	
Superior frontal gyrus	32	20	51	3.32	
Insula	**34**	**−81**	**15**	**3.18**	**48**
Inferior occipital gyrus	**26**	**−90**	**−9**	**3.10**	**21**
Middle temporal gyrus	**67**	**−43**	**−11**	**3.05**	**68**
Inferior temporal gyrus	**67**	**−19**	**−24**	**3.00**	**13**
Middle temporal gyrus	**46**	**−62**	**12**	**2.98**	**16**
Middle occipital gyrus	**55**	**−63**	**−10**	**2.88**	**1**
Left hemisphere					
Middle frontal gyrus	**−44**	**18**	**43**	**4.53**	**1,773**
Middle frontal gyrus	−50	23	23	3.49	
Angular gyrus	**−44**	**−68**	**37**	**4.21**	**4,624**
Middle temporal gyrus	−59	−39	−5	4.13	
Middle temporal gyrus	−59	−43	−11	4.05	
Superior temporal gyrus	**−61**	**−14**	**−4**	**3.08**	**24**

Bold markings indicate the maximum within a cluster; subsequent nonbold markings delineate further submaxima within the same cluster.

fig. 1). No positive correlations between relative glucose metabolism and B-ADL scores were found in any brain region.

Model 3: Educational Group by B-ADL Score Interaction (i.e. Different Regression Slopes)

A significant educational group by B-ADL score interaction was found in the right middle occipital gyrus [cluster of 314 contiguous voxels, maximum in Talairach space at x/y/z 32/-73/13, Brodmann area (BA) 19, Z = 3.29, fig. 2]. A steeper regression slope was found for the low-EDU group with respect to the high-EDU group in this particular brain region (fig. 2). Conversely, significantly steeper regression slopes for the high-EDU group compared with the low-EDU group were not found in any brain region.

Discussion

Impaired everyday abilities are a mandatory criterion for the diagnosis of dementia. Standardized instruments such as the B-ADL scale support the clinician in the routine assessment of impaired day-to-day competence. The aims of the present study were to emphasize the neural substrate of a widely used ADL scale to better understand its contribution to global dementia severity assessment in LB-associated disorders, and to relate the association between ADL performance and relative metabolic deficit to CR. A total score of the B-ADL scale was used to rate a patient's global ability to function in his daily environment, with high scores representing more severe impairment. We report a significant inverse association between the B-ADL score and the rCMRglc in extensive cortical areas including regions in the prefrontal, temporoparietal, and occipital cortex and the precuneus. These areas are not only typically affected by neuropathology in LB-associated disorders; they also considerably overlap re-

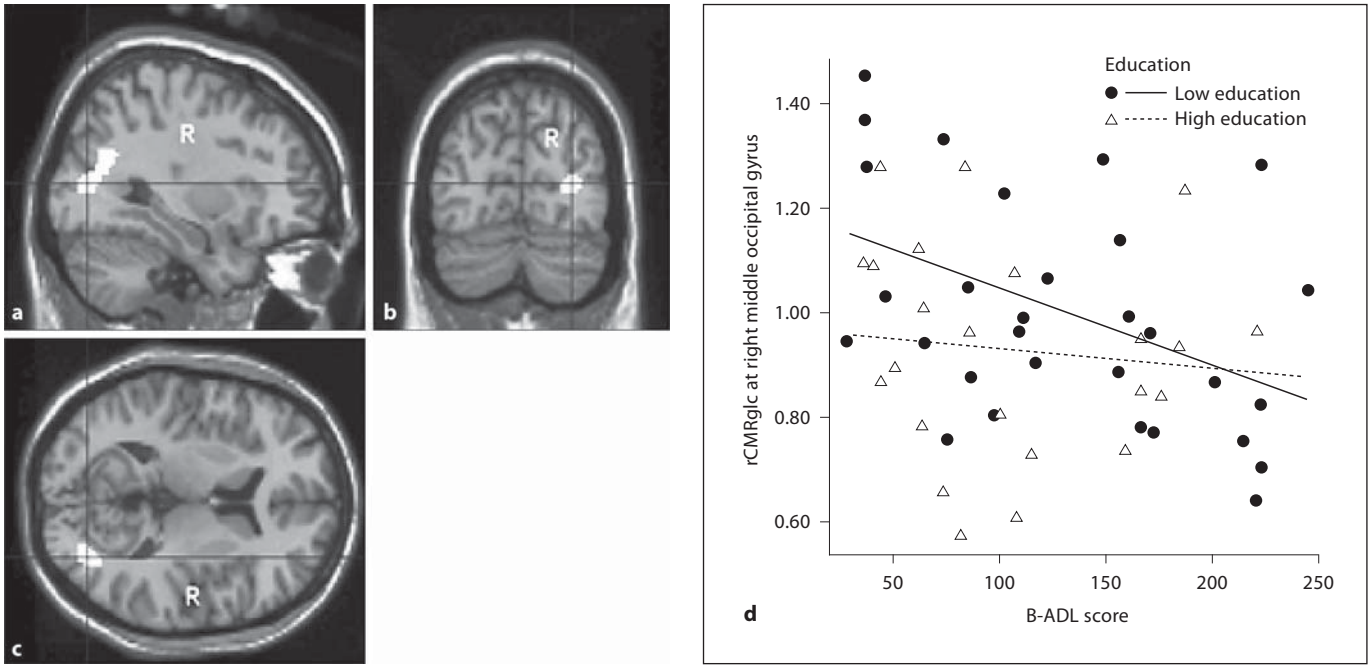

Fig. 2. Significantly different regression slopes for the association between rCMRglc and B-ADL score between the low-EDU and high-EDU groups. Anatomical localization as projected on sagittal (**a**), coronal (**b**), and axial (**c**) sections of a normal MRI, spatially normalized to the MNI template ($p < 0.001$ uncorrected, maximum in Talairach space at x/y/z 32/–73/13, right middle occipital gyrus, BA 19), right side indicated (R), cross bars located at the global maximum. **d** Scatterplot between the relative rCMRglc extracted from the right middle occipital gyrus (BA 19) and the B-ADL score in both educational groups; higher B-ADL scores indicate worse daily performance.

gions associated with ADL performance in AD before. Salmon et al. [9] reported a correlation between a cortical network, comprising bilateral parietal and temporal regions, the precuneus, as well as the left middle frontal cortex and several instruments for dementia staging. These associative cortices are known to be involved in various consciousness-related functions such as attention, working memory, episodic memory, language and conscious perception, which are known to play a crucial role in everyday functioning. Damage to frontal and parietal association cortices, and disconnection between anterior and posterior networks are particularly associated with attention deficits, which are an early clinical feature of AD [29]. According to the controlled process impairment theory [30], AD primarily affects cognitive processes requiring more attentional resources at early stages. According to those data, attentional deficits are amongst the earliest clinical signs of AD and disease progression is associated with attentional deterioration [29]. Therefore, damage to attention-related brain functions negatively affects everyday competence, and the additional damage to occipital association areas involved in feature extracting and shape recognition in addition to attention in LB-associated disorders further adds to this effect [31].

In addition to the neural substrate of daily functioning, we were also interested in the modifying effect of educational attainment on the association between rCMRglc reductions and ADL impairment. Although there was no significant metabolic difference between the two educational groups, significantly different associations between the rCMRglc and the B-ADL score were detected in the right middle occipital gyrus (BA 19). The analysis revealed a steeper regression slope for this association in the low-EDU group as compared with the high-EDU group, pointing to a stronger correlation between metabolic and everyday deficits in the low-EDU group. In the present study, significantly different regression slopes between the two educational groups were located in BA 19. This area is the differentiation point of the two visual streams. The dorsal stream on the one hand is essentially involved in the perception and interpretation of spatial

relationships, accurate body image, and the learning of tasks involving the coordination of the body in space. The ventral stream on the other hand is associated with object recognition and form representation [32]. Although these brain regions are typically affected by pathology in LB-associated disorders [33], we do not claim that the reported effect of education is limited to BA 19. We rather assume that similar effects can also be found in most brain regions affected by neurodegeneration. This suggestion is supported by the fact that significant results were found in more extensive brain regions once the significant threshold was lowered in an exploratory manner (results not shown). We do furthermore by no means suggest that education protects against neurodegeneration. Our present results merely indicate that the association between metabolic deficits and clinical symptoms differs by education.

Limitations of our study include the relatively small sample size and the recruitment of patients at university-based departments, which restricts the generalization to the entire population with LB-associated disorders. Our study furthermore lacks a pathological verification of the clinical diagnoses. However, our aim was not to differentiate distinct LB-associated disorders in the present study, and current clinical diagnostic guidelines for PD and DLB yield a high accuracy for separating these disorders from AD [34]. Patients with DLB can have concomitant AD neuropathology even if clinical diagnostic criteria for DLB are strictly applied. Therefore, the contribution of the AD pathology cannot be totally established in a clinical study. Patients meeting both clinical criteria for AD and DLB were not excluded from the study. Although consensus guidelines are available for the clinical differentiation between DLB, classical PD, and PDD, the pathological entity of DLB has not been sufficiently established and its boundaries to PD are still unclear [35]. Furthermore, the spectrum of PD, PDD, and DLB is also continuous both on clinical and neuropathological grounds, the time between the onset of cognitive decline and motor signs of PD being the only criterion for separating PDD from DLB [34]. LB-associated disorders therefore show significant continuity, both on pathological and on clinical grounds and the boundaries between the three diagnostic subgroups are fluent. We therefore decided to cover the entire spectrum of LB-associated disorders in the present study, in order to facilitate the transfer of findings to clinical practice. To conclude, our results contribute to a better understanding of the functional brain changes involved in ADL impairment and their interaction with education in LB-associated disorders.

Acknowledgement

P.H. received research grants from the Technische Universität München and the German PD Foundation. The sponsors played no role in the study design or the analysis and interpretation of the data.

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