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Longitudinal Changes of Cerebral Glucose Metabolism in Semantic Dementia

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Key Words
Positron emission tomography · Semantic dementia · Frontotemporal dementia · Follow-up · Glucose metabolism

Abstract
Background: Semantic dementia (SD). ***Objective:*** To identify the pattern of decline of cerebral glucose metabolism in SD using cerebral ^{18}F-fluoro-2-desoxy-D-glucose positron emission tomography scanning (^{18}F-FDG-PET). ***Methods:*** Eight patients with SD underwent ^{18}F-FDG-PET at baseline and at re-examination in average 15 months later. ***Results:*** Compared with healthy control subjects, patients with SD showed a significant asymmetrical (left > right) hypometabolism of the temporal lobes, particularly of the anterior poles, at baseline. At follow-up, we observed a deterioration of cognitive abilities. However, in addition to the temporal lobes no other cortical or subcortical region showed a significant reduction of glucose metabolism except the anterior cingulate cortex (pcorr < 0.05). ***Conclusion:*** Subtle functional changes suffice to produce significant neuropsychological deterioration.

Introduction

With a prevalence of 2 in 100,000 persons [1], frontotemporal lobar degenerations (FTLD) are a relatively rare cause of dementia. FTLD are characterized by the progressive loss of cerebral tissue primarily in the frontal and anterior temporal lobes. Diagnostic criteria for FTLD [2, 3] differentiate three clinical syndromes: Frontotemporal dementia (FTD), progressive non-fluent aphasia (NFPA) and semantic dementia (SD), also termed 'temporal variant of FTD' or 'fluent progressive aphasia.

SD is associated with brain atrophy predominantly in the anterior temporal lobes.

The most prominent clinical picture of SD is a progressive semantic impairment. Patients lose conceptual knowledge about the world, affecting their ability to understand the meaning of the words, visual percepts, sounds, tastes and odours. Patients are significantly impaired in word comprehension and confrontation naming [4], however, speech is fluent and grammatically correct. Non-verbal memory, perceptual and visuospatial abilities are preserved in the earlier stages of the disease [5]. Although semantic deficits dominate the clinical picture, behavioural alterations also occur [6, 7]. SD is characterized by a loss of embarrassment, irritability, disinhibition, selfishness, exclusive preferences for food, neglect of hygiene, stereotyped, perseverative and compulsive behaviours [8].

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Several studies using magnetic resonance imaging (MRI) have demonstrated bilateral or asymmetric temporal lobe atrophy in SD. SD is associated with atrophy of the anterior temporal lobes, which involves the polar and inferolateral regions with relative sparing of the superior temporal gyrus [9–13].

Serial imaging of patients allows to demonstrate the progression of a neurodegenerative process, as has been shown in various studies in Alzheimer's disease (AD) [14, 15]. However, there are no longitudinal studies using MRI to detect and quantify the pattern and rates of change of structural alterations in SD. Only two studies [16, 17] analysed the differences of global and regional atrophy between AD, FTD and SD.

Several PET studies in AD, FTLD and FTD have been performed [18–20]. However, to our knowledge, there are – with one exception [9] – no studies in SD that take advantage of PET in cross-sectional or longitudinal studies, although using abnormalities of metabolic activity as a marker, this technique can identify neurodegenerative processes before atrophy becomes apparent on structural imaging [21].

The aim of this study was to determine the progression of changes in cerebral glucose metabolism in SD in a follow-up study using ^{18}F-fluoro-2-desoxy-D-glucose positron emission tomography scanning (^{18}F-FDG-PET). We investigated reductions in regional cerebral glucose metabolism of 8 patients with SD compared to cognitively healthy control (HC) subjects at baseline and in average 15 months later and sought to identify specific brain regions showing maximal decline. We applied a voxel-based approach (Statistical Parametric Mapping, SPM 99; Wellcome Department of Cognitive Neurology, London, UK), which allows automated measurement of reduction of cerebral glucose metabolism.

Patients and Methods

The study refers to 8 right-handed patients (6 male, 2 female) who were diagnosed with SD at the *Centre for Cognitive Disorders of Technische Universität München*, Munich, according to the revised Lund-Manchester-criteria [3]. Clinical diagnosis was based on information gathered from neurological and neuropsychiatric examination, informant interview and a laboratory screening. All patients underwent neuropsychological evaluation using the German version of the Consortium to Establish a Registry in Alzheimer's Disease Neuropsychological Battery (CERAD-NP) [22], which incorporates the Mini-Mental State Examination (MMSE) [23]. Severity of dementia was rated using the Clinical Dementia Rating Scale (CDR) [24] (0.5 = questionable, 1 = mild, 2 = moderate, 3 = severe dementia). All patients had either cranial computed tomography or MRI to exclude other causes of focal brain damage. Patients were excluded who fulfilled diagnostic criteria for FTD, NFPA, dementia in AD, Lewy body disease or cerebrovascular disease.

Follow-up visits were carried out 15.4 (± 4.1) months after baseline on average. At these visits the diagnostic schedule was repeated, with the exception of structural brain imaging. In 3 patients neuropsychological re-examination other than the MMSE was not possible due to dramatic cognitive deterioration or poor compliance.

The study also included 15 cognitively healthy control subjects (HC) (male: 7; female: 8; age: 61.8 ± 9.1 years). These individuals were spouses of unrelated patients who had been examined at the same unit as the FTD patients. HC had no history of neurological or psychiatric disorders and did not complain about cognitive deterioration. An extensive interview was performed to rule out dementia.

Patients and controls underwent ^{18}F-FDG-PET at baseline. PET scans were repeated at the follow-up visit in the patient group.

Regional cerebral glucose metabolism was measured in standard resting conditions (eyes closed, in dimmed ambient light, and silent environment). Three hundred and seventy MBq ^{18}F-FDG were injected at rest, and 30 min later PET imaging was performed using a Siemens ECAT/EXACT HR+ PET scanner (CTI, Knoxville, Tenn., USA). A sequence of three frames of 10 min was started (2D mode, total axial field of view of 16.2 cm) and later combined into a single frame. Attenuation correction was done using a transmission scan, performed immediately after completion of the emission scan (hot transmission). Data were corrected for random, dead time and scatter, and images were reconstructed by filtered back-projection with a Hamm filter (cut-off frequency 0.5 cycles/projection element) resulting in 47 slices in a 128 × 128 pixel matrix (pixel size = 2.0 mm) and interplane separation of 3.447 mm. Image analysis was performed on a SGI O2 workstation (Silicon Graphics Inc., Mountain view, Calif., USA). For stereotactical normalization of the PET data an established automated routine (NEUROSTAT, University of Michigan) was used which has been previously evaluated for scientific use in patients with dementia. For statistical analysis, we used the SPM 99 software (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK). Individual global counts were normalized by proportional scaling to a mean value of 50 mg/100 ml/min. All normalized data was smoothed using a Gaussian kernel (12 × 12 × 12 mm FWHM). Cerebral glucose metabolism was compared between SD patients and controls at baseline and at follow-up examinations in order to determine cortical areas affected in the SD group and to detect changes of metabolism (two sample t test, $p < 0.05$, corrected for multiple testing). Testing for differences between groups was performed on a voxel-by-voxel basis on glucose metabolism.

Results

Demographic and Neuropsychological Data of Patients with SD (table 1)

At baseline, patients mean age was 62.8 years (± 3.8). The mean score on the MMSE at baseline was 25.1 (± 4.8) points, reflecting a mild but significant cognitive impair-

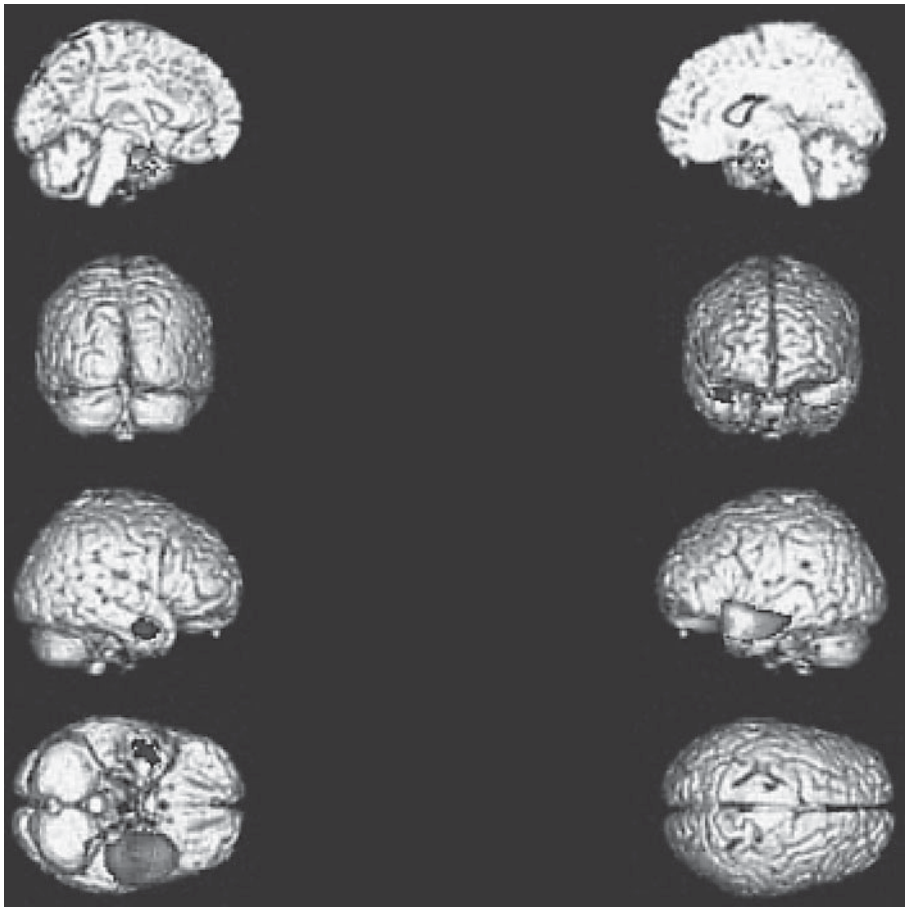

Fig. 1. Group comparison: 8 patients with SD compared with cognitively healthy control persons at baseline. Areas with significantly reduced glucose metabolism were coloured. Figures obtained within SPM using a statistical threshold of p value < 0.05 corrected for multiple comparison. Projection on a three-dimensional standard brain.

Table 1. Demographic data of patients with SD, results in MMSE and severity of dementia rated on CDR at baseline and follow-up

No	Initials	Gender	Age at onset	Baseline			Inter-scan interval, months	Follow-up		
				age	MMSE	CDR		age	MMSE	CDR
1	RH	male	60	63	28	1	25	66	10	2
2	LH	male	56	62	26	1	14	63	22	2
3	WC	female	57	60	25	0.5	14	61	23	1
4	KA	male	62	64	28	0.5	13	65	28	1
5	OJ	male	55	65	25	2	12	66	14	2
6	FD	male	53	61	27	0.5	14	62	21	2
7	MJ	female	67	70	15	2	15	71	14	2
8	SJ	male	57	57	30	0.5	16	59	29	1
Mean (SD)			58.4 ± 4.5	62.8 ± 3.8	25.1 ± 4.8		15.4 ± 4.1	64.1 ± 3.7	20.1 ± 6.8	

SD = Standard deviation.

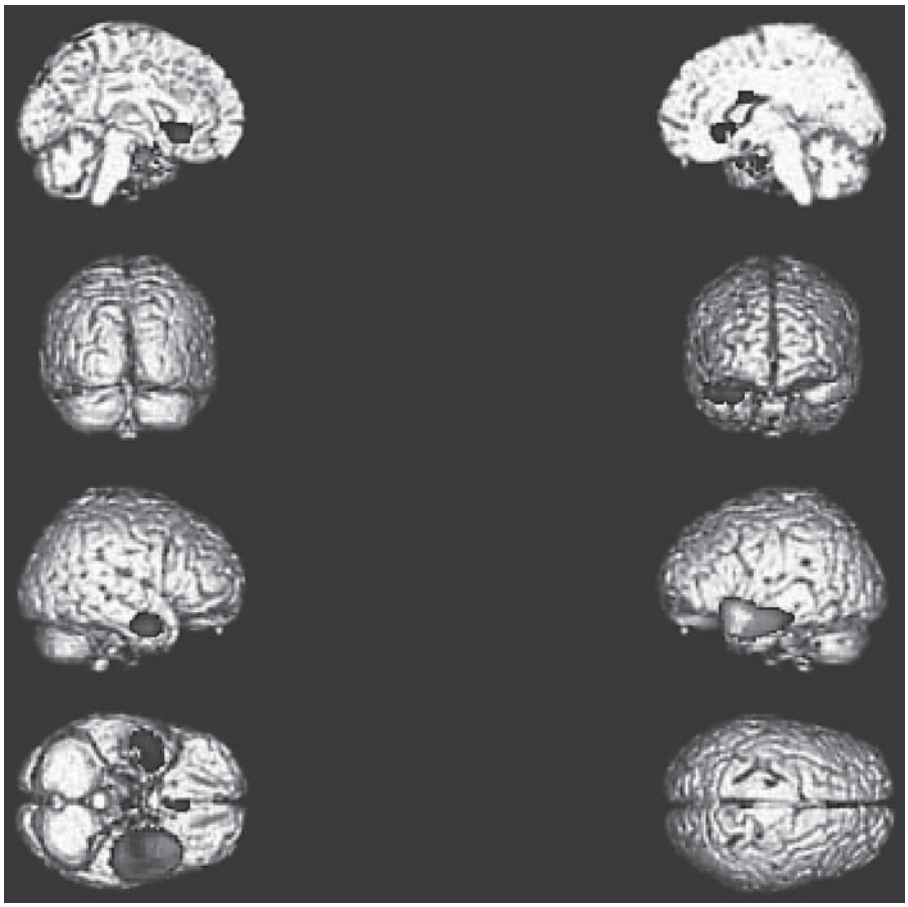

Fig. 2. Group comparison: 8 patients with SD compared with cognitively healthy control persons at follow-up. Areas with significantly reduced glucose metabolism were coloured. Figures obtained within SPM using a statistical threshold of p value < 0.05 corrected for multiple comparison. Projection on a three-dimensional standard brain.

ment [25]. At baseline, 6 patients were mildly demented, 2 patients suffered from moderate dementia.

At follow-up examination, in average 15.4 (± 4.1) months after baseline, patients' mean age was 64.1 (± 3.7) years and their mean MMSE score was 20.1 (± 6.8) points. Severity of dementia had got worse in most of the patients: On the CDR, dementia status was mild in 3 patients, moderate in 5 patients.

Cerebral Glucose Metabolism of Patients with SD Compared to Healthy Controls at Baseline (fig. 1)

Compared to HC, patients with SD as a group showed a significantly lower, asymmetrical glucose metabolism in the temporal lobes bilaterally, with maxima in the temporal poles (left > right) (left: cluster of 6,439 voxels, maximum in Tailarach space at x/y/z –32/–9/–27, anterior portion of left inferior temporal gyrus; right: cluster of 4,290 voxels, maximum in Tailarach space at x/y/z 43/2/–25, anterior portion of right medial temporal gyrus). On the left side, hippocampus and amygdala showed a significant reduction of glucose metabolism. Compared to HC, patients with SD as a group did not show statistically significant glucose reduction of metabolic activity in any other cerebral region (pcorr < 0.05). A reduction of glucose metabolism in the insula bilaterally, the anterior cingulate cortex and the mediofrontal cortex did not reach statistical significance after correction for multiple testing.

Cerebral Glucose Metabolism of Patients with SD Compared to Healthy Controls at Follow-Up (fig. 2)

At follow-up in average 15 months after baseline, the pattern of reduction of glucose metabolism in patients with SD as a group compared to HC was similar to the pattern at baseline. Compared to HC, we observed a reduction of metabolism in the temporal lobes bilaterally. In addition, the anterior cingulate cortex showed a significant hypometabolism. A reduction of metabolism in the insula bilaterally and the mediofrontal cortex did not reach statistical significance after correction for multiple testing (pcorr < 0.05).

A statistical comparison between metabolism at baseline and at follow-up revealed that there was no statisti-

cally significant decrease of glucose metabolism in any region. A reduction of metabolism in both temporal lobes did not reach clinical significance after correction for multiple testing.

Discussion

Previous functional imaging data on SD is extremely limited; however, the baseline results of the study are in good accordance to findings of previous morphological studies [10–13, 16, 26]. Using MRI, studies in 8–18 patients with SD showed a cerebral atrophy mainly of the anterior temporal cortex bilaterally. In later stages of the disease, the posterior temporal lobes and the anterior cingulate cortex were demonstrated to be involved in the process of atrophic neurodegeneration [10, 13]. In agreement with our findings on metabolic abnormalities, the observed atrophic changes were left-dominant in earlier stages, including the amygdala and the hippocampus, later accompanied by a progressive affection of right-hemispheric temporal regions. In addition, atrophy was also observed in the amygdala, the hippocampus, the insula, the ventromedial cortex, the posterior orbital cortex and the caudate nuclei [13].

In the current study, we were able to identify subtle hypometabolic changes in several corresponding regions; however, these abnormalities did not reach significance with the predefined statistical threshold. Differences in patient numbers, applied statistical thresholds, parametric mapping procedures and in the mean stage of the disease may account for these divergences between morphologic and functional findings. In the current study, smoothing of the images was performed prior to statistical analysis. As a consequence, changes below the selected smoothing threshold may have been missed.

The longitudinal changes in the current study were just very subtle. These results are supported by a previous longitudinal study on the morphological changes that show isolated increase of atrophy in patients with SD in the right inferolateral temporal gyrus [17]. Chan et al. [16] observed that patients with temporal variant FTD showed a lower rate of brain atrophy and less variation than patients with frontal variant FTD.

The anterior cingulate cortex was the only region to show newly emerging extratemporal hypometabolism at the follow-up examination in the current study. It is not clear why the anterior cingulate cortex appears to be the first cortical region outside of the temporal cortex, affected by the disease progress. The anterior cingulate cortex belongs to the limbic system; so do the hippocampus and the amygdala, which have been shown to be injured by the disease. Therefore, the observed decrease of cerebral glucose metabolism in the anterior cingulate cortex may in part represent functional deactivation. However, MRI studies confirm atrophy of the anterior cingulate cortex in SD, thus suggesting ongoing local neurodegenerative changes.

A surprising result of the current study was, that despite of just minor changes in cerebral glucose metabolism, the population of SD patients showed a significant cognitive deterioration during the observation period. In contrast, our own group was able to show a significant decrease of cerebral glucose metabolism during 18 months in patients with FTD going along with a deterioration of cognitive and behavioural symptoms [27]. A longitudinal PET-study of patients with AD also revealed significant declines of glucose metabolism in various brain regions within 1 year, corresponding with a significant worsening in the MMSE and other neuropsychological tests [28]. It remains unclear, why in SD – in contrast to FTD and AD – the decline of cognitive function is not associated with a significant reduction of cerebral metabolism.

Conclusion

Conclusively, in the current study we were able to confirm a typical hypometabolic pattern in SD and to demonstrate that longitudinal changes are relatively subtle and predominantly involving initially affected temporal cortical regions. Regarding the generally low prevalence of the FTLD-type dementias, multicentric studies should be initiated, so that a larger patient sample and long interscan intervals may lead to a better insight in the order, in that distinct, non-temporal cortical regions are affected in the course of the SD.

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References

1 Ratnavalli E, Brayne C, Dawson K, Hodges JR: The prevalence of frontotemporal dementia. Neurology 2002;58:1615–1621.
2 McKhann GM, Albert M, Grossman M, Miller B, Dickson D, Trojanowski JQ: Clinical and pathological diagnosis of frontotemporal dementia. Arch Neurol 2001;58:1803–1809.
3 Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al: Frontotemporal lobar degeneration. A consensus on clinical diagnostic criteria. Neurology 1998;51:1546–1554.
4 Diehl J, Monsch A, Aebi C, Wagenpfeil S, Krapp S, Grimmer T, Seeley W, Förstl H, Kurz A: Frontotemporal dementia, semantic dementia and Alzheimer's disease: the contribution of standard neuropsychological tests to differential diagnosis. J Geriatr Psychiatry Neurol 2005;18:39–44.
5 Garrard P, Hodges JR: Semantic dementia: clinical, radiological, and pathological perspectives. J Neurol 2000;247:409–422.
6 Bozeat S, Gregory C, Ralph M, Hodges J: Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? J Neurol Neurosurg Psychiatry 2000;69:178–186.
7 Liu W, Miller B, Kramer J, Rankin K, Wyss-Coray C, Gearhart R, Phengrasamy I, Weiner M, Rosen HJ: Behavioral disorders in the frontal and temporal variants of frontotemporal dementia. Neurology 2004;62:742–748.
8 Snowden J, Neary D, Mann D (eds): Frontotemporal Lobar Degeneration, Frontotemporal Dementia, Progressive Aphasia and Semantic Dementia. London, Churchill Livingstone, 1996.
9 Diehl J, Grimmer T, Drzezga A, Riemenschneider M, Förstl H, Kurz A: Cerebral metabolic patterns at early stages of frontotemporal dementia and semantic dementia. A PET study. Neurobiol Aging 2004;25:1051–1054.
10 Galton CJ, Gomez-Anson B, Antoun N, Scheltens P, Patterson K, Graves M, et al: Temporal lobe rating scale: application to Alzheimer's disease and frontotemporal dementia. J Neurol Neurosurg Psychiatry 2001;70:165–173.
11 Gorno-Tempini ML, Dronkers NF, Rankin KP, Ogar JM, Phengrasamy L, Rosen HJ, Johnson JK, Weiner MV, Miller BL: Cognition and anatomy in three variants of primary progressive aphasia. Ann Neurol 2004;55:335–346.
12 Mummery CJ, Patterson K, Price CJ, Ashburner J, Frackowiak RSJ, Hodges JR: A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory. Ann Neurol 2000;47:36–45.
13 Rosen HJ, Gorno-Tempini ML, Goldman WP, Perry RJ, Schuff N, Weiner M, Feiwell R, Kramer JH, Miller BL: Patterns of brain atrophy in frontotemporal dementia and semantic dementia. Neurology 2002;58:198–208.
14 Fox N, Crum W, Scahill R, Stevens J, Janssen J, Rossor M: Imaging of onset and progression of Alzheimer's disease with voxel-compressing mapping of serial magnetic resonance imaging. Lancet 2001;358:201–205.
15 Jack CR, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, Boeve BF, Tangalos EG, Kokmen E: Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. Neurology 2000;55:484–489.
16 Chan D, Fox NC, Jenkins R, Scahill RI, Crum WR, Rossor MN: Rates of global and regional cerebral atrophy in AD and frontotemporal dementia. Neurology 2001;57:1756–1763.
17 Whitwell JL, Anderson VM, Scahill RI, Rossor MN, Fox NC: Longitudinal patterns of regional change on volumetric MRI in frontotemporal lobar degeneration. Dement Geriatr Cogn Disord 2004;17:307–310.
18 Ibach B, Poljanski S, Marienhagen J, Sommer M, Manner P, Hajak G: Contrasting metabolic impairment in frontotemporal degeneration and early onset Alzheimer's disease. Neuroimage 2004;23:739–743.
19 Ishii K, Sakamoto S, Sasaki M, Kitagaki H, Yamaji S, Hashimoto M, Imamura T, Shimomura T, Hirono N, Mori E: Cerebral glucose metabolism in patients with frontotemporal dementia. J Nucl Med 1998;39:1875–1878.
20 Jauss M, Herholz K, Kracht L, Pantel J, Hartmann T, Jensen M, Essig M, Schroder J: Frontotemporal dementia: clinical, neuroimaging and molecular biological findings in 6 patients. Eur Arch Psychiatry Clin Neurosci 2001;251:225–231.
21 Herholz K: PET studies in dementia. Ann Nucl Med 2003;2:79–89.
22 Thalmann B, Monsch AU: CERAD. The Consortium to Establish a Registry for Alzheimer's Disease. Neuropsychologische Testbatterie. Basel, Memory Clinic Basel, 1997; www.memoryclinic.ch.
23 Folstein MF, Folstein SE, McHugh PR: 'Mini Mental State'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatry Res 1975;12:189–198.
24 Morris JC: The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurology 1993;43:2412–2414.
25 Aebi C: Validierung der neuropsychologischen Testbatterie CERAD-NP. Doktorarbeit, 2002; www.memoryclinic.ch.
26 Edwards-Lee T, Miller BL, Benson DF, Cummings JL, Russell GL, Boone K, Mena I: The temporal variant of frontotemporal dementia. Brain 1997;120:1027–1040.
27 Diehl-Schmid J, Grimmer T, Drzezga A, Bornschein S, Riemenschneider M, Schwaiger M, Förstl H, Kurz A: Decline of cerebral glucose metabolism in frontotemporal dementia: a longitudinal 18F-FDG-PET-study. Neurobiol Aging (2006); in press.
28 Alexander GE, Chen K, Pietrini P, Rapoport SI, Reiman EM: Longitudinal PET evaluation of cerebral metabolic decline in dementia: a potential outcome measure in Alzheimer's disease treatment studies. Am J Psychiatry 2002;159:738–745.