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Temporal Lobe Hypoperfusion in Isolated Amnesia with Slow Onset: A Single Photon Emission Computer Tomography Study

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Key Words
Amnesia · Single photon emission computer tomography · Neuropsychology · Temporal lobe · Mild cognitive impairment

Abstract
Single photon emission computer tomography (SPECT) applied early in the course of Alzheimer's disease (AD) may identify regions with impaired brain function. Moreover, it may be relevant to characterize SPECT perfusion patterns in patients with mild cognitive impairment (MCI), in particular the subgroup of MCI patients with isolated amnesia, as these patients have been demonstrated to convert to AD in more than half of the cases within 3 years. The primary aim of the present study was to characterize the regional cerebral blood flow (CBF) in patients with neuropsychologically verified isolated amnesia. We examined 32 patients (11 men/21 women) with isolated amnesia according to strict neuropsychological criteria and 15 healthy volunteers (11 men/4 women). All subjects had an SPECT-^{99m}Tc-*d,l*-HMPAO perfusion study and neuropsychological assessments. Cranial MRI or CT was performed in all subjects. Semiquantitative (cerebellar relative) flow values were calculated and statistically compared. Patients with isolated amnesia had significant hypoperfusion in several cortical regions of interest compared to control subjects, most prominently in the left temporal cortex. Additionally, there was a trend towards globally reduced CBF in the patients, although this was not significant. These findings may indicate the presence of a progressive degenerative illness affecting multiple brain regions at its early or preclinical stage.

Introduction

Single photon emission computer tomography (SPECT) is a widely available diagnostic adjunct, which has been demonstrated to be relevant in the diagnostic evaluation of dementia and possible Alzheimer's disease (AD) [1]. Properly performed, high-resolution brain perfusion SPECT is sensitive to AD, with the characteristic findings of temporoparietal hypoperfusion frequently accompanied by uni- or bilateral frontal hypoperfusion [1–5]. It is plausible that functional brain deficits are likely to appear prior to structural brain damage in AD [6]. Therefore, it may be relevant to examine patients with function-

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Table 1. Demography and patient characteristics

Variable	Control (n = 15)	Isolated amnesia (n = 32)
Men	11	11
Women	4	21
Age, years	71.3 ± 4.7	72.6 ± 8.4 (n.s.)
MMSE	29.2 ± 0.8	24.9 ± 2.6*

Age and MMSE given as mean ± SD. * $p < 0.001$. n.s. = Not significant.

al imaging as early as possible in the course of AD, in order to identify areas with impaired brain function and ideally administer treatment with antidementia drugs. Moreover, it would be of interest to characterize SPECT perfusion patterns in patients with mild cognitive impairment (MCI) [7], in particular patients with isolated amnesia. These patients have been demonstrated to progress to AD in more than half of the cases within a time span of about 3 years [8, 9].

The primary aim of the present study was to characterize cerebellar relative regional cerebral blood flow (rCBF) as measured with SPECT in patients with neuropsychologically verified isolated amnesia.

Materials and Methods

During a 5-year period (September 1995 to September 2000) a total of 900 patients were examined at the Memory Disorders Research Unit. Forty-nine of the 900 originally referred patients had a cognitive profile characteristic of isolated amnesia and fulfilled both strict neuropsychological criteria (see Neuropsychology) and DSM-IV [10] criteria for the amnesic syndrome. None of the patients fulfilled NINCDS-ADRDA criteria for AD [11]. Based on the clinical history and interviews with patients and relatives, the symptoms and subjective complaints of memory impairment progressed slowly over months. Thus, the onset of symptoms was slow in all patients in contrast to the abrupt onset that would be typical for most nondegenerative disorders.

Of these 49 patients, 17 with known or suspected specific causes of amnesia or with severe concomitant diseases were excluded from the study. Seven of these were alcoholics, and there were 2 with a Wernicke episode. One patient had a history of cerebral vascular disorder and 1 had concomitant parkinsonism. One patient had received electroconvulsive therapy treatment for depression. One had been operated on for a pituitary tumor and 4 had cerebral infarcts on CT; 1 had multiple infarcts, 1 had an infarct in the insula, 1 had infarcts in the left thalamus and left internal capsule and finally 1 had an infarct in the right internal capsule. In 2 patients SPECT was not performed.

The remaining 32 consecutively referred patients (11 men/21 women) with isolated amnesia had a mean age of 72.6 ± 8.4 years (range 44–88 years), and their mean Mini-Mental Status Examination (MMSE) score [12] was 24.9 ± 2.6 (range 21–30) (table 1). An estimation of the duration of memory impairment was performed on the basis of interviews with relatives; the average time span from the onset of symptoms to referral was 2 years. Fifteen healthy volunteers, 11 men and 4 women, were included in the study. The volunteers were recruited by an advert in a local Copenhagen newspaper. The mean age was 71.3 ± 4.7 years (range 64–79 years) and the mean MMSE score was 29.2 ± 0.8 (range 28–30). The volunteers did not have any subjective impairment of memory or other cognitive skills, did not satisfy criteria for any current or previous psychiatric disorder, had no known cardiovascular or cerebrovascular disease, and did not use centrally acting drugs. All volunteers and patients had a full physical and neurological examination as well as blood test screening for potential risk factors for cognitive dysfunction. The volunteers all had normal physical and neurological examinations, no hypertension, normal ECG and standard laboratory test screening. The study subjects were not quantitatively scored for depression, but the physicians found no significant symptoms of depression.

In all subjects an SPECT perfusion study and a standardized neuropsychological assessment were performed. All volunteers had a cranial MRI, and cranial CT or MRI was obtained in all patients as part of the routine investigation program. In all control subjects informed consent was obtained. The SPECT examinations of the patients were conducted as part of the routine evaluation program in the memory clinic.

Neuropsychology

The neuropsychological assessment consisted of 29 tests in six cognitive domains, lasting approximately 2 h (table 2). This test battery has been composed for elderly patients for the assessment of possible dementia, particularly AD [13]. Some of the tests were modified compared to the originally validated versions (table 2) [14–19]. The test battery included 3 tests of retrograde memory and 7 tests examining either visual or verbal anterograde memory. Only 1 of the memory tests is not internationally known, a modified retention test of geometrical figures [16]. Test data had been adjusted according to the age and educational level of the subjects. The standardization was based on a total of 112 elderly normal subjects divided into three age groups (<70 years, 70–80 years, >80 years) and with two educational levels.

Test scores were converted to Z-scores (mean 0, SD 1) based on the performance of the 112 normal subjects in relevant subgroups. In each cognitive domain, composite Z-score means were computed and restandardized.

To operationalize our criteria of amnesia, we required a composite memory score (Z-score) of 2.0 SD below the mean of healthy people from the same age group. All other cognitive domains (composite Z-scores) had to be within the normal range, i.e. 1.9 SD below expected or higher. In addition, the difference between the memory score and the lowest other cognitive domain had to be at least 1.0 SD.

The applied criteria for isolated amnesia are different from the emerging concept of MCI [7] in the sense that the described test battery challenging various cognitive domains was applied in all patients. According to the original MCI concept, no strict recommendations for the neuropsychological assessment have been advised.

Table 2. Neuropsychological tests and classification of cognitive domains

Memory
Information (seven questions about common geography and public persons) [14]
Verbal learning (selective reminding ad modum Buschke, 10 items) [15]
Recognition (20 famous faces, block designs, drawings of 12/30 common objects)
Recall (three words, three objects and their localization, geometric figures [16], drawings of 30 common objects)
Concentration/attention
Digit span forwards (WAIS)
Auditory motor attention (AMA)
Stroop color naming (simplified Xs and words on 50 successive stimulus cards)
Serial subtraction
Abstraction and problem solving
Proverb interpretation
Concept formation (six categories of 30 common objects)
Picture arrangement (subtests 2–4 from the WISC and 1–3 from the WAIS)
Language
Auditory comprehension (token test, 36-item version) [17]
Sentence repetition (10 items from the NCCEA) [17]
Naming (30 drawings of common objects, 20 photos of famous persons)
Word fluency (animal names and words beginning with S in 1 min)
Visual perception
Analysis (three stimulus cards with Poppelreuter's superimposed figures) [18]
Closure (Street completion test, 20 Thurstone fragmented figures) [19]
Identification (30 drawings of common objects, 20 photos of famous persons)
Visuoconstruction
Copying (cross, star, cube and house, four simple nonmeaningful geometrical figures)
Two-dimensional block construction (six Koh's designs)
Miscellaneous
Orientation (personal, time, place)

SPECT

In a quiet room with dimmed lights the patient was injected intravenously with a dose of 800–1,000 MBq ^{99m}Tc-*d,l*-HMPAO (Amersham International, London, UK). High-resolution SPECT was carried out with Tomomatic 564 (Medimatic, Copenhagen, Denmark), a rapidly rotating and highly sensitive brain-dedicated 9-slice instrument. Twenty minutes after injection of the tracer the radioactivity distribution in the brain was obtained in a 64 × 64 matrix mode. Nine slices were obtained simultaneously, and by repositioning of the high-resolution collimator, a total of 27 consecutive slices parallel to the orbitomeatal plane were obtained. For parametric analysis of the images, the 27 slices (fig. 1) were recompressed to a total of 9 slices (adjacent slices were summarized three and three). After normalization of CBF to mean blood flow in the cerebellum, semiquantitative values for global CBF and rCBF in several cortical regions of interest, side-to-side asymmetry indexes (SAI) and anterior-posterior ratios were calculated. The SAI was calculated as the difference between the right and left regional flow value divided by the larger of the two and multiplied by 100 to give the percentage of the difference. The calculation of global/hemispheral CBF included the contribution from subcortical structures and CSF space. The regions of interest were drawn with a superimposed template, which was adjusted to the individual brain size by adjusting the outer border of the region set to the cortical rim. All together, 10 template sets were applied referring to 10 anatomical reference slices (fig. 2). In each subject the nine template sets with the best fit were selected for the 9 SPECT slices. In each case it was visually assured that the template regions included just cortical structures, but no formal correction for partial volume effects/atrophy was applied in this study. The regions were contiguous and varied in size from 4 to 14 cm^2. The image analysis was done by the same examiner in all subjects (patients and controls), and the examiner was blinded to the subject type. The methods for parametric analysis have previously been described in detail [20].

The average time span between SPECT study and MMSE was 1.1 months (SD 0.9 month, range 0–4 months) and between SPECT study and neuropsychometry 1.5 months (SD 2.8 months).

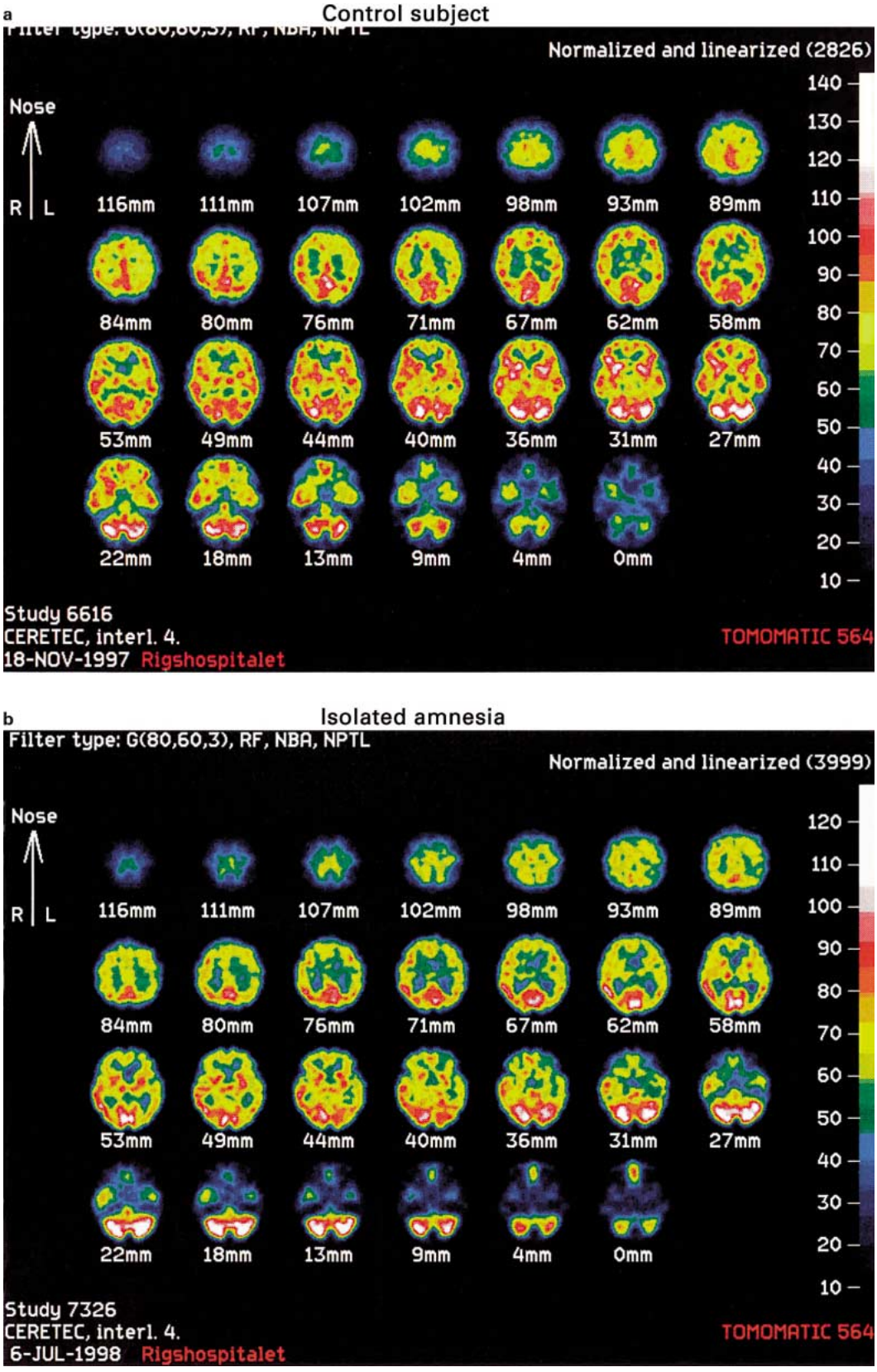
No brain mapping software (e.g. SPM, SSP) was available for analysis of the present data set emerging from the Tomomatic 564 scanner.

Statistical Analysis

In order to focus the statistical analysis of the rCBF data, two statistical models for logistic regression analysis were constructed. The first model was defined to identify global regions of particular interest. In this model the patient type (control or isolated amnesia) was the dependent variable whereas hemispheral CBF, frontal rCBF, temporal rCBF, parietal rCBF, and occipital rCBF were the predictors. In the second model, a focused analysis of the global region of interest (temporal lobe) was performed, to identify subregions with significantly reduced rCBF in the isolated amnesia patients. Finally, nonparametric statistics (Mann-Whitney, region-to-region comparisons) were carried out to confirm the significant differences in rCBF predicted by the initial statistical models (tables 3, 4). Corrections for multiple comparisons were not introduced.

Results

The degree of amnesia ranged from mild to severe with memory scores from –2.0 SD to –7.7 SD (mean –4.4, SD 1.5). All the subjects included fulfilled the criteria described with regard to the degree of memory deficits and at least one SD between the memory score and the lowest score in any other cognitive domain. Regarding test scores in other cognitive domains, all except 1 patient had scores within the normal range (± 2.0 SD). In one case a Z-score of –2.0 SD in visual perception was considered artifactual and accepted as normal.


a
Control subject
Normalized and linearized (2826)
Nose
R L
116mm 111mm 107mm 102mm 98mm 93mm 89mm
84mm 80mm 76mm 71mm 67mm 62mm 58mm
53mm 49mm 44mm 40mm 36mm 31mm 27mm
22mm 18mm 13mm 9mm 4mm 0mm
140 130 120 110 100 90 80 70 60 50 40 30 20 10
Study 6616
CERETEC, interl. 4.
18-NOV-1997 Rigshospitalet
TOMOMATIC 564
b
Isolated amnesia
Filter type: G(80,60,3), RF, NBA, NPTL
Normalized and linearized (3999)
Nose
R L
116mm 111mm 107mm 102mm 98mm 93mm 89mm
84mm 80mm 76mm 71mm 67mm 62mm 58mm
53mm 49mm 44mm 40mm 36mm 31mm 27mm
22mm 18mm 13mm 9mm 4mm 0mm
120 110 100 90 80 70 60 50 40 30 20 10
Study 7326
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TOMOMATIC 564

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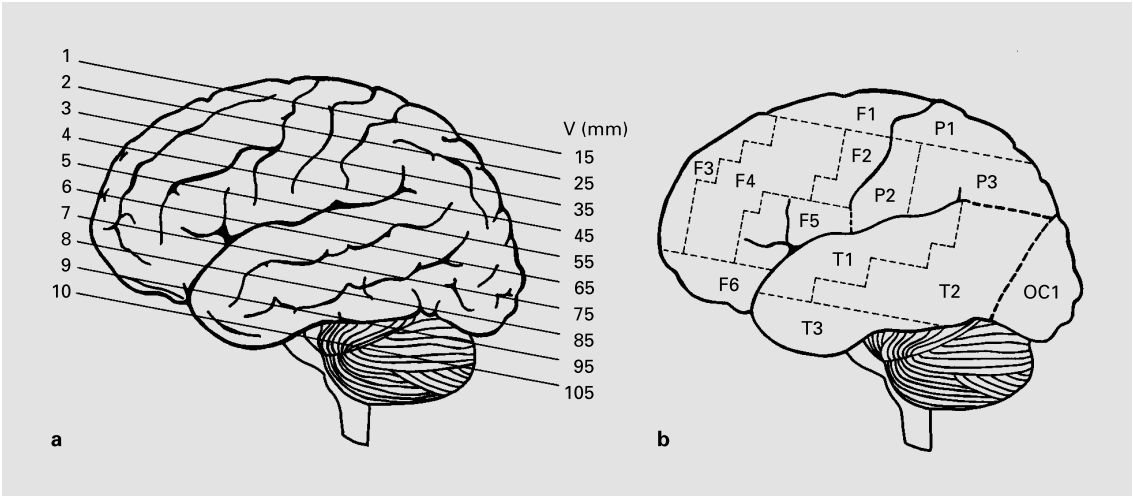

Fig. 2. Schematic drawing of a lateral view of the left hemisphere with localization of the 10 anatomical reference slices (**a**) and cortical regions of interest (**b**). V indicates distance from the vertex of the atlas brain. Complete list of regions of interest: F = frontal cortex; F1 = upper frontal cortex; F2 = precentral gyrus; F3 = superior frontal gyrus and cingulate gyrus; F4 = middle frontal gyrus; F5 = inferior frontal gyrus; F6 = orbitofrontal gyrus; T = temporal cortex; T1 = superior temporal gyrus and insula cortex; T2 = inferior and middle temporal gyrus; T3 = temporal poles; P = parietal cortex; P1 = upper parietal cortex; P2 = postcentral gyrus; P3 = supramarginal and angular gyrus; OC1 = occipital cortex.

The patients and controls were considered to be comparable with respect to age, although the mean age in the patient group was slightly higher than in the controls (not significant) (table 1). The unequal distribution of gender (isolated amnesia: 11 men/21 women, control: 11 men/4 women) was not considered critical, as no significant sex difference in rCBF in healthy volunteers or neurodegenerative disorders has previously been demonstrated.

When the semiquantitative rCBF values from patients and controls were statistically compared, the patients had several cortical regions of interest with hypoperfusion. The differences between the groups were significant in the left temporal cortex (logistic regression $p < 0.01$, standard error 0.09, z-value 3.14) and in the right occipital cortex (logistic regression $p < 0.05$, standard error 0.06, z-value 2.25). The subregional analysis of the temporal lobes suggested focusing the subsequent semiquantitative analysis on the left temporal pole (logistic regression $p < 0.01$). The a priori focus on the temporal lobe was confirmed by the subsequent nonparametric analyses, in which the superior temporal gyrus and insula, and the temporal pole were found to be significantly hypoperfused in the isolated amnesia patients compared to controls (tables 3, 4). It was noted that patients with isolated amnesia had lower rCBF values in *all* cortical regions measured compared to controls (tables 3, 4). Also considered noteworthy, when the patients' individual temporal rCBF values were assessed, was that only 19 patients had reduced rCBF values in the left temporal lobe and 20 patients in the right temporal lobe compared to mean control values minus 1 SD.

The SAI values and the anterior-posterior ratios were not significantly different in the patients compared to controls.

Fig. 1. ^{99m}Tc-HMPAO SPECT images from randomly selected control subject (**a**) and representative isolated amnesia patient (scaling comparative) (**b**). A global CBF reduction in the patient is suggested by the visual impression. Although barely visually detectable, a predominant hypoperfusion of the temporal regions, in particular the left, can be identified (bottom images).

Discussion

This study showed that patients with isolated amnesia have significant hypoperfusion in the temporal lobe, in particular in the left hemisphere, demonstrated by SPECT. Although not significant, there was a trend that global cortical hypoperfusion also characterized these pa-

Table 3. Results from SPECT image analysis – global values

Region	Control (n = 15)	Amnesia (n = 32)	p
Hemisphere H			
$F_{i(L)}$	70.9 ± 5.3	66.5 ± 6.4	0.08
$F_{i(R)}$	71.3 ± 5.7	67.2 ± 6.4	0.10
SAI	1.6 ± 0.8	2.1 ± 1.7	0.67
Frontal cortex F			
$F_{i(L)}$	67.5 ± 5.5	63.7 ± 6.7	0.15
$F_{i(R)}$	67.3 ± 5.3	63.1 ± 7.0	0.13
SAI	1.7 ± 1.3	1.9 ± 1.3	0.64
Temporal cortex T			
$F_{i(L)}$	76.5 ± 5.9	69.0 ± 7.2	0.019
$F_{i(R)}$	77.5 ± 5.2	71.7 ± 6.9	0.047
SAI	3.4 ± 2.2	4.2 ± 3.6	0.84
Parietal cortex P			
$F_{i(L)}$	64.6 ± 8.1	62.8 ± 8.7	0.67
$F_{i(R)}$	65.5 ± 8.6	62.9 ± 8.7	0.45
SAI	2.5 ± 1.7	3.0 ± 2.1	0.73
Occipital cortex OC1			
$F_{i(L)}$	84.4 ± 6.6	81.9 ± 8.6	0.38
$F_{i(R)}$	84.5 ± 10.9	82.9 ± 8.3	0.42
SAI	3.8 ± 3.0	3.9 ± 3.6	0.91

All values given as mean ± 1 SD (standard deviation). Statistical comparison of group rCBF values using nonparametric statistics (Mann-Whitney). rCBF values in left $F_{i(L)}$ and right $F_{i(R)}$ hemispheres and SAI in cerebral regions of interest. $F_{i(L)}$ = Left hemispheric rCBF given relative to mean rCBF in the cerebellum; $F_{i(R)}$ = right hemispheric rCBF given relative to mean rCBF in the cerebellum; SAI = numerical value of SAI given in percent by: $[(F_{i(H)} - F_{i(V)})/F_{i,\,max}] \times 100$.

tients, and all rCBF values in the cortical subregions were lower in patients compared to controls. These findings converge with the known importance of temporal lobe structures in learning and memory, as well as with the known high risk of progression to AD in patients with isolated amnesia. Unfortunately we were not able to further explore substructures in the mesial temporal lobe (e.g. hippocampus, entorhinal cortex) given the limitations in the applied technology (spatial in-plane resolution >10 mm FWHM).

It may be noted that the observed mean MMSE (24.9) could indicate that some of the amnesic patients were already demented. However, none of the patients fulfilled the DSM-IV criteria for dementia. The observed low MMSE scores in some patients were influenced by severe amnesia in these cases.

It is well known that AD is associated with temporoparietal hypoperfusion or hypometabolism as demonstrated by SPECT or positron emission tomography (PET). However, there have also been previous studies on functional imaging in amnesia. Most of these previous studies were small and included patients categorized merely on a clinical impression rather than conventional neuropsychometry. The patients in these previous studies have therefore been categorized with less diagnostic accuracy.

One study demonstrated that SPECT abnormalities were already demonstrable in patients with 'questionable AD' and useful in discriminating 'converters' (patients

Table 4. Results from SPECT image analysis – temporal (T) regional values

Subregion		n	Control	n	Amnesia	p
Superior gyrus and insula T1	$F_{i(L)}$	15	78.4 ± 6.5	32	72.0 ± 7.2	0.035
	$F_{i(R)}$	15	78.2 ± 6.5	32	72.1 ± 7.9	0.034
	SAI	15	3.3 ± 2.6	32	3.0 ± 2.1	0.90
Inferior and middle gyrus T2	$F_{i(L)}$	15	77.7 ± 6.8	32	72.2 ± 9.1	0.13
	$F_{i(R)}$	15	79.7 ± 5.5	32	76.5 ± 7.6	0.28
	SAI	15	3.9 ± 4.0	32	6.7 ± 5.9	0.23
Temporal pole T3	$F_{i(L)}$	15	68.6 ± 6.9	29	58.0 ± 7.7	0.004
	$F_{i(R)}$	15	69.3 ± 6.0	29	60.8 ± 6.2	0.008
	SAI	15	4.7 ± 3.3	29	7.1 ± 6.8	0.36

All values given as mean ± 1 SD (standard deviation). Statistical comparison of group rCBF values using nonparametric statistics (Mann-Whitney). rCBF values in left $F_{i(L)}$ and right $F_{i(R)}$ hemispheres and SAI in cerebral regions of interest. $F_{i(L)}$ = Left hemispheric rCBF given relative to mean rCBF in the cerebellum; $F_{i(R)}$ = right hemispheric rCBF given relative to mean rCBF in the cerebellum; SAI = numerical value of SAI given in percent by: $[(F_{i(H)} - F_{i(V)})/F_{i,\,max}] \times 100$; n = number of patients in whom the region was drawn.

progressing to AD) from 'nonconverters' [21]. However, the patients in this study were categorized merely on the basis of their Clinical Dementia Rating (CDR) score. Only 18 out of 136 patients 'converted' during the follow-up period of 2 years. The hypoperfused regions suggested to be critical to 'conversion' were anatomically small (hippocampal-amygdaloid complex, anterior and posterior cingulate and anterior thalamus) taking into account the technical limitations.

Two previous studies demonstrated that SPECT was sensitive in detecting abnormal perfusion in patients with 'mild AD' and mild cognitive impairment [22, 23], and in a prospective study a 82% probability of conversion from amnesia to AD within 1 year was found in patients with initial bilateral temporoparietal hypoperfusion [24].

In a PET study [9], 20 patients with isolated memory impairment were examined and it was suggested that PET abnormalities (temporoparietal) were prominent in these patients and that PET was sensitive in identifying patients likely to develop progressive cognitive impairment. The classification of patients with isolated memory impairment in this study was based on a more extensive neuropsychological battery, although still considered limited and less accurate compared to the methods applied in the present study.

Similar findings of hypometabolism in isolated memory impairment (both progressive and nonprogressive cases) or in patients with known familial risk of AD were reported in other smaller PET studies (11 patients [25], 11 patients [26], 1 patient [27], 10 patients [28], 1 patient [29], 1 patient [30], 24 patients [31]).

In an SPECT study of early AD it was concluded that lower rCBF in the left temporal region was associated with higher death rates, lowering median survival by 1.7 years [32]. Another SPECT study – although technically limited (low-resolution Xe-133 study) – found that patients with age-related cognitive decline and temporoparietal asymmetry were more likely to progress into dementia on clinical follow-up than others [33]. Two recent PET studies suggested that hypoperfusion in the left temporoparietal region might be of particular interest in predicting progression from isolated memory impairment or MCI to impairment of other cognitive domains or to AD [9, 34]. Another recent study combined the diagnostic value of SPECT with the diagnostic value of CSF markers, and found this approach very accurate (sensitivity 88.5% and specificity 90%) in calculating an index predicting the conversion from MCI to AD [35].

Although not directly comparable, previous studies on transient global amnesia and functional imaging [36–39] have suggested that these patients may have widespread impairments on functional imaging.

In summary, several of the previous studies were specifically supportive of a primary temporal lobe hypoperfusion in patients with amnesia or early AD. Moreover, some studies have focused on the possible dysfunction of the posterior cingulate, the hippocampal-amygdaloid complex and other limbic structures, and the left supramarginal and middle temporal gyri [40–43].

We suggest that the application of SPECT can demonstrate early significant hypoperfusion in patients with isolated amnesia, who are generally thought to have a high risk of progression to AD. The finding (see Results) that just 19 (left temporal) and 20 (right temporal) patients had temporal rCBF values below control mean minus 1 SD suggests that reduced temporal rCBF may help to identify a patient subgroup – possibly the subgroup of patients with the highest risk of progression. No identified concomitant condition might potentially be associated with cerebral hypoperfusion. All patients had normal CT/MRI scans of the brain, although some white matter lesions were reported. The reported white matter lesions were not considered clinically relevant in the majority of the patients, and the frequency and extent of such lesions were not considered to be of significance to memory. Likewise, our patient sample did not include patients with cerebral infarcts of conceivable relevance to memory. The SPECT normalization procedure (cortical values normalized to mean cerebellar rCBF) is conventional, as the cerebellum is generally thought to be unaffected by the degenerative process in AD, at least until the very late stages. No significant pathology was identified in the cerebellum by structural imaging in any of the subjects.

Statistical corrections for multiple comparisons were not introduced, which may be a limitation of the study. However, independent statistical methods (regression analysis and Mann-Whitney) gave converging results.

The specific finding of temporal hypoperfusion may be due to the selection of MCI patients by strict neuropsychological criteria for isolated memory impairment and a comprehensive test program. According to the original definition [7], it is not clear which exact neuropsychological tests are necessary to assess the severity of cognitive dysfunction. This implies the risk of overlooking significant cognitive dysfunction in various nonmemory domains and the group of MCI patients thus defined may in fact be neuropsychologically heterogeneous. This heterogeneity may evolve from completely distinct etiologies. That is, some cognitive deficits may be due to degenerative disorders whereas others may be of vascular or other

origin. The described neuropsychological criteria for isolated amnesia may, in particular for research purposes, give more specific information on the pure degenerative disorders and their progression pattern. The patients with temporal lobe rCBF reductions and selective amnesia will be followed closely in order to assess clinical progression and possibly demonstrate the additional predictive value of SPECT compared to other clinical and paraclinical methods.

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