Temporal hypometabolism at the onset of cryptogenic temporal lobe epilepsy

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Abstract. Most patients with intractable temporal lobe epilepsy (TLE) exhibit temporal glucose hypometabolism. The reasons for the development of this abnormality are as yet unclear. The current notion is that an initial injury causes seizures, which in turn give rise to hypometabolism. The aim of this study was to assess whether temporal reductions in glucose metabolism in non-lesional TLE are the result of repeated seizures or whether hypometabolism represents an initial disturbance at the onset of disease. Glucose consumption was assessed with fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) in 62 patients with cryptogenic non-refractory TLE in different stages of disease. Twelve subjects without neurological illness served as controls. Patients with onset of epilepsy at least 3 years prior to the PET scan were defined as having chronic TLE. Using this criterion, the whole patient cohort included 27 patients with de novo TLE and 35 patients with chronic TLE. The groups were matched for age and sex. The appearance of high-resolution magnetic resonance images of the brain was unremarkable in all patients. In the total cohort, number, duration and frequency of seizures had a significant relation to the magnitude of hypometabolism. Temporal hypometabolism was exhibited by 26 of the 62 patients (42%), including 8 out of 27 (30%) with newly diagnosed TLE and 18 out of 35 (51%) with chronic TLE. The disturbances were more extensive and more severe in patients with chronic TLE. It is concluded that temporal hypometabolism may already be present at the onset of TLE, but is less frequent and less severe in newly diagnosed than in chronic TLE. The metabolic disturbance correlates with the number of seizures. These findings suggest that an initial dysfunction is present in a considerable number of patients and that hypometabolism is worsened by continuing epileptic activity.

Keywords: Temporal lobe epilepsy – Fluorine-18 fluorodeoxyglucose – Positron emission tomography – Glucose consumption

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Introduction

In 1977, positron emission tomography (PET) was introduced for the non-invasive measurement of regional cerebral glucose consumption [1]. Since then, a wealth of studies have shown that a reduction in temporal glucose consumption can be detected in a high percentage of patients with medically intractable temporal lobe epilepsy (TLE). All available evidence indicates that this metabolic abnormality is indicative of the epileptogenic focus and that it can also be found in regions that are structurally intact even on high-resolution magnetic resonance (MR) images (for review see [2, 3]). Consequently, the PET investigation of glucose consumption has been recommended for the presurgical work-up of patients with medically intractable TLE [4, 5, 6, 7, 8, 9, 10, 11].

Evidence on brain metabolism in focal epilepsy stems primarily from the investigation of presurgical patients; patients with TLE of new onset have as yet only rarely been studied [12, 13].

It is still unknown whether this metabolic abnormality is only a result of severe and multiple repetitive seizures, or whether at least mild disturbance of glucose consumption might be present in the initial stages of focal epilepsy. To address this question, we sought to determine the frequency, magnitude and spatial extension of metabolic abnormalities in the temporal cortex of patients with

medically controllable and non-lesional TLE of varying duration.

Materials and methods

Patients. Sixty-two patients with cryptogenic TLE and normal-appearing MRI of the head were studied with ^{18}F-FDG PET. This study was approved by the local ethics committee; informed consent was obtained from all of the patients. The diagnosis of cryptogenic TLE was based on personal history, neurological examination, seizure type and symptoms, and interictal and/or ictal EEG findings. Patients with primarily generalised seizures or symptomatic epilepsy according to the ILAE criteria [14], as well as patients with other neurological or systemic disease, were excluded. All remaining patients were admitted into a longitudinal epilepsy study established at our departments. In the present study only those patients were included who showed clinical improvement after anticonvulsive therapy had been started or modified following the initial ^{18}F-FDG PET.

The patients were divided into two subgroups depending on the duration of TLE: Patients with onset of partial seizures at least 3 years prior to the PET scan were defined as having chronic TLE (n=35, Table 2). The other patients were classified as "newly diagnosed" (n=27, Table 1), in accordance with published data [12, 15, 16]. Nineteen of the newly diagnosed patients (70%) had their first seizure in the same year as the PET scan. Four of the 27 patients of this group had recently been put on anti-epileptic medication, as indicated in Table 1. However, in most patients initial drug treatment was insufficient. After optimisation of the anti-epileptic therapy, seizures declined in frequency and severity and none of the patients had to be included in a program for epilepsy surgery.

Median seizure frequency at the time of investigation (estimation based on the last 3 months before PET) was slightly higher in chronic TLE (two seizures per month, range 0–83) than in de novo TLE (one seizure per month, range 0–13); this difference did not attain significance (P>0.05, Mann-Whitney U test). Age and gen-

Table 1. Demographic and clinical data of the patients with newly diagnosed TLE

Pt. no.	Age (yrs)/ gender	Seizures			MRI[d]	EEG[e]	FDG[f]	Drugs[g]
		Duration (years)[a]	Frequency per month[b]	Sum class[c]				
1	27/m	0.2	1.0	1	Temporal horn, R>L	Normal	–	–
2	21/m	0.2	0.1	1	Normal	Slow L temp	–	–
3	30/m	0.3	2.5	1	Normal	Slow L fro-temp	–	–
4	16/f	0.5	0.8	1	Normal	Normal	–	–
5	61/f	0.2	0.8	1	Normal	Slow L temp	–	–
6	62/m	0.5	0.3	1	Normal	Slow L temp	–	–
7	23/m	0.4	3.0	2	Normal	Normal	–	–
8	62/f	0.1	3.0	1	Normal	Normal	–	–
9	21/f	0.4	0.3	1	Normal	Normal	–	–
10	54/m	0.1	6.7	1	Normal	Slow R fro	–	–
11	34/m	0.2	1.5	1	Normal	Normal	–	–
12	38/f	0.4	0.3	1	Normal	Normal	–	–
13	21/f	0.4	0.3	1	Normal	Slow L temp	–	–
14	21/m	0.5	0.5	1	Normal	Slow R fro-temp	–	–
15	33/m	0.5	12.5	3	Arachnoidal cyst, L occ	Normal	–	–
16	25/f	0.3	0.4	1	Normal	Normal	–	–
17	25/f	1.5	2.0	2	Normal	Slow L temp	L	–
18	21/m	1.0	0.2	1	Normal	Normal	–	–
19	33/f	0.7	0.3	1	Normal	Slow R temp-occ	R	–
20	24/f	1.3	0.6	1	Normal	EA R fro-temp, slow L fro-temp	R	–
21	18/m	1.5	2.0	2	Normal	EA L fro-temp	L	–
22	39/f	1.0	0.3	1	Normal	Normal	–	CBZ
23	16/f	2.0	2.0	2	Ventricle, L>R	Slow R fro-temp	–	–
24	26/f	1.3	12.5	3	Normal	EA L fro-temp	L	CBZ
25	33/f	1.5	0.3	1	Normal	Slow L fro-temp	L	CBZ
26	27/f	3.0	0.4	2	Normal	EA R fro-temp, slow R temp	R	–
27	33/m	3.0	1.7	3	Normal	Slow L fro-temp	L	DPH

[a] Duration of TLE in years
[b] Frequency of seizures per month
[c] Classified total number of seizures in the history of TLE (class 1, ≤10 seizures); class 2, 11–50 seizures; class 3, 51–500 seizures)
[d] Findings of magnetic resonance imaging: L, left; R, right
[e] Epileptic pattern on electroencephalography: L, left; R, right; slow, slow waves; EA, epileptiform activity (spike/sharp waves); fro, frontal; temp, temporal; occ, occipital
[f] Lateralisation of temporal hypometabolism on ^{18}F-FDG PET
[g] Anti-epileptic medication: CBZ, carbamazepine; DPH, phenytoin

der distribution were comparable in the two groups. Median duration of epilepsy was 6 months in the group with newly diagnosed TLE (range 1 month to 3 years), and 12 years in the group with chronic TLE (range 4–42 years, Tables 1 and 2).

Besides seizure frequency and duration of epilepsy, total number of seizures in the patient's history, including isolated auras, simple partial seizures and complex partial seizures (CPS) with or without generalisation, were included in the data analysis. The estimation of this parameter was unproblematic in patients with a short history and/or a low frequency of seizures. In patients with a long history of epilepsy and/or a higher seizure frequency, the total number of previous attacks was approximated using an arbitrary classification with the following categories: class 1, ≤10 seizures; class 2, 11–50 seizures; class 3, 51–500 seizures; and class

Table 2. Demographic and clinical data of the patients with chronic TLE

Pt. no.	Age (yrs)/ gender	Seizures			MRI[d]	EEG[e]	FDG[f]	Drugs[g]
		Duration (years)[a]	Frequency per month[b]	Sum class[c]				
1	57/f	4.0	1.2	3	Temporal lobe, R>L	EA R/L fro-temp Slow L fro-temp	R	–
2	75/m	5.0	0.1	1	Normal	Slow L fro-temp	L	–
3	23/f	5.0	0.1	1	Normal	Slow R temp	–	–
4	39/m	10.0	0.1	1	Normal	Slow L fro-temp	–	–
5	60/f	5.0	0.1	1	Normal	EA/slow L fro-temp	–	–
6	18/m	6.0	0.1	1	Normal	EA L fro-temp	L	DPH
7	54/f	35.0	6.7	4	Temporal horn, R>L	Normal	–	–
8	61/m	17.0	0.1	1	Normal	EA L fro-temp	L	–
9	21/f	6.0	58.0	4	Normal	Normal	–	–
10	66/f	30.0	83.0	4	Normal	EA L temp, slow R/L temp	–	-–
11	33/m	8.0	0.3	2	Normal	Normal	–	–
12	26/m	16.0	1.7	3	Temporal horn, R>L	Normal	L	–
13	21/f	7.0	5.0	3	Normal	Slow R/L fro-temp	–	–
14	28/f	19.0	0.1	2	Temporal horn, R>L	Normal	L	–
15	20/f	19.0	2.0	3	Normal	EA/slow R fro-temp	R	DPH
16	31/m	23.0	17.0	4	Normal	Slow L fro-temp	–	CBZ/LTG
17	29/f	13.0	2.0	3	Normal	EA L fro-temp	–	CBZ/VGT
18	38/f	15.0	1.0	3	Normal	EA/slow L fro-temp	–	CBZ
19	51/f	21.0	12.5	4	Temporal horn, R>L	Slow L fro-temp	R	CBZ/PRI/LTG
20	45/m	42.0	17.0	4	Normal	EA/slow R fro-temp	R	CBZ/VAL
21	19/f	9.0	1.5	3	Normal	EA/slow L fro-temp	–	LTG/DPH
22	60/f	9.0	0.5	3	Normal	EA/slow R fro-temp	R	VAL
23	41/f	5.0	12.5	4	Normal	EA R temp	R	CBZ
24	26/m	13.0	8.3	4	Normal	EA R/L fro-temp, slow L fro-temp	L	CBZ/LTG
25	21/m	10.0	8.0	4	Normal	Normal	R	CBZ/VAL/LTG
26	19/m	15.0	1.7	3	Normal	Normal	–	CBZ
27	62/f	9.0	2.5	3	Normal	Slow L temp	L	GBP
28	24/m	6.0	0.2	2	Normal	Normal	–	DPH
29	60/m	6.0	0.8	3	Normal	Normal	–	DPH
30	37/f	17.0	2.0	3	Normal	EA R fro-temp	L	CBZ/PB/LTG
31	29/f	17.0	7.0	4	Normal	EA R fro-temp	L	CBZ
32	43/f	15.0	17.0	4	Normal	Normal	–	CBZ/LTG
33	31/ f	24.0	8.3	4	Normal	Slow R/L fro-temp	–	CBZ/GPT
34	30/f	18.0	4.2	4	Normal	EA R fro-temp, slow R/L temp	R	VAL/LTG
35	20/m	4.0	83	4	Normal	EA/slow L fro-temp	L	GPT

[a] Duration of TLE in years

[b] Frequency of seizures per month

[c] Classified total number of seizures in the history of TLE (class 1, ≤10 seizures); class 2, 11–50 seizures; class 3, 51–500 seizures; class 4, >500 seizures)

[d] Findings of magnetic resonance imaging: L, left; R, right

[e] Epileptic pattern on electroencephalography: L, left; R, right; slow, slow waves; EA, epileptiform activity (spike/sharp waves); fro, frontal; temp, temporal; occ, occipital

[f] Lateralisation of temporal hypometabolism on ^{18}F-FDG PET

[g] Anti-epileptic medication: CBZ, carbamazepine; VGT, vigabatrine; PRI, primidone; VAL, valproate; DPH, phenytoin; LTG, lamotrigine; PB, phenobarbital; GPT, gabapentine

4, >500 seizures. As expected, a significantly higher number of seizures was found in chronic than in newly diagnosed TLE [median class: 1 (de novo TLE) vs 3 (chronic TLE); $P<0.001$, Mann-Whitney U test].

Control subjects were individuals in whom neurological or major psychiatric disease had been excluded. The control group included five men and seven women. Mean age was comparable to that of the epilepsy patients (38±15 years).

Electroencephalography (EEG). In all patients, EEGs were performed under baseline conditions and after provocation methods, using scalp electrodes placed according to the international 10–20 system with supplementary electrodes in T1/T2. The recordings lasted at least 15 min (routine) or 30 min (sleep deprivation); referential, bipolar and source derivation techniques were used in each EEG.

All patients underwent EEG after photic stimulation, hyperventilation (3 min) and sleep deprivation; only in a few patients was 24 h video-EEG monitoring performed.

At least two unprovoked, partial seizures with or without secondary generalisation according to classification criteria established by the International League Against Epilepsy were clinically documented in all patients either before the PET scan or thereafter [14]. Ictal recordings were not achieved.

Bilateral EEG abnormalities were found in 7 of the 62 patients studied: EEG lateralisation was decided upon on the basis of the leading EEG abnormalities (for details, see Tables 1 and 2).

Magnetic Resonance Imaging. MRI was performed with a 1.5-T Magnetom (SP 63, Siemens, Erlangen, Germany) using spin-echo (SE) and turbo spin-echo (TSE) sequences to generate standard axial T1- and T2-weighted images. In addition, coronal and axial T2-weighted TSE sequences were acquired parallel and perpendicular to the hippocampal axis using a 3 mm slice thickness and a 256^2 matrix. A blinded visual assessment of sclerosis or atrophy within the temporal lobe was performed by an experienced neuroradiologist (G.S.). Volumetric measurements of the hippocampus or amygdala were not performed.

PET data acquisition. Details of the scanning procedure have been reported previously [17]: After a 4-h fast, patients were investigated interictally (185 MBq ^{18}F-FDG) using an ECAT EXACT 921/47 PET scanner (Siemens CTI, Knoxville, Tenn., USA; field of view=16.3 cm; 47 slices) under standardised conditions. Room noise was minimised and lights were dimmed. Attenuation was corrected using transmission scans, and filtered back-projection was used for reconstruction (Hanning filter, cut-off frequency of 0.5 cycles/pixel, pixel size 2.1 mm^2, matrix 256^2, slice thickness 3.4 mm).

PET data analysis. Details of the data analysis have been reported and discussed in more depth elsewhere, so only a brief description is given here [13, 17]: The image sets were realigned to coronal planes perpendicular to the hippocampal axis. To calculate asymmetry indices, activity profiles were extracted from six anatomically defined planes.

Temporal glucose metabolism was quantified on six contiguous coronal planes through the temporal lobe. On each of these slices, along the cortical ribbon, the pixels with maximal uptake were manually selected. The starting point was the superior temporal gyrus, and the end-point, the hippocampal area. This procedure yielded line profiles of the maximal uptake for each side and each slice. On each slice, the line profile was subdivided into two parts of equal length, i.e. a lateral and a mesial part. By summarising the uptake values from the three anterior and the three posterior temporal planes, pixel-weighted mean values for the lateral and mesial frontal and the lateral and mesial occipital regions of the temporal cortex were calculated. The resulting mean values were used to calculate indices of asymmetry (ASY) according to the following formula:

$$\text{ASY}=200 \times (\text{left temporal value}-\text{right temporal value})/(\text{left temporal value}+\text{right temporal value}).$$

The inter-observer reproducibility of this approach to regional analysis was tested in a randomly selected subset of 25 patients; correlation coefficients between regional ASY values determined by two independent observers were 0.94, 0.94, 0.97 and 0.91 in the frontolateral, frontomesial, occipitolateral and occipitomesial temporal regions, respectively [13, 17].

Statistical analysis. Using the mean value (X) and the standard deviation (SD) determined in the controls, the patients' ASY values were transformed into Z-scores according to the formula:

$$\text{Z-score}=(\text{ASY value of the patient}-X)/SD.$$

All Z-scores greater than |2.2| were considered to indicate a statistically significant difference; these values represent the 95% confidence intervals of the control data (appropriate t value: 2.2). Group differences in means were assessed using the non-parametric Mann-Whitney U test, and group differences in frequencies using the chi-square test. Analyses of correlation were performed using Spearman's correlation coefficients. Significance was accepted for P values of less than 0.05.

Results

A representative example of the patients studied is given in Fig. 1. Twenty-six of the 62 patients (42%) showed a significant temporal hypometabolism. This abnormality

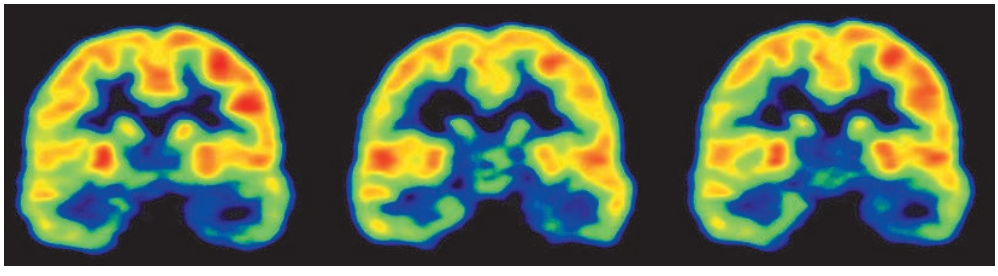

Fig. 1. ^{18}F-FDG PET: consecutive coronal slices of the left temporal hypometabolism in a patient (no. 21) with newly diagnosed TLE. The image represents cerebral glucose consumption and is scaled to its own maximum

Table 3. Correlation between duration of TLE, total number of partial seizures and seizure frequency and the magnitude or extension of temporal hypometabolism

r, Spearman's correlation coefficient; NS, non-significant
*Significance level: $P<0.05$
**Significance level: $P<0.001$

Group	Hypo-metabolism	Duration of TLE	Total no. of seizures	Frequency of seizures
Newly diagnosed (n=27)	Z-score	r=0.43*	NS	NS
	Extension	r=0.72†	r=0.48*	NS
Chronic TLE (n=35)	Z-score	NS	r=0.40*	NS
	Extension	NS	NS	NS
Whole population (n=62)	Z-score	r=0.44**	r=0.46**	r=0.28*
	Extension	r=0.37*	r=0.38*	NS

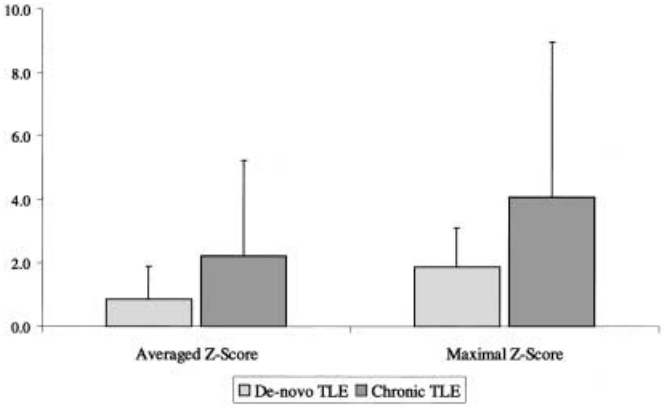

Fig. 2. Comparison of maximal and global Z-scores of temporal asymmetry in both groups of patients

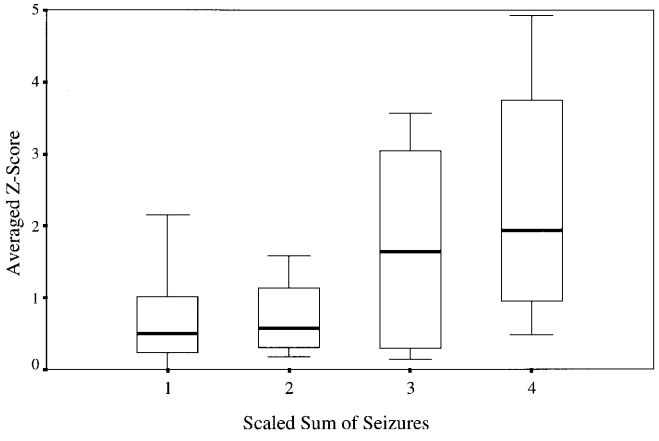

Fig. 3. Correlation between the degree of temporal hypometabolism (averaged Z-score, vertical axis) and the classified total number of seizures [horizontal axis: *1*, class 1 (≤10 seizures); *2*, class 2 (11–50 seizures); *3*, class 3 (51–500 seizures); *4*, class 4 (>500 seizures)]

was found in eight of the 27 patients (30%) with newly diagnosed TLE in at least one of the four temporal regions studied. In seven of these patients, one temporal region exhibited a pathological Z-score, while in one patient, four temporal regions did so. The distribution of the maximal temporal hypometabolism within the temporal ROIs was as follows: frontolateral ROI (n=2), frontomesial ROI (n=1), occipitolateral ROI (n=3) and occipitomesial ROI (n=2).

Eighteen of the 35 patients (51%) with chronic TLE had a significantly pathological temporal Z-score. This proportion was slightly higher than in patients with newly diagnosed TLE, but the difference did not attain statistical significance (P=0.08, χ^2=3.0). The number of regions with a pathological Z-score was one in five patients, two in five patients, three in four patients, and four in four patients. In patients with chronic TLE, maximal temporal hypometabolism was distributed as follows: frontolateral ROI (n=3), frontomesial ROI (n=2) and occipitolateral ROI (n=13).

The mean number of affected ROIs was significantly higher in chronic TLE than in newly diagnosed TLE (1.2±1.5 vs 0.4±0.8, U=331, P< 0.05). This was also true with regard to maximal as well as to averaged Z-score values of temporal asymmetry (Fig. 2).

In the whole patient population, there was a significant correlation between the number of significantly asymmetrical ROIs per patient as well as the magnitude of asymmetry on the one hand, and the duration of epilepsy or the total number of seizures in the patient's history on the other (Fig. 3, Table 3). There was also a significant correlation between frequency of seizures and the magnitude of asymmetry, but not between the frequency of seizures and the extension of asymmetry. An overview of coefficients of correlation and the corresponding significance levels in both groups of patients are given in Table 3.

Discussion

This study reports on 62 medically controllable patients with cryptogenic TLE. Despite the normal appearance of the MRI of the brain, about 40% of such patients exhibit reductions of temporal glucose metabolism as measured by ^{18}F-FDG PET.

A considerably lower frequency of temporal hypometabolism was present in our patient group than is found in patients with chronic intractable TLE, more than 90% of whom display this abnormality. It is well known that ^{18}F-FDG PET is an important instrument in the preoperative work-up of patients with medically intractable sei-

zures [6, 10, 11, 18]. One might expect that ^{18}F-FDG PET could also be used to detect epileptogenic foci in patients who are in the initial stage of TLE. In view of our results, however, ^{18}F-FDG PET cannot be considered a first-line method for the detection of epileptogenic foci in patients with well-controlled TLE owing to its limited sensitivity in this patient group.

Significant asymmetries in temporal glucose consumption were found in 30% of newly diagnosed patients, just a few months after their first apparent seizure. This observation is new, and may cast light on the still unsettled question of whether hypometabolism is solely the result of refractory seizures after a long history of epilepsy. The presence of significant temporal hypometabolism at the onset of partial epilepsy is inconsistent with the notion that this metabolic disturbance is only a consequence of sustained seizure activity.

The finding that temporal hypometabolism may occur in newly diagnosed TLE is consistent with the observation that asymmetries in hippocampal volume may also be found in the early stages of epilepsy [15, 16, 19]. Furthermore, these results are in agreement with previous histopathological data reported by Mathern and co-workers in 1996. These authors postulated an initial precipitating injury which leads to primary damage of the hippocampus with neuronal loss and mesial temporal sclerosis (MTS) [20].

MTS is the most frequent pathological finding in patients with TLE, and histopathologically, MTS is characterised by severe neuronal loss involving in particular the hippocampal segments CA3/4 and CA1 (for review see [21]). Both neuronal loss and hippocampal atrophy have been shown to coexist with decreases in temporal glucose metabolism as measured by ^{18}F-FDG PET [8, 22, 23, 24, 25, 26], but hippocampal atrophy seems not to be the major determinant of temporal hypometabolism [27].

Furthermore, Mathern et al. found that the magnitude of neuronal loss was greater in patients with a long history of TLE, suggesting some secondary loss of neurones in the course of repetitive seizures [20]. This suggestion is supported by our observation that temporal hypometabolism was more extensive and significantly more severe in the patient group with chronic TLE than in patients with de novo TLE; these results, obtained with PET, are, in a sense, a confirmation of the classical kindling concept. Recent MRI and experimental data lend further support to the hypothesis of secondary neuronal losses in epilepsy: there is a close relationship between the number of seizures and hippocampal cell losses [28, 29]. Analogously, hippocampal atrophy has been shown to correlate with the duration of epilepsy in humans [30, 31].

In the absence of histopathological analysis in our study, we cannot define what pathology caused glucose hypometabolism in the study cohort. None of the patients had neurological or relevant systemic disease other than epilepsy, and MRI excluded post-traumatic defects, tumours, malformations and other macroscopic abnormalities. Major hippocampal atrophy was also excluded, so that in the majority of patients, beginning and mild hippocampal sclerosis without massive atrophy was the most likely histopathological correlate. Focal reduction in cerebral glucose consumption despite normal macroscopic morphology might be caused by loss of neurones without major atrophy or by disturbed neuronal function (reversible or irreversible, e.g. sclerosis). As yet it is impossible to clarify the pathogenesis of this disturbance, as until now none of the patients have had to be included in a program for epilepsy surgery.

In our patients, maximal hypometabolism occurred in lateral as well as in mesial parts of the temporal lobe, and the occipito-lateral ROI was most frequently affected, although partial seizures are predominantly generated in the mesial temporal lobe. These results are in agreement with comparative studies using ^{18}F-FDG PET and carbon-11 flumazenil PET in patients with TLE: the groups of Savic and Debets independently reported that benzodiazepine receptor density was focally reduced in the mesial temporal cortex, while in the same subjects, maximal glucose hypometabolism was confined to outside the suspected sclerotic lesion in the lateral formation of the temporal lobe [32, 33]. These authors concluded that the reduction in the net metabolic ratio in the lateral temporal cortex is a consequence of a lateral deactivation occurring over the course of mesial inhibition [32].

One limitation of the present study is the visual analysis of the MRI data. An additional volumetric analysis would be very interesting as patients with TLE exhibit reductions in mesial temporal volume [16, 19, 34]. Furthermore, the MRI protocol was suboptimal in that 3-mm sections were used, whereas today a smaller slice thickness is routinely employed for the investigation of TLE.

The absence of the gold standard histopathology or invasive EEG recordings to study the correlation between hypometabolism and epileptogenic pathology is a second limitation of this work. This limitation is inherent to our selection criteria, however, as patients with medically controlled seizures do not undergo invasive procedures for obvious medical and ethical reasons.

In the course of the data analysis the whole cohort of patients was subdivided into two groups comprising subjects with newly diagnosed and subjects with chronic TLE. These subgroups were compared according to their seizure characteristics and their PET findings in temporal lobes; however, it cannot be excluded that the two patient classes differed in more criteria than duration of epilepsy. This is clearly an inherent problem with the cross-sectional design of the study. A further limitation is the potentially different effects of anti-epileptic medication in patients with a long duration of disease as compared to those with de novo epilepsy. Relevant changes in global glucose consumption after drug administration have been reported [35, 36]. The data presented here are the first results of a longitudinal epilepsy study. To date,

most of the initially investigated patients (about 85%) are still included in follow-up, which will in the future yield more details about the natural history of TLE in each patient.

In conclusion, temporal hypometabolism may already be present at the onset of TLE, though it is less frequent and less severe in newly diagnosed TLE than in chronic TLE. The metabolic disturbances correlate with the estimated number of previous seizures. These findings suggest that an initial dysfunction may be present and that hypometabolism is worsened by continuing epileptic activity in cryptogenic TLE.

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