

Epilepsy surgery improves regional glucose metabolism on PET scan

A case report

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Summary. A patient with medically intractable complex partial epilepsy was evaluated for epilepsy surgery by electroencephalograph recording with depth electrodes and ¹⁸F-fluorodeoxyglucose positron emission tomography (PET). A small calcified arteriovenous malformation was excised from the left parietal lobe, and the patient became seizure free. Baseline and language stimulation PET scans were obtained preoperatively and 10 months postoperatively. There was a significant increase in glucose metabolism of the left temporal lobe postoperatively, which we interpret as evidence of improved neuronal function. We suggest that this case represents evidence for a functional, and reversible, inhibition of neuronal metabolism by epileptic activity.

Key words: Complex partial epilepsy – Positron emission tomography – 2-Deoxyglucose – Epilepsy surgery

Introduction

The surgical treatment of medically intractable complex partial epilepsy has been available since the turn of the century [11, 17]. In addition to the obvious benefits such surgery provides the patient, the pre- and postsurgical, multidisciplinary diagnostic evaluations have contributed important basic information about epilepsy. One of the more recently developed tools to evaluate these patients is positron emission tomography (PET) of the brain. PET using ¹⁸F-2-fluoro-2-deoxyglucose (2-FDG) is able to measure local cerebral glucose utilization in humans. In patients with complex partial epilepsy, 2-FDG PET performed interictally has frequently revealed areas of hypometabolism which have correlated with the ictal focus [9]. The etiology of this hypometabolic zone is still unclear despite human and animal experiments.

There are two current hypotheses to explain this hypometabolism, and they are not mutually exclusive [9]. One suggests an anatomical substrate such as loss of dendritic spines and synapses. The other suggests a functional substrate related to inhibition or inactivation of healthy neuronal elements by the epileptic process. A functional etiology could be reversible if the epilepsy were controlled. However, no studies have been able to test this hypothesis because either

the epilepsy is medically intractable or control is obtained by surgically removing the area of hypometabolism. Once the tissue is removed, a follow-up PET scan would be meaningless. Nevertheless, there is indirect evidence supporting a functional etiology. First, these hypometabolic zones can become hypermetabolic during a seizure [9]. Second, a patient has been reported with Lennox-Gastaut syndrome in whom a hypometabolic temporal lobe returned to normal following commissurotomy and clinical improvement [6]. Third, a case has been described of complex partial epilepsy with a right occipital focus and right occipital and temporal hypometabolism which improved when the patient was seizure free [4, 9].

We present a case of complex partial epilepsy which addresses the hypothesis of a functional etiology for epilepsy-induced regional hypometabolism. We employed a strategy of baseline and language stimulation PET scans to enhance our ability to uncover a lesion that could be functionally silent under baseline conditions, as suggested by Mazziotta and Engel [9].

Materials and methods

¹⁸F-2-FDG was prepared by the method of Tewson [15] from ¹⁸F-fluoride, produced on the University of Wisconsin EN tandem Van de Graaff. The Tewson synthesis is known to result in 2-FDG without contamination with ¹⁸F-fluoro-deoxymanose. Head contour and attenuation correction in the data planes were defined with a transmission source prior to each study. Forty minutes following the intravenous administration of 2-FDG, three cross-sectional images were obtained with an ECAT-II tomograph (EG + G Ortec) at 3, 4.5 and 6 cm above the orbitomeatal line. These sections will be referred to as low, middle and high, respectively. The preoperative scans used shadow shields producing a resolution of 1.7 cm full width at half maximum (FWHM). Postoperatively, we used shields which allowed for a 1.3 cm FWHM because of the availability of more isotope. Glucose utilization rates were computed according to the method of Hutchins et al. [7].

Data were transferred to a Gamma 11 system for analysis. Homologous left-right regions were outlined to include frontal, temporal and parietal cortex. The ratio of the region of interest/whole slice mean was calculated for each slice and then averaged to yield a final dimensionless value for each brain area. These values are presented in Table 1, and the left/right ratio is calculated from these averages.

Informed consent was obtained for the PET scans. Pre-operatively, a baseline scan was obtained, followed 4 days later by a language stimulation scan. The patient did not have any seizures during this interval. Ten months postoperatively, a baseline and language stimulation scan were obtained separated by 1 day. The patient had been seizure free for the preceding 6 months. The patient was on long-term phenytoin and carbamazepine during both pairs of PET scans. A protocol was devised to evaluate the effect of language on glucose metabolism which would both maximize attentiveness and minimize memory requirements.

Language stimulations. Language stimulation was provided with a tape-recorded list of 150 single words presented binaurally through earphones at a rate of 2/min. The stimuli were randomly selected from the Thorndike and Lorge list of most frequently occurring words. These words were then tape-recorded in random order so that they occurred at a rate of 2/min for 50 min. Interstimulus intervals were also determined randomly so that within each minute one word would appear any time between 1 and 25 s and the second word would appear any time between 30 and 55 s. The first ten were used as orientation and practice stimuli and the rest as experimental stimuli.

Prior to actual testing the patient was told he would be blindfolded and fitted with a pair of earphones, and that he would then hear a list of words presented to both ears. He was told his task was to elevate his left and right index fingers simultaneously each time he heard a word containing the /s/ sound. He recognized the difference between the "s" letter and the /s/ sound and understood that his task was to identify only the sound. The grapheme-phoneme difference was emphasized so that the task involved phonemic or sound analysis, which is primarily a left or dominant hemisphere task, rather than grapheme analysis, which may be more of a function shared by the two hemispheres. The patient was then positioned in the scanner, reinstructed as to the task, and then fitted with the eyepatch and earphones. Next, the ten sample items were presented binaurally to determine the most comfortable loudness level for stimulus presentation and to guarantee that the patient understood the task.

Presentation of the test stimuli began 10 min before injection and then continued for 45 min. The patient's responses were entered on an answer sheet by one of the experimenters, who also monitored the patient's attention to the task and roused him if his concentration waned. The patient made only three mistakes during each of the language stimulation procedures, which was within normal limits.

Baseline. In the baseline condition the patient was told that he would periodically be touched on both arms and that he was to respond by simultaneously elevating his left and right index fingers. He was then positioned in the scanner, wearing a blindfold and earphones, and was reinstructed. Next he was stimulated ten times at irregular intervals and at a rate of 2/min to guarantee that he understood the task. Tactile stimulation and the index finger response were selected because non-linguistic stimulation with the same kind of patient response as in the language stimulation condition was required.

Tactile stimulation at the rate of 2/min began 10 min prior to injection and continued for 45 min after injection was complete. The experimenter roused the patient, if he failed to respond to each touch, by raising his index fingers.

Case report

Seizures

This 37-year-old, right-handed shipping clerk had had complex partial epilepsy for 16 years. His seizures varied from none to several a week and were refractory to phenytoin, phenobarbital, primidone, carbamazepine, valproic acid and methsuximide. Many of his seizures were preceded by a blank stare, while others started with hyperextension of his neck and closing his eyes. He frequently turned to the left and flexed his extremities. This was followed by automatisms (not all were present during each seizure) including the following: picking with his hands, rocking, spitting and smearing the spit with his hands, masturbation with and without ejaculation. The patient was amnesic for these events.

Past medical history

The patient had no medical problems. The findings of a neurologic examination were normal and his full-scale IQ was 103. Three years prior to his epilepsy surgery, a CT scan had revealed a small calcified lesion in the floor of the lateral wall of the left ventricular atrium. An arteriogram was normal.

Language profile

The patient was first evaluated for speech and language pathology 3 years prior to his epilepsy surgery. At that time and at all subsequent evaluations, he was given a standard language battery consisting of: the Mayo Clinic procedures for language evaluation (unpublished), and adaptation of Schuell's short examination for aphasia [13], Token test [3], word fluency measure [1], Boston naming test [5], reading comprehension battery for aphasia [8], Raven's coloured progressive matrices [12] and a standard speech sample [18] to elicit spontaneous and imitative speech and reading aloud.

Phase I evaluation

The patient's neurologic examination, CT scan, full-scale IQ and language function had not changed over the last 3 years. His speech-language profile was most consistent with an anomic aphasia. Deficits in auditory and reading comprehension were mild and consisted primarily of delayed but correct responses rather than outright errors. Scalp EEG with closed-circuit video monitoring confirmed the etiology of the patient's spells as being complex partial seizures which started in the left hemisphere.

Phase II

The patient had depth electrodes (Rhodes Medical Co., California) stereotaxically implanted under CT guidance into the orbitofrontal, hippocampal and amygdala regions bilaterally. Spontaneous seizures were seen first in the left hippocampus and amygdala electrodes and then spread to other areas. Epileptiform activity never started in the frontal electrodes. No clinically silent electrographic seizures were ever recorded from any of the six electrodes. Moreover, the electrographic seizure was delayed by as much as 40 s from the onset of the clinical seizure. This suggested that the ictal focus was not at the recording sites. Afterdischarge threshold testing revealed a higher threshold in the left hippocampus compared with the

right. At higher currents, auras and seizures could be produced from both hippocampi and both amygdala but not from either frontal region. A thiopental activation test was not contributory. A right intracarotid sodium amytal injection produced memory dysfunction without language dysfunction. A left-sided injection produced no memory abnormalities but did impair language function. The amytal test results were consistent with the left hemisphere as the site of both language dominance and memory dysfunction.

Phase III

Two weeks following the removal of the depth electrodes the patient had his first pair of PET scans. A stereotaxic biopsy of the calcified lesion was then performed and a single depth electrode implanted near this site. Hundreds of electrographic seizures were recorded from this electrode. Electrical stimulation at this site produced afterdischarges; when these afterdischarges were over 40 s in duration, they induced a significant worsening of his anomia aphasia.

Surgery

The neurosurgery was done with the patient awake. A corticectomy was performed at the site of the electrode entry tract. The resection was carried out to the floor and lateral wall of the atrium. The lesion was a small arteriovenous malformation (AVM). No language abnormalities developed until the resection had extended to the deep white matter.

Follow-up

One week after surgery the patient still had severe Wernicke's aphasia with near total inability to read, write, and name; numerous paraphasias; and significantly impaired auditory comprehension. Nevertheless, he shortly returned to work and was seizure free for several months. The patient decided to discontinue his antiepileptic medications, which provoked a number of seizures. The medications were restarted, and he was 6 months without a seizure at the time of the second pair of PET scans. His speech-language performance had significantly recovered and approached his presurgical performance. Anomia continued to be the outstanding residual, but auditory and reading comprehension had returned to 80% of the presurgical level. Language diagnosis was once again anomia aphasia. A complete description of this patient's speech-language functions will be the topic of a future paper. The patient has now remained seizure free for 3 years on medication.

Results

Figure 1 shows the unenhanced CT scan through the calcified lesion preoperatively and the healed surgical ablation 10 months later at the time of the second pair of PET scans. Figure 2 is a color-scaled montage of all four 2-FDG distributions.

Preoperative PET study

Table 1 includes the PET data from both the baseline and stimulation preoperative study. Since we have not accumulated a series of normal control volunteers, the baseline data for this patient cannot be interpreted directly for abnor-

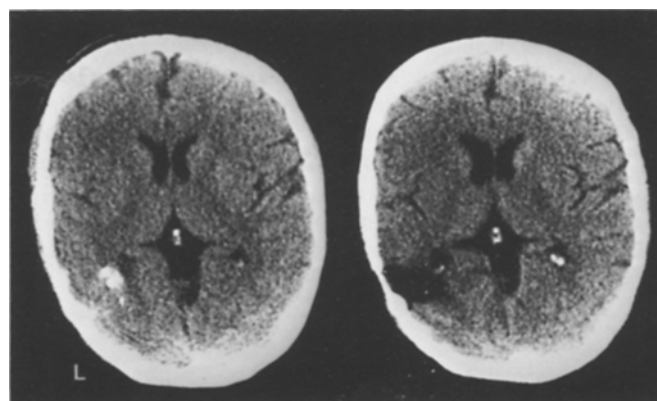


Fig. 1. Unenhanced CT scans of the epileptogenic lesion pre- and postoperatively. The *left slice* shows the maximal cross-sectional size of this partially calcified arteriovenous malformation. The *right slice* was taken 10 months postoperatively and shows the healed surgical site at the time of the second pair of PET scans

Table 1. PET study

	Region of interest/whole slice mean			
	Region	Left	Right	Left/right
Baseline preoperative	Frontal	1.17	0.96	1.22
	Temporal	1.21	1.14	1.06
	Parietal	1.27	1.38	0.92
Stimulated preoperative	Frontal	1.22	1.34	0.91
	Temporal	1.17	1.21	0.97
	Parietal	1.26	1.43	0.88
Baseline postoperative	Frontal	1.42	1.20	1.18
	Temporal	1.25	1.00	1.25
	Parietal	1.12	1.38	0.81
Stimulated postoperative	Frontal	1.43	1.24	1.15
	Temporal	1.32	1.09	1.21
	Parietal	1.13	1.42	0.80

malities. However, the patient can serve as his own control and changes in the range of 10% between baseline and stimulation may be of clinical significance [10]. Language stimulation did not affect any of the left brain regions. However, right frontal increased from 0.96 to 1.34, and the L/R ratio decreased frontally from 1.22 to 0.91 and temporally from 1.06 to 0.97.

Postoperative PET study

Table 1 shows the PET data obtained 10 months following the epilepsy surgery. The patient was on the same antiepileptic drugs as when the first pair of PET scans were performed, and his language abilities had returned nearly to the preoperative level. He was seizure free. Language stimulation produced only a modest effect this time and was restricted to the temporal region, increasing on the left side from 1.25 to 1.32 and on the right from 1.00 to 1.09.

Preoperative vs. postoperative PET

A direct comparison of the effects of surgery on regional brain glucose metabolism during the baseline PET scans can be seen

in Table 1. The left parietal region decreased markedly from 1.27 to 1.12, whereas the right parietal region remained unchanged at 1.38. The L/R ratio fell from 0.92 to 0.81. The left parietal region was the site of the operation, and the finding of decreased metabolism postoperatively serves as a biologic standard to validate the sensitivity of our PET scan techniques. The right temporal region decreased from 1.14 to 1.00 with a resulting increase in the L/R ratio from 1.06 to 1.25. The frontal region increased bilaterally such that the L/R ratio did not change.

Preoperative vs. postoperative stimulation PET

A direct effect of surgery on the language stimulated PET scans can be seen in Table 1. As with the baseline scans, the operated left parietal region has decreased from 1.26 to 1.13, the right side remained the same and the L/R ratio fell from 0.88 to 0.80. The decreases in the right frontal and temporal regions from 1.34 to 1.24 and 1.21 to 1.09 respectively, and the increases on the left side, from 1.22 to 1.43 and 1.17 to 1.32 respectively, produce a very marked increase in the L/R ratios of 0.91 to 1.15 frontally and 0.97 to 1.21 temporally.

Discussion

Patients with complex partial epilepsy of temporal lobe origin have frequently been found to have hypometabolism in the epileptic temporal lobe using 2-FDG PET techniques [9]. It remains unanswered whether the etiology for this is structural (and thus irreversible) or functional (and thus reversible). Further, it does not seem possible to answer this problem since the temporal lobe must be removed surgically to effect seizure control. Our patient's circumstances seem unique in that 2-FDG PET techniques implicated temporal lobe dysfunction, yet the epileptic focus was extratemporal. The surgical excision of the epileptic focus produced complete seizure control, and temporal lobe function appeared to normalize using 2-FDG PET techniques.

Stimulation preoperative PET

The effect of language stimulation in the preoperative study caused a dramatic reversal of the L/R ratio in the frontal and temporal regions. This paradoxical result of lower metabolism in the language dominant hemisphere compared with the contralateral hemisphere was, in fact, expected. In normal subjects, glucose metabolism has been demonstrated to be bilaterally increased in the frontal and temporal lobes by all types of behavioral stimulation, including auditory language stimulation [10].

Our patient clearly had an abnormal brain, as evidenced by (1) a calcified AVM in the left parietal lobe; (2) left parietal and temporal lobe seizures; (3) abnormal left temporal lobe memory and language function clinically and on the intracarotid amylal test; and (4) an elevated electrical after-discharge threshold in the left hippocampus. We postulate that our attempt to stimulate the dominant hemisphere selectively produced some stimulation of the nondominant (right) hemisphere as well. The left hemisphere was unable to respond, whereas the right hemisphere could and did respond. The result was a relatively selective increase in metabolism of the right hemisphere, which reversed the left/right ratios.

The inability of the left hemisphere to respond to language stimulation implies focal dysfunction.

Baseline postoperative PET

The postoperative baseline scan showed a pattern of increased frontal metabolism and decreased right temporal and left parietal metabolism. The parietal hypometabolism was from the removal of brain tissue in that area. The frontal hypermetabolism is less easily explained. It might represent a rebound phenomenon following seizure control.

Stimulation postoperative PET

The effect of language stimulation was less dramatic postoperatively than when performed preoperatively. We postulate that language stimulation was again effective in producing right hemisphere stimulation and increased glucose metabolism, but now the left hemisphere was also capable of increasing metabolism in response to the stimulation. The result was a muting of the effect on reversing the left/right ratios observed in the first pair of scans. We propose that this difference between pre- and postoperative language stimulation studies was the result of improved left frontal and temporal lobe function. It is noted that "improved function" on PET did not equate with improved language function, and in fact the patient's aphasia was worse. However, his epilepsy was improved.

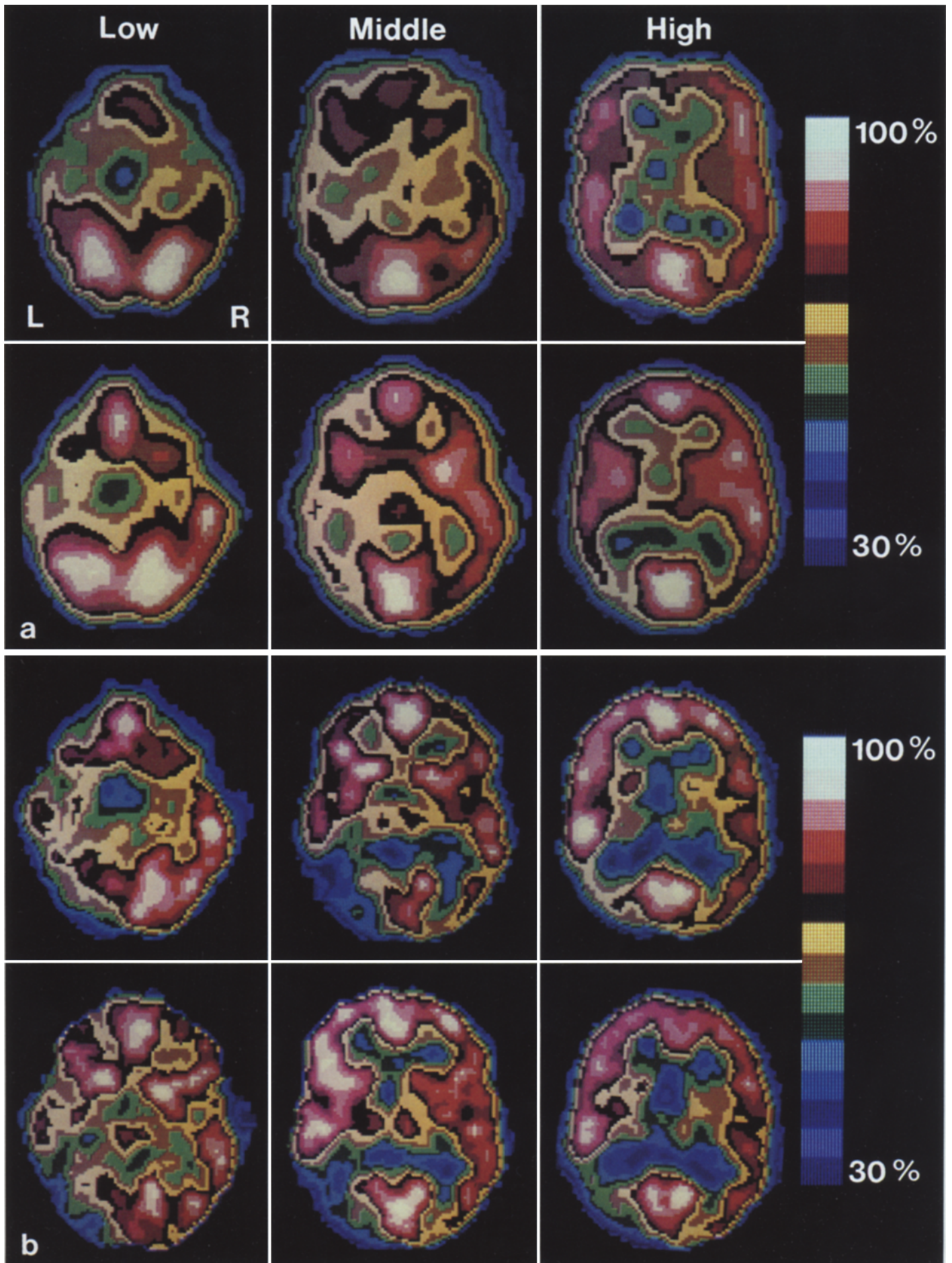
Seizure-induced hypometabolism

Improved function of the left temporal lobe as measured by glucose metabolism on PET in our patient supports the theory of a functional (and reversible) cause for the abnormal metabolism found in patients with temporal lobe epilepsy. The unanswered question in this case is what is the anatomy, or pathology, in the left temporal lobe. Although there is electrophysiologic, behavioral and 2-FDG PET evidence for an abnormal left temporal lobe, epileptic patients with similar findings at this and other centers have had anatomically normal anterior temporal lobes removed at surgery.

Caveat: seizure classification

Delgado-Escueta and Walsh [2,16] have proposed that the success of surgical treatment for patients with complex partial epilepsy depends on the anatomy of the epilepsy. Type I complex partial seizures are preceded clinically by a motionless stare and originate from a temporal lobe. Type II are not preceded by a motionless stare and originate extratemporally. Clinically, our patient had both type I and II seizures. Yet the EEG data and excellent results of surgery argue for an extratemporal origin of his seizure. The mixture of both types of seizures in one patient raises the question of the adequacy of this classification scheme.

Fig. 2a, b. Color-scaled FDG scans. Each of the 12 images is scaled to 100% of its own maximum glucose utilization rate. A lower threshold of 30% is used to provide optimum resolution using the 15-color code shown to the right. Cross-sectional images were obtained at 3, 4.5 and 6 cm above the orbitomeatal line. These are referred to respectively as low, middle and high. Details are given in the text. **a** Preoperative study; **b** post-operative study; *upper rows*: baseline; *lower rows*: language stimulation



The difficulty in predicting the ictal focus in epileptic patients is further illustrated by this patient's sexual automatisms. A previous report had stated that the frontal lobe was the ictal focus in patients who had sexual automatisms with their complex partial seizures [14]. Our patient's case clearly documents that a parietal lobe focus can also cause sexual automatisms. Despite the increasingly sophisticated testing available, identification of the habitual ictal focus in epileptic patients remains difficult.

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