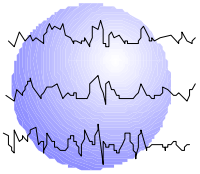
# THE RELATIONSHIP BETWEEN $^{11}$C-FLUMAZENIL PET TEMPORAL LOBE ABNORMALITY AND NEUROPSYCHOLOGICAL PERFORMANCE IN EPILEPSY PATIENTS

Robert C. Doss, PsyD
John R. Gates, MD
Harry T. Chugani, MD



This paper has been prepared specifically for:

American Epilepsy Society Annual Meeting
Boston, MA
December 5 - 10, 2003
Please consider this information to be preliminary findings.

Minnesota Epilepsy Group, P.A.®
225 Smith Avenue N., Suite 201
St. Paul, MN 55102
Phone: (651) 241-5290
Fax: (651) 241-5248

# REVISED ABSTRACT


## RATIONALE

No study has been published on the cognitive correlates of temporal lobe abnormality as determined by 11C-flumazenil (FMZ) positron emission tomography (PET). The use of FMZ PET is helpful in localizing temporal lobe seizure onset because of decreased central benzodiazepine receptor binding in the region of epileptogenic zone. The objective of this study was to evaluate cognitive performance in patients demonstrating temporal lobe FMZ PET abnormality in isolation and in the presence of a MRI-defined lesion, including mesial temporal sclerosis. It is hypothesized that those patients demonstrating both structural lesions and FMZ binding abnormality will perform worse on neuropsychological (NP) measures as compared to patients showing only FMZ binding abnormality in the temporal lobe.

## METHODS

The sample was eight patients who underwent FMZ PET as part of a presurgical epilepsy evaluation. All scans were interpreted by one of the co-authors (H.T.C.). Four patients showed FMZ PET abnormality in only the temporal lobe (3 left, 1 right) in the absence of a MRI lesion (+PET/-MRI). Four patients showed only temporal lobe abnormalities (2 left, 2 right) on FMZ PET but also had an identifiable MRI lesion (+PET/+MRI). Data were retrospectively collected. The NP and PET exams occurred within 16 months of each other for all patients. The average time between MRI and PET exams was nine months. The two groups were compared on demographic, medical, and measures of NP function. Descriptive, parametric, and nonparametric statistical analyses were utilized to assess group differences and relationship to temporal lobe FMZ PET abnormality.

## RESULTS

There were no significant differences between the two groups for age of seizure onset, age at PET scan, and education. Nevertheless, age of seizure onset was substantially younger for the +PET/+MRI group (M = 8.0 vs. 20.5 years). There was also a significant difference in gender ($p < .05$) with the +PET/-MRI and +PET/+MRI groups being comprised of 100% and 25% males, respectively. Descriptive statistics showed the NP performance of the +PET/-MRI group to be largely within normal limits save for mild impairment on a test of visuoconstruction. The +PET/+MRI group however, showed impaired to borderline impaired scores on measures of verbal memory, confrontational naming, and visuoconstruction. There was a clear but nonsignificant trend for the +PET/+MRI group to score lower (1 - 48%) than the +PET/-MRI group on most measures.

## CONCLUSION

These preliminary data indicate greater cognitive impairment in patients who demonstrate a FMZ binding abnormality in the temporal lobe and a structural lesion vs. those who show the same FMZ temporal lobe abnormality without a structural lesion. The profile of cognitive difficulty was typical for dysfunction of the temporal lobes. There is a need to replicate this study with a larger series of patients and to compare the sensitivity among FMZ PET, MRI, and NP testing in corroborating epileptogenic focus.



***Epilepsia 44 Suppl. 9:300 (Abst. 2.364), 2003***

## RATIONALE

Investigators have shown a relationship between cognitive impairment and prefrontal metabolic disturbances using 2-deoxy-2-[$^{18}$F]fluoro-D-glucose (FDG) positron emission tomography (PET) in temporal lobe epilepsy patients[1]. There has been no study on the cognitive correlates of temporal lobe abnormality as determined by $^{11}$C-flumazenil (FMZ) PET in epilepsy patients.

The use of FMZ PET is helpful in localizing temporal lobe seizure onset because of decreased central benzodiazepine receptor binding in the region of epileptogenic zone[2-3]. The FMZ PET has been found to be significantly more sensitive than FDG PET in detecting cortical regions of seizure onset and frequent interictal spiking[4].

The objective of this study was to evaluate cognitive performance in patients demonstrating temporal lobe FMZ PET abnormality in isolation and in the presence of a MRI-defined lesion, including mesial temporal sclerosis. It is hypothesized that those patients demonstrating both temporal lobe structural and FMZ binding abnormality will perform worse on neuropsychological (NP) measures as compared to patients showing only FMZ binding abnormality in the temporal lobe.

## METHODS

The sample was eight patients who underwent MRI and FMZ PET as part of a presurgical epilepsy evaluation at the Minnesota Epilepsy Group, P.A. The MRIs were obtained at United Hospital, St. Paul, MN using a thin-cut epilepsy protocol and clinically interpreted by a staff neuroradiologist. All FMZ PET studies were performed in accordance with policies of the Wayne State University Institutional Review Board in Detroit. The FMZ PET study was performed using a CTI-Siemens Exact/High Resolution whole body positron tomograph located at Children's Hospital of Michigan in Detroit. For FMZ PET, a 60-minute dynamic PET scan of the brain was performed (sequence: 4 × 30 seconds, 3 × 60 seconds, 2 × 150 seconds, 2 × 300 seconds, and 4 × 600 seconds) beginning at the time of injection. Summed images representing activity concentration between 10 and 20 minutes were used to display $GABA_A$ receptor binding in brain. All patients underwent a FDG PET study one day prior to the FMZ PET. The EEG was monitored throughout all PET examinations to verify that all scans were interictal. All FMZ PET scans were interpreted by one of the co-authors (H.T.C.). All patients also underwent diagnostic inpatient evaluation including video-EEG monitoring and comprehensive NP assessment. Figure 1 Illustrates FMZ PET and MRI scans from a patient with left temporal lobe epilepsy.

Patient characteristics are listed in Table 1. Four patients showed FMZ PET abnormality in only the temporal lobe (3 left, 1 right) in the absence of a MRI lesion (+PET/-MRI). Four patients showed only temporal lobe abnormalities (2 left, 2 right) on FMZ PET but also had an identifiable MRI lesion (+PET/+MRI). Data were retrospectively collected. The NP and PET exams occurred within 16 months of each other for all patients. The

average time between MRI and PET exams was nine months. The two groups were compared on demographic, medical, and measures of NP function. Descriptive, parametric, and nonparametric statistical analyses were utilized to assess group differences and relationship to temporal lobe FMZ PET abnormality.

## RESULTS

There were no significant differences between the two groups for age of seizure onset, age at PET scan, and education. Nevertheless, age of seizure onset was substantially younger for the +PET/+MRI group (M = 8.0 vs. 20.5 years). There was a significant difference in gender ($p < .05$) with the +PET/-MRI and +PET/+MRI groups being comprised of 100% and 25% males, respectively.

Table 2 and Figure 2 shows the NP performance by group. Group descriptive statistics show the NP performance of both groups to be below average with respect to normative data. However, the +PET/-MRI remains largely within normal limits save for impairment on a test of visuoconstruction. By contrast, the +PET/+MRI group shows impaired to borderline impaired scores on measures of verbal memory, confrontational naming, and visuoconstruction. There was a clear trend for the +PET/+MRI group to score lower (1 - 48%) than the +PET/-MRI on most measures. However, all group comparisons were n.s.

## CONCLUSIONS

- These preliminary data indicate greater cognitive impairment in patients who demonstrate a FMZ binding abnormality in the temporal lobe and a structural lesion vs. those who show the same FMZ temporal lobe abnormality without a structural lesion.
- The cognitive profile of the +PET/+MRI group relative to the +PET/-MRI group included greater difficulty with naming and verbal learning, which is characteristic for temporal lobe dysfunction.
- Functional neuroimaging abnormalities in the absence or presence of structural lesions may represent different degrees of progression of intractable epilepsy.
- There is a need to replicate this study with a larger series of patients and to compare the sensitivity among FMZ PET, MRI, and NP testing in corroborating epileptogenic focus.

**REFERENCES**


1 Jokeit, H., Seitz, R.J., Markowitsch, H.J., Neumann, N.J., Witte, O.W., & Ebner, A. (1997). Prefrontal asymmetric interictal glucose hypometabolism and cognitive impairment in patients with temporal lobe epilepsy. Brain, 120, 2283-2294.

2 Koepp, M.J., Richardson, M.P., Brooks, D.J., Poline, J.B., Van Praesschen, W., Friston, K.J., & Duncan, J.S. (1996). Cerebral benzodiazepine receptors in hippocampal sclerosis: An objective in vivo analysis. Brain, 119, 1677-1687.

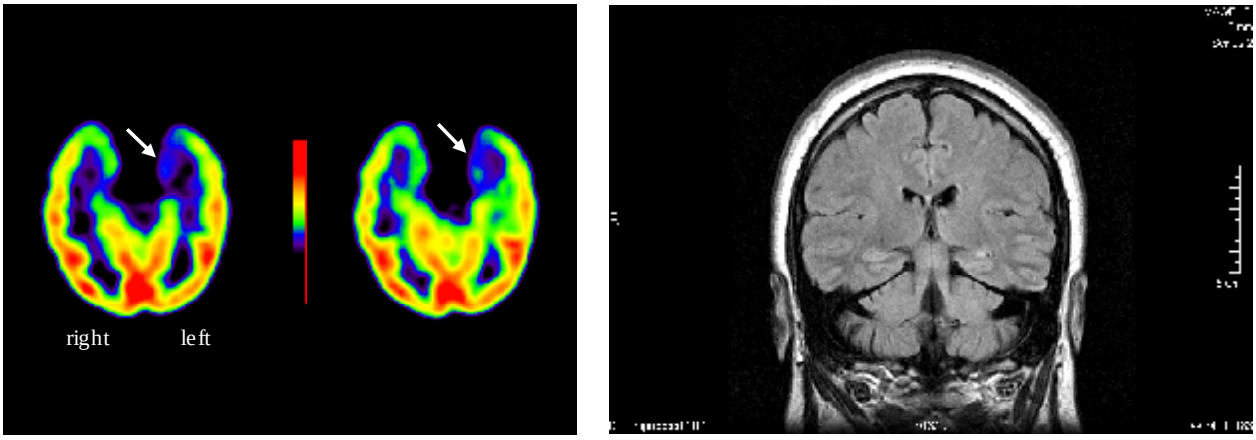
3 Henry, T.R., Frey, K.A., Sackellares, J.C., Gilman, S., Koeppe, R.A., Brunberg, J.A., Ross, D.A., Berent, S., Young, A.B., & Kuhl, D.E. (1997). In vivo cerebral metabolism and central benzodiazepine-receptor binding in temporal lobe epilepsy. Neurology, 43, 1998-2006.

4 Muzik, O., da Silva, E. A., Juhasz, C., Chugani, D. C., Shah, J., Nagy, F., Canady, A., von Stockhausen, H.M., Herholz, K., Gates, J., Frost, M., Ritter, F., Watson, C., & Chugani, H. T. (2000). Intracranial EEG versus flumazenil and glucose PET in children with extratemporal lobe epilepsy. Neurology, 54, 171-179.

**Figure 1.**

## LEFT TEMPORAL LOBE EPILEPSY

**FMZ PET** **MRI**




**Patient T.W.**

**Table 1.**

## PATIENT CHARACTERISTICS

| | +PET/-MRI | +PET/+MRI |
|---|---|---|
| ***n*** | **4** | **4** |
| **FMZ PET Focus** | | |
| **Left** | **3** | **2** |
| **Right** | **1** | **2** |
| **MRI Focus** | | |
| **Left Temporal** | **-** | **2** |
| **Right Temporal** | **-** | **1** |
| **Left Frontal** | **-** | **1** |
| **Age[1]** | **37.3(13.9)** | **33.5(8.0)** |
| **Gender (% Male)*** | **100%** | **25%** |
| **Education[1]** | **14.5(1.9)** | **12.3(1.0)** |
| **Age of Seizure Onset[1]** | **20.5(18.9)** | **8.0(11.4)** |
| **Duration of Seizures (years)[1]** | **16.8(15.0)** | **25.5(7.5)** |
| **No of AEDs[1]** | **2.5(.6)** | **2.3(.5)** |

**[1] = *M*(*SD*)**
***p* < .05**

**Table 2.**

## NEUROPSYCHOLOGICAL DESCRIPTIVES*

| | +PET/-MRI | +PET/+MRI |
|---|---|---|
| WAIS-III Full Scale IQ (FSIQ) | 92.0(13.3) | 84.5(11.7) |
| Vigil CPT (Attention) | 89.0(15.1) | 88.5(14.2) |
| BNT (Naming) | 85.3(22.9) | 45.0(41.8) |
| Animals (Semantic Verbal Fluency) | 96.5(22.0) | 99.0(3.9) |
| vSRT-LTS (Verbal Memory) | 93.5(5.1) | 76.7(18.9) |
| RCFT-Delay (Nonverbal Memory) | 102.1(16.7) | 90.0(12.9) |
| RCFT-Copy (Visuoconstruction) | 52.5(31.1) | 50.8(36.0) |
| Porteus Mazes (Planning) | 107.3(9.6) | 92.0(21.6) |
| WCST-Errors (Problem Solving) | 93.3(16.1) | 99.0(22.2) |

* Standard Scores expressed in *M* (*SD*)
WAIS-III = Wechsler Adult Intelligence Scale-Third Edition
BNT = Boston Naming Test
vSRT = Buschke Verbal Selective Reminding Test
RCFT = Rey Osterrieth Complex Figure Test
WCST= Wisconsin Card Sorting Test

**Figure 2.**

## NEUROPSYCHOLOGICAL TEST PERFORMANCE BY GROUP