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Abnormal Temporal Lobe Metabolism in Violent Subjects: Correlation of Imaging and Neuropsychiatric Findings

David Seidenwurm, Thomas R. Pounds, Albert Globus, and Peter E. Valk

PURPOSE: To search for metabolic correlates of clinical and electrophysiological abnormalities in violent subjects. **METHODS:** Seven subjects with histories of extremely violent behavior were studied with positron emission tomography (PET) with fludeoxyglucose F 18 (FDG), brain electrical area mapping, MR imaging, neuropsychiatric and neuropsychological testing, and clinical examination during medical evaluation associated with legal proceedings. Nine control subjects without evidence of organic brain disease were also studied with FDG-PET. Quantitative PET data were calculated as standardized uptake values comparing the highest occipital region with the lowest temporal region. **RESULTS:** Temporal lobe metabolism was decreased in the study group relative to the control subjects. Medial temporal lobe metabolism was 39% lower than that in the occipital cortex in study subjects and only 27% lower than that in control subjects. These groups differed by Mann-Whitney U test and by Wilcoxon's two-sample test. Metabolic differences correlated with limbic neuropsychiatric and electrophysiological abnormalities in the violent group. **CONCLUSION:** In this selected population of violent subjects, FDG-PET scans showed metabolic abnormalities in the temporal lobes. These abnormalities correlated with limbic abnormalities seen at electrophysiological and neuropsychiatric evaluation.

Index terms: Brain, metabolism; Brain, temporal lobe

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The relationship between the temporal lobes of the brain and violent and aggressive behavior has been recognized for many years. In 1939 Kluver and Bucy (1) performed bilateral temporal lobectomies in primates and reported increased aggression in social interactions in which it was not normally seen. Numerous studies (2-28) have documented the presence of violence and aggression among the behavioral abnormalities seen in patients with complex partial seizures or temporal lobe epilepsy. Most conclusively, Bear and Fedio (3) reported the results of a quantitative analysis of the interictal behavioral abnormalities in temporal lobe epilepsy. Among other findings, they observed ag-

gression, paranoia, altered sexuality, and obsessive behavior.

In many studies, psychiatric and neurologic abnormalities have been reported in violent subjects along with neuropsychological, electrophysiological, and imaging abnormalities. In the majority of these studies, however, the location of the abnormalities was not well defined (5, 10-14, 16, 29-40). Perhaps because neurons located in the temporal lobes radiate to the opposite hemisphere as well as to the ipsilateral frontal and parietal lobes (41), electrophysiological and neuropsychological abnormalities may simply be the result of the influence of neuronal connections from the temporal lobes. A constellation of clinical findings—including unprovoked, unpredictable, or impulsive violence; perinatal neglect; childhood physical or sexual abuse; head injury; sexual disturbance; and low intellect—appear to characterize a subgroup of violent persons (2-4, 24, 30-37).

We tested the hypothesis that relative temporal lobe metabolism would be altered in violent subjects as compared with control subjects.

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Subjects and Methods

Seven subjects studied with positron emission tomography (PET) during medical evaluation associated with legal proceedings constituted our study population. As determined by forensic psychiatric evaluation, these subjects were considered to have signs of possible organic brain disease and were required to undergo medical examination, including PET studies. Criminal violence not associated with or out of proportion to property crime was the index behavior in each case. Detailed clinical evaluation was done by means of extensive psychiatric interviews and neurologic examination by a board-certified psychiatrist. Formal neuropsychiatric and neuropsychological evaluations were performed in six of the seven subjects; one was unable to cooperate. The index behavior, other abnormal or unusual behaviors, features of personal history, education, drug use, and mental status were recorded. A psychiatric diagnosis consistent with criteria in the Diagnostic and Statistical Manual of the American Psychiatric Association was made.

A quantitative electrophysiological examination was performed by means of electrical activity mapping of the brain. Electrophysiological examination consisted of electroencephalography, spectral power analysis, and auditory and visual evoked response testing. Magnetic resonance (MR) imaging at 1.5 T consisted of sagittal T1- and axial T2-weighted images. In some subjects, axial or coronal T1-weighted images or coronal T2-weighted images were acquired. All images were obtained with routine clinical parameters. Axial T2-weighted imaging parameters were 2800/30,80 (repetition time/echo times); parameters for the T1-weighted images were 750/20.

Nine control subjects were imaged for vague generalized symptoms, and objective neurologic diagnoses were made in this group. All study and control subjects gave informed consent.

PET studies were performed with a device that has 24 rings of bismuth germinate detectors containing 9216 crystal elements and that acquires 47 contiguous image planes with a section thickness of 3.4 mm. The imaging aperture was 56.2 cm and the longitudinal field of view was 16.2 cm. Full width at half-maximum axial resolution was 5.4 mm. Emission data were stored in a 128×128 computer matrix. An automated attenuation correction program was then applied to the stored data. The attenuation correction matrices were computed on the basis of line projections through the image outline, assuming a constant attenuation coefficient. Images were then reconstructed from this file by using a Parzen filter 0.9 cutoff.

Fluorine-18 was produced with a cyclotron and fludeoxyglucose F 18 (FDG) was synthesized by the Hamacher method. All patients fasted a minimum of 4 hours before receiving intravenous injection of 0.143 mCi/kg FDG. Average dose was 10 mCi (370 MBq). After a 30-minute uptake period, 20-minute emission scans were acquired for image production. Both the study subjects and the control subjects were at rest with eyes open, in a well-lighted area during uptake. Both groups were

monitored by medical personnel; the study subjects were manacled and under armed guard.

Irregular regions of interest (ROI) based on anatomic atlas reference and MR images, approximately 1×1 cm, were drawn with computer assistance for semiquantitation of uptake activity by a nonblinded observer. The ROI was selected to include the primary limbic structures of the medial temporal lobe, the amygdala, the hippocampus, and the parahippocampal gyrus. Care was taken to avoid cerebrospinal fluid spaces, white matter, and regions of artifactual low signal. Owing to the volumetric nature of our PET acquisition, coronal, axial, and sagittal images were cross-referenced to avoid confounding by irregular anatomy. We did not attempt to differentiate the various temporal lobe structures because of the inherent limitation in spatial resolution of PET. Standardized uptake values (SUV) were calculated and decay was corrected, where $SUV = \text{tissue activity concentration in ROI (mCi/g)}/\text{injected dose (mCi)}/\text{body weight (g)}$. In all study and control subjects, the calcarine occipital cortex demonstrated the highest cortical level of metabolism. The region of the occipital lobe with the highest activity was compared with the region of the medial temporal lobe with the lowest activity, and the percentage of decreased activity was calculated. This method was used because of the invasive nature of determining absolute metabolic activity. The SUV was considered a reliable proxy. Since each person served as his or her own control subject, any systematic error in metabolic activity assessment would be manifest equally in the occipital and temporal lobes. The occipital calcarine cortex was used as the reference because it was the cortical region that reliably exhibited the highest cortical activity. Occipital lobes were used because, owing to their anatomic and physiological similarity to the temporal lobes, these features are not present in basal ganglionic and cerebellar gray matter regions.

Statistical analysis was performed by means of the Mann-Whitney U test and Wilcoxon's two-sample test (42, 43).

Results

A summary of the subjects' index behavior, other unusual behavior, personal history, education, and drug use appears in Table 1. Table 2 provides information on mental status, psychiatric diagnosis based on the clinical and laboratory data, and neuropsychological test findings. Brain electrical area mapping and MR imaging and PET data are given in Table 3. The study group consisted of six men and one woman, ranging in age from 17 to 39 years. The violent acts were all characterized as unprovoked in the sense that they did not occur in self-defense. These acts were often repetitive, stereotyped, and prolonged—for example, multiple stabbings or gunshots—and they were not

TABLE 1: History of seven violent subjects with abnormal temporal lobe metabolism

Subject	Age, y/Sex	Index Behavior	Other Behavior	Personal History	Education	Drug Use
1	33/M	Killed four 14-y-old boys	Genital self-mutilation	Parents divorced, domestic violence	Special ed, dyslexia, graduated from high school	Alcohol, marijuana
2	20/M	Shot police officer	Lived in brothel	Left home very early, field worker	Poor education in Mexico	No abuse
3	17/M	Repeatedly stabbed one person fatally	Extremely dependent	Serious dehydration as infant, delayed development	Special ed	Alcohol
4	29/F	Eviscerated mother and daughter	Solitary, bizarre, stereotyped motions; exhibitionic behavior	Poverty	Special ed	Amphetamine
5	17/M	Beat and fatally strangled girlfriend	Reckless motorcycle rider, death rock music, bizarre dress	Domestic violence, in utero drug exposure	Special ed, visual perception problems, math problems	Amphetamine inhalants (usually gasoline)
6	39/M	Shot policeman during prison escape	Boxer	Electroconvulsive therapy, multiple head injuries	High school	Amphetamine, cocaine, alcohol
7	20/M	Shot, raped stepmother, hid body in closet	Unpredictable violence	Domestic violence	Special ed	Polydrug abuse: amphetamines, cocaine

TABLE 2: Clinical findings in study group

Subject	Mental Status	Psychiatric Diagnosis	Neuropsychological Testing
1	Thought disorder, variable affect, grossly delusional, hostile	Chronic paranoia, schizophrenia with acute exacerbations	Uncooperative
2	Perseveration, reserved	Organic brain syndrome	Visual, spatial, memory impairment; impaired problem-solving abilities
3	Flat affect	Organic brain syndrome	IQ 71, organic mental disorder
4	Flat affect, impoverished thought pattern, delusional	Chronic undifferentiated schizophrenia	IQ 82, psychotic, no evidence of brain damage
5	Paranoid, secretive, violent fantasies	Antisocial personality disorder, organic brain syndrome, paranoid	IQ 84, organic mental disorder, impulsivity, low frustration tolerance
6	Paranoia, impulsive, violent aggressive	Organic brain syndrome, organic personality disorder	Frontal, occipitoparietal, and hippocampal abnormalities; reduced intelligence
7	Excessive dependency, poor social judgment	Organic brain syndrome and adjustment disorder	Mild impairment of visual, spatial, and memory processing, R more than L hemisphere

isolated incidents. While the consequences of violence varied in that death resulted in some cases and not in others, this was more related to setting and circumstance than to any variation in the behavior itself; for example, some shootings were not fatal while some stabbings resulted in death. Pertinent characteristics of subjects in the control group are presented in Table 4.

The relative metabolism in the medial temporal lobes was lower in the violent subjects than in the control group (Fig 1). The average

percentage of decrease for the control group was 27%, with a range 9% to 38% (Figs 1 and 2). The average percentage of decreased activity for the violent behavior group was 39%, with a range of 33% to 54% (Table 3, Figs 3 and 4). The activity was significantly decreased in the violent group ($P < .005$ by Mann-Whitney U test and $P < .05$ by Wilcoxon's two-sample test).

The PET and neuropsychiatric findings correlated well with the limbic abnormalities of the electrophysiological study. Each subject who completed the evaluation had neuropsychiatric

TABLE 3: Imaging and electrophysiological findings in study group

Subject	Electrophysiological Studies	MRI findings	PET, %*
1	Patient uncooperative	Normal	-.49
2	Diffuse cerebral dysfunction	Normal	-.34
3	Temporal, R frontal abnormality	Normal	-.33
4	Bilateral temporal abnormalities, frontal dysfunction	Normal	-.34
5	R frontotemporal abnormality	Normal	-.33
6	Normal	Focal thinning of corpus callosum, mild atrophy	-.38
7	Bilateral temporoparietal abnormalities	Asymmetric temporal lobes	-.54

* Percentage of decreased temporal lobe activity.

TABLE 4: Characteristics of control subjects

Subject	Age, y/Sex	Presenting Symptoms	Neurologic Findings
1	30/F	Fatigue	None
2	40/F	Headache, fatigue	None
3	38/F	Fatigue	None
4	39/F	Fatigue	None
5	43/F	Fatigue	None
6	65/F	Fatigue	None
7	46/F	Fatigue	None
8	45/F	Fatigue	None
9	35/F	Fatigue	None

and/or electrical abnormalities related to limbic structures. Of the six subjects who were able and willing to cooperate, five had temporal lobe abnormalities. In four of these subjects, the abnormality was focal; in the fifth subject, diffuse cerebral abnormality was observed, including the temporal lobes.

Neuropsychiatric testing of the same six subjects revealed abnormalities in each case. The subject who had normal electrical studies had hippocampal abnormalities, the subject with diffuse electrical abnormalities had memory impairment, localized to the temporal lobes. Low intelligence was observed in three of the four remaining subjects, one of whom had no organic findings by this method. The final subject had poor memory function, suggesting temporal lobe abnormality.

In general, MR imaging was not helpful in this

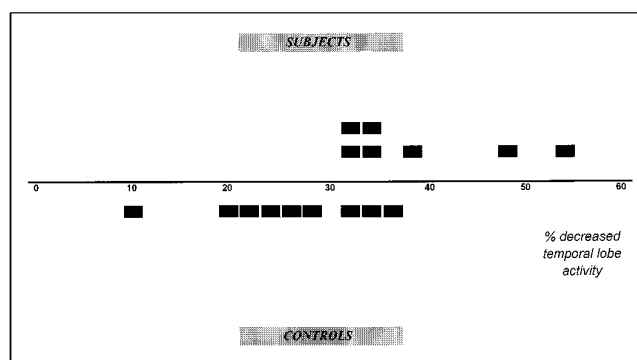


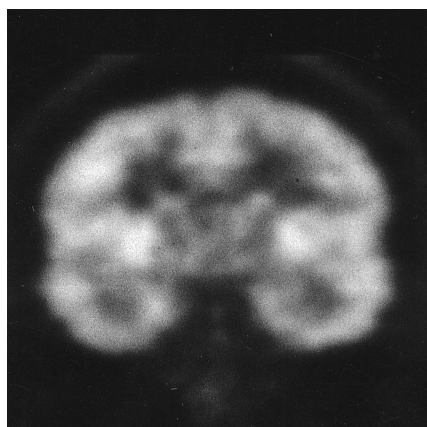
Fig 1. Scattergram depicts relative temporal lobe metabolism in study group and control group.

population except insofar as it aided in the construction of ROIs and excluded structural anomalies (such as atrophy, cystic masses, arteriovenous malformation, and benign neoplasm) as the cause of low relative activity in the temporal lobes at PET. In one subject, nonspecific temporal lobe asymmetry without definite volume loss was observed; in another, diffuse mild atrophy, a nonspecific finding, was noted.

Discussion

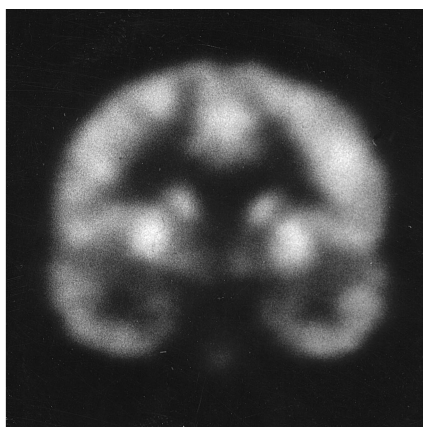
Our data support the hypothesis that abnormalities in glucose metabolism in the temporal lobes correlate with violent behavior in human subjects. Whether this is a secondary effect related to abnormalities elsewhere or whether this is a primary abnormality is uncertain. This finding is in accord with a large body of experimental and clinical data that link the function of the temporal lobes to aggressive or violent behavior (1-28).

Our study confirms the results of Volkow and Tancredi (40), who found temporal lobe hypometabolism in two aggressive psychiatric patients. Our observations in part confirm those of Raine et al (38, 39) that limbic system abnormalities may be found with PET in persons accused or convicted of capital crimes in whom psychiatric factors were considered during legal proceedings. Differences between the results of Raine et al and ours may be explained by important differences in technique. Those investigators used a frontal lobe stimulation test while we studied patients who were resting quietly during the period of FDG uptake. These methodological differences probably account for the differences in the structures that were found to be abnormal in each of the studies. Since recip-



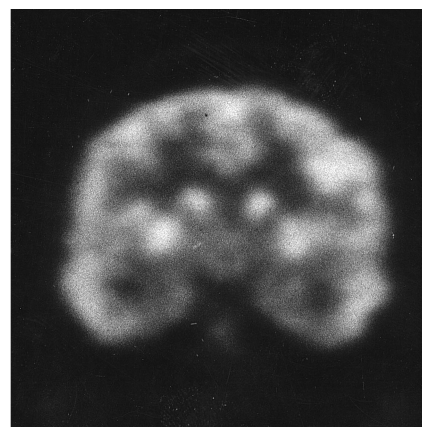
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Fig 2. Coronal FDG PET scan in control subject. Note relatively homogeneous temporal lobe metabolism.



3

Fig 3. Coronal FDG PET scan in subject 4. Note low metabolic activity in medial temporal lobes.



4

Fig 4. Coronal FDG PET scan in subject 7. Note low metabolic activity in medial temporal lobes.

rocal connections between prefrontal and mesial temporal structures are well established, stimulation or inhibition of metabolism in one area by physiological or pathologic states could result in the differences observed in these closely interconnected and functionally related structures (27, 41).

Resting temporal lobe metabolism was our experimental variable, because baseline function was known to us (42). The range of normal variation is well known through the established use of PET scanning in medically refractory epilepsy (24, 44–47). Furthermore, quantitative studies by Tyler et al (48) reported coefficients of variation of intrasubject regional cerebral glucose utilization of 10% and intersubject values of 16.5%. Clark et al (45) developed a model for analysis of cerebral glucose metabolism measured with PET that supports the conclusion that patterns of glucose utilization are consistent and reproducible. The sources of variability they isolated were differences in global metabolic function, regional variations, and error. They found that 75% of total variability was due to differences in global metabolic rates and that 16% was due to variations in regional distribution patterns among subjects. They also found that regional variation was similar across subjects and that PET could be used to evaluate the regional integrity of the cerebral cortex. Camargo et al (46) also examined the variability of regional brain metabolism and found intersubject and intrasubject coefficients of variation of 14% and 7%, respectively. The excellent reproducibility of regional cortical metabolism within

and between subjects supports the validity of our approach. The differences in activity pattern within healthy subjects is small. Therefore, relative activity is a reliable and noninvasive proxy that can be used in difficult clinical settings. The measurement of mesial temporal dysfunction in patients with epilepsy is performed at quiet rest, except in the case of fortuitous occurrence of a seizure or abnormal electrical discharge during the uptake period. Our study subjects and control subjects were examined under our standard clinical protocol.

An internal control for differences in regional cerebral metabolism was present in our comparison of the highest occipital lobe segment with the lowest medial temporal segment. Since the visual cortex is reliably the most metabolically active region, we had an internal standard for relative metabolism. The ROI analysis was performed by an observer who was familiar with multiplanar anatomy of the temporal lobes. Temporal lobe atrophy was not observed on MR images so we were not erroneously including ventricles and cisterns in our ROI in the study group.

Further work is required in the selection of control subjects. We were not able to obtain control subjects who truly matched our study subjects in a number of potentially relevant variables. Age, sex, socioeconomic and educational background, and drug use are potential confounding variables. We recognize that ethical considerations prevent a truly controlled study, since one cannot inject radioactive materials intravenously in incarcerated subjects

unless they can be expected to derive direct medical benefit. The optimum control population would be matched subjects whose crime was property related and nonviolent.

Our control population included more women than did the study population. This should strengthen the conclusions we drew, because medial temporal lobe metabolism is known to be lower in females than in males. A recent study reports higher temporal limbic metabolism in males, yet in our male-predominant study population, the metabolism in this region was lower than in the female-predominant control population. The regions involved are virtually identical, including the amygdala, hippocampus, and parahippocampal gyrus (49).

Our study revealed a statistically significant difference between temporal lobe metabolism in violent subjects and that in nonviolent subjects. This observation is consistent with findings from multiple disciplines in the neurosciences that have established a link between the temporal lobes and violent behavior.

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