Relationships Between Verbal Memory Performance and the Cerebral Distribution of Fluorodeoxyglucose in Patients With Schizophrenia

Lyn Harper Mozley, Ruben C. Gur, Raquel E. Gur, P. David Mozley, and Abass Alavi

Quantitative resting fluorodeoxyglucose–positron emission tomography scans were performed on 42 patients with schizophrenia. Magnetic resonance imaging-based regions of interest were transposed onto the corresponding positron emission tomography images. Region to whole brain ratios were calculated from the mean regional activity per pixel across both hemispheres (left plus right). Laterality scores were calculated from the difference between the mean activity in homotopic regions of the two hemispheres (left minus right). Subjects were tested contemporaneously with the Logical Memory subtest of the Wechsler Memory Scale. The subtest was scored with modified criteria to provide information about verbal recall, perseverations, and other components of verbal memory. Deficits in recall were associated with increased metabolism in selected regions of the left hemisphere that are known to mediate aspects of verbal memory. The findings support hypotheses suggesting that the left hemisphere is functionally overactive in schizophrenia.

Key Words: Schizophrenia, FDG-PET, verbal memory, neuropsychological tests

BIOL PSYCHIATRY 1996;40:443–451

Introduction

Neuropsychological studies of schizophrenia have found deficits in list learning, word recognition (Goldberg et al 1989), story recall (Wood and Flowers 1990), visual memory, and visual learning (Kolb and Wishaw 1983; Hoff et al 1992). Some investigators have suggested that schizophrenia is characterized by global cognitive impairment with verbal learning and memory being most severely affected (Saykin et al 1991, 1992); however, others have found global deficits, but not differential impairment (Blanchard and Neale 1994). Studies of verbal memory and learning have indicated that patients with schizophrenia have difficulty imposing organizational structure on material to facilitate recall (Koh et al 1973; Calev 1984; Harvey et al 1986; Yurgelun-Todd and Waternaux 1991). Performance may improve when an organizational structure is imposed experimentally (Koh et al 1976; Bauman 1971).

Neuroimaging has been used to examine the neural substrates of schizophrenia. Measurements of regional

From the Department of Psychiatry (LHM, RCG, REG) and the Division of Nuclear Medicine (PDM, AA), University of Pennsylvania Medical Center, Philadelphia, Pennsylvania.

Address reprint requests to Dr. Lyn Harper Mozley, 10 Gates Building, H.U.P., 3600 Spruce Street, Philadelphia, PA 19104.

Received August 26, 1994; revised May 25, 1995.

0006-3223/96/$15.00
SSDI 0006-3223(95)00421-1

cerebral glucose metabolism (CMRglu) with positron emission tomography (PET) have implicated several brain regions and systems in the pathophysiology of the disorder, including the frontal lobes, several subcortical regions, and laterality in temporal regions (Buchsbaum et al 1990; Gur and Pearlson 1993 for reviews). There is some evidence that regional physiologic abnormalities in schizophrenia are accentuated during the application of neurobehavioral probes. For example, Buchsbaum et al (1990) reported that patients had abnormally decreased metabolism in right frontal and temporoparietal regions during performance of an attentional task; in contrast, controls had increased metabolism in these regions. These studies have not yet been integrated with the neuropsychological test profiles, however.

The purpose of this study was to focus on the verbal memory impairment in patients with schizophrenia, and relate cognitive performance to glucose metabolism in brain regions that mediate verbal memory. The regional metabolism in patients with severe memory deficits was compared to the distribution of activity in patients with relatively preserved memory. We hypothesized that patients who were more impaired in recall would have greater metabolism in left hemispheric regions purported to be involved in verbal memory, including midtemporal and hippocampal regions, than patients with stronger recall. Similarly, patients with more perseveration errors were hypothesized to have greater frontal lobe metabolism.

Methods and Materials

Subjects

The sample included 42 patients who met DSM-III-R criteria for schizophrenia (APA 1987). The relationship between metabolism and clinical symptomatology in this sample has been reported in Gur et al (1995b). The diagnosis was made by research psychiatrists using standardized procedures that have been previously described (Gur et al 1991; Shtasel et al 1992). These evaluations consisted of physical, neurological, and psychiatric examinations, including the Structured Clinical Interview for Diagnosis (Patient Version) (SCID-P; Spitzer et al 1987). The laboratory blood tests included screening for bone marrow function, thyroid function, renal function, liver function, and autoimmune diseases. Urine specimens were sent for routine analysis and toxicology screens. Only patients without a lifetime history of medical disorder or event that could potentially affect brain structure or function were included in the study. None of the patients had a history of another axis I psychiatric disorder, including drug or alcohol abuse.

Clinically, 25 patients were characterized as paranoid, 2 were catatonic, 4 were disorganized, and 11 had an undifferentiated form of the disorder. Using Carpenter et al's (1988) classification system, 16 were deficit and 26 were nondeficit patients. Twenty-seven were evaluated while they were psychiatric inpatients and 15 were outpatients. Twenty-one patients were in the midst of their first psychotic episode and were neuroleptic-naive when they entered the study. The other 21 patients had been off medications for an average of 71.9 weeks ($\pm$ 116.8; range of 1–442 weeks).

There were 29 men and 13 women. Twenty were Caucasian and 22 were African-American. Their mean age was 30.5 $\pm$ 8.1 years (range 18–44), and their average education was 12.5 $\pm$ 2.2 years. Paternal education was 12.8 $\pm$ 2.8 years; maternal education was 12.3 $\pm$ 2.6 years. The mean age of onset was 24.3 $\pm$ 7.6 years. The duration of illness was $\leq$ 2 years for 12 first-episode, neuroleptic-naive patients and 9.5 $\pm$ 5.4 years for the rest (range 2–19). A total of 22 patients were studied during their first hospitalization. The average number of prior hospitalizations for the rest was 3.8 $\pm$ 5.4 (range 1–25). There were 37 right-handed patients, and 5 left-handed patients.

Measures of Cognitive Function

All patients were administered the Logical Memory subtest of the Wechsler Memory Scale, Form I, (WMS; Wechsler 1945) with a 30-min delayed recall procedure (Russell 1975, 1988). The test batteries and neuroimaging procedures were performed as contemporaneously as possible, which was usually within 2 days. The WMS data from relatively comprehensive initial evaluations were used for 23 patients. Subsequently, the research approach was changed to assess cognitive functioning on patients' initial presentation to the research protocol with a brief screening battery. Comprehensive evaluations were obtained approximately 1 month later when patients were more stable clinically. WMS scores from this second testing session were used for the remaining 19 patients

The WMS was scored with a modified system that has high interrater reliability (Gangarosa et al 1988) and strong concurrent validity with the California Verbal Learning Test (unpublished data). The Gangarosa et al system was developed in light of criticisms of the ability of the WMS to differentiate brain-damaged and psychiatric populations (e.g., Wysocki and Sweet 1985) and deficiencies in its scoring method (e.g., Prigatano 1978). The Gangarosa scoring system includes a list of acceptable full and half-point responses for recall, and allows independent scoring of organization or thematic sequencing (TS) and content distortions (CD). CD scores were then

further divided into subscores for confabulations (CDC), confusion of details within a given Logical Memory story (CDM), and the inclusion of extraneous details that are semantically related to the story content (CDE). A score to represent perseverations (PSV) was generated by recording the number of duplicated responses.

Neuroimaging Procedures

All subjects were scanned after an overnight fast. A radial artery was catheterized with a 20-gauge Teflon cannula under local anesthesia (2% xylocaine). A venous line was placed in the contralateral antebrachium. The lines were kept patent with a physiological saline solution. Approximately 185 MBq (5 mCi) of ^{18}F-labeled 2-fluoro-2-deoxy-D-glucose (FDG) were administered intravenously while the subjects lay recumbent in a quiet, dimly lit room with their eyes open and their ears unoccluded.

Arterial samples (250 μL) were drawn through a three-way stopcock attached to the arterial cannula to determine the arterial input function. Samples were taken every 15 sec initially and at progressively increasing intervals thereafter. Activity was measured in a dose calibrator (Tennelec 707, Memphis, TN) after a 3–4 hour decay interval.

Image acquisition began after 40 min of uptake. The subjects were positioned in a custom-molded, rigid foam head holder with the assistance of two lasers focused on the head at right angles to each other. Brain images were acquired on a PET scanner (PENN-PET, UGM Medical Systems, Philadelphia, PA) with a 9-cm axial field of view in its fixed gantry. The spatial resolution averaged 5.5 mm (full width of photopeak measured at half maximum count) in all directions near the center of the field (Karp et al 1990). An average of 30 million counts were collected over the next 50 min, and the data were sorted into 45 transaxial slices with a voxel size of 2 mm^3.

The projection data were corrected for nonuniform sensitivity that resulted from the decreasing number of coincident angles toward the axial edges of the field. A background subtraction was then performed on the sinogram to compensate for scatter. A standardized correction for attenuation was placed around the head by multiplying the linear attenuation coefficient for water by 1.10 to account for the bone density of the skull (Chang 1978). An optimized Hanning filter was applied during backprojection. The projection data were reorganized into 6-mm transaxial images. Each image was constructed by adding three slices together with an overlap of two between images to give a new center of mass (centroid) every 2 mm. The images were then exported over an ethernet into a graphics workstation (Sun Microsystems, Mountain View, CA) for processing along with the corresponding magnetic resonance image (MRI) of each subject.

Image Analysis

Image analysis procedures are described in detail in Resnick et al (1993). Proton and T2-weighted MRI scans were acquired on a 1.5-Tesla instrument (GE Medical Systems, Milwaukee, WI) with a repetition time (TR) of 3000 msec and echo times (TE) of 30 and 80 msec (Gur et al 1994; Mozley et al 1994). Each transaxial slice was constructed by adding 6 pixels together. Each pixel was 0.78 mm thick. The slices were subsequently overlapped by 1 pixel for a final distance between slice centers of 5 pixels, or 3.9 mm.

Using a computerized image analysis program, interhemispheric fissure midlines were drawn on transaxial and coronal slices of MRI images. A line was drawn through the plane connecting the anterior and posterior commissures (AC-PC line) in the sagittal plane, and the entire set of MRI images was resliced. A set of templates based on an atlas (Talairach and Tournoux 1988) comprised of 42 regions of interest (ROIs) per hemisphere was custom-fitted to each MRI slice by operators who were blind to diagnosis. Individual template regions could be deleted, moved, rotated, made smaller or larger, or redrawn as necessary to correspond to the anatomy on a given MRI slice. Three ROIs were excluded because they were not well defined, and one additional region was not included because interrater reliability was relatively low. Interrater reliability was $> .85$ (intraclass correlation) for the final group of regions included in the study (Resnick et al 1993). Counts per pixel for each region, volume averaged across all slices in which the region appeared, were used to calculate reliability coefficients.

Corresponding PET images were resliced using the same procedures. The MRI-based ROIs were transposed onto the resliced PET images after they were displayed on a dichotomous color scale that used a cutoff for color of 50% of the counts in the pixel of maximum intensity. The fit of the ROIs was accomplished by overlaying the whole brain boundaries on the images at the level of the diencephalon. All the other ROIs were moved in synchrony with the whole brain boundaries as a single unit. The ROIs were resized as necessary, using the whole brain boundaries as a guide to optimize the fit, but no regions were manipulated individually. The mean counts per pixel in the ROIs were measured automatically and imported into a relational database slice by slice, region by region.

The mean counts per pixel were measured in the following cortical regions: superior frontal (SF), lateral dorsal prefrontal (DL), medial dorsal prefrontal (DM),

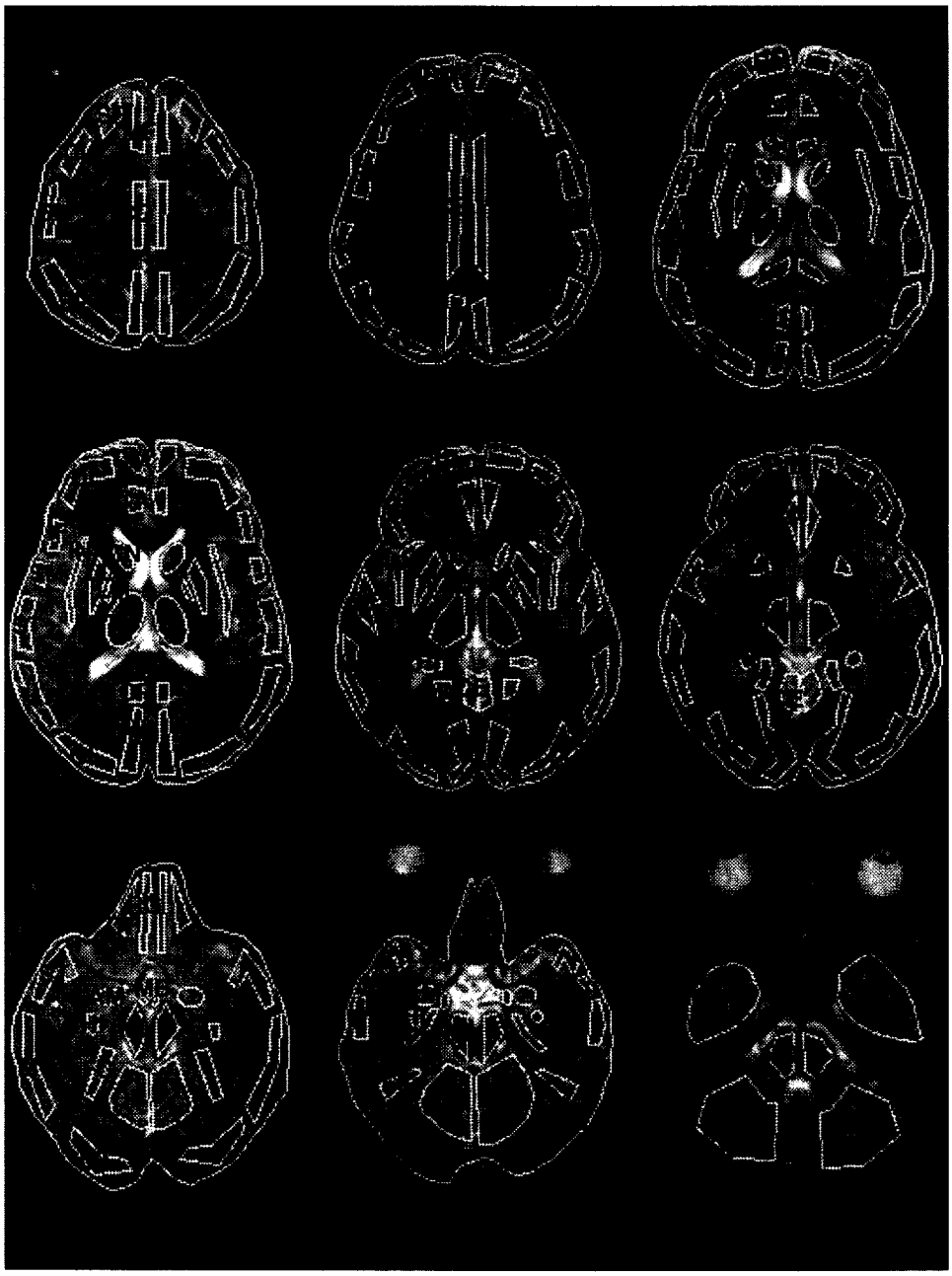

Figure 1. Representative MRI images and corresponding ROIs. (Reprinted with permission from *Science* 1995;267: 528-531. Copyright 1995 American Association for the Advancement of Science.)

midfrontal (MF), inferior frontal (IF), sensory–motor (SM), paracentral lobule (PC), superior parietal (SP), supramarginal gyrus (SG), lateral occipital (OL), medial occipital (OM), lingual gyrus (LI), fusiform gyrus (FG), anterior corpus callosum (C1), posterior corpus callosum (C2), temporal pole (TP), superior temporal (ST), midtemporal (MT), inferior temporal (IT), and occipital–temporal (OT). Subcortical regions included parahippocampus (PH), hippocampus (HI), uncus (UN), amygdala (AM), insula (IN), orbital frontal (OF), rectal gyrus (RG), anterior cingulate gyrus (CA), cingulate gyrus (CG), posterior cingulate gyrus (CP), caudate nucleus (CN), medial lenticular region (globus pallidus) (LM), lateral lenticular region (putamen) (LL), mammillary bodies (MB), thalamus (TH), midbrain (MI), pons (PO), and cerebellum (CE). Figure 1 shows representative MRI slices and corresponding ROIs.

We conducted further analyses addressing the question of small ROIs. In an unrelated PET study, employing identical image analysis techniques and identical opera-

tors, subjects were found to have significant activation in the mammillary bodies. On the PET images of the subjects demonstrating the most activation, we drew 10 pairs of test regions of similar size and shape adjacent to the original mammillary body ROIs, so that the original regions were in effect enclosed by the test regions. The test regions were also placed one slice above and one slice below the slice with the original MB ROIs. Statistical analyses involving the 30 pairs of test regions and the original MB ROIs demonstrated significant effects in the original mammillary body regions only, suggesting that we are able to accurately measure activity in these small regions.

Data Analysis

To compare memory performance within the patient sample, each patient's WMS recall score (sum of immediate and delayed scores) was transformed into a Z score using the mean and standard deviation of the entire patient sample. Patients with Z scores $\geq .5$ standard deviation were classified as the group with relatively preserved verbal recall, while patients with performances $\leq -.5$ SD were classified as the group with relatively impaired recall. Patients whose performances fell between .5 and $-.5$ were excluded from analyses to ensure differentiation between "good" and "poor" performers. For perseverations, where higher scores represent increased errors, subjects with Z scores $\leq .5$ were classified as "poor" performers and those with Z scores $\geq .5$ were classified as "good" performers. Only recall and perseverations were chosen as grouping variables in view of the reported frontal and temporal lobe dysfunction in schizophrenia and to limit the potential for type I error.

Most subjects had variable performance when all of the memory components were considered, with only 2 subjects being classified as "poor" performers on every variable. Three subjects were "good" performers and 4 subjects were "poor" performers when only recall and perseverations were considered.

For both recall and perseveration grouping variables, analyses of variance (ANOVAs) were performed to test the hypothesis that good and poor performers differ in the regional distribution of metabolic activity. To preserve favorable subject/variable ratios in each analysis they were performed separately on the region to whole brain (r/wb) values averaged across hemispheres and the relative laterality indices [defined as (left CMRglu − right CMRglu)/whole brain CMRglu], and separately for the following groups of regions: frontal (5 regions), parietal (7), temporal (5), limbic (10), corpus callosum (2), basal ganglia (3), diencephalon (2), and brainstem–cerebellum (3). The hypothesized region × group interaction was tested by the F ratio using Greenhouse–Geisser corrected p values. Significant interactions were decomposed with univariate ANOVAs (SAS, GLM PROCedure).

Relationships between memory and metabolic variables in the whole patient sample were examined using a computer program, after Olkin and Finn (1990), designed to test intercorrelations. This program uses the following model: "$r(A, B) = r(A, C) = r(A, D)\ldots$," where variable 1 is correlated with variables 2 through x, followed by correlations of variable 2 with variables 3 through x, and so forth, through the entire correlation matrix. The output of this analysis is an overall χ^2 with additional χ^2 values for each row of the contrast matrix.

Some patients do not have values for all ROIs because occasionally the subject's placement in the MRI scanner differed from their placement in the PET scanner to the extent that when the images were resliced and aligned, upper and/or lower slices were eliminated.

Results

Metabolic data for patients grouped on the basis of recall are provided in Figure 2. Mean data are provided in the upper graph; laterality data are in the lower graph. For the laterality graph, values > 0 indicate higher CMRglu in the given left hemispheric ROI than in the right. Values < 0 indicate higher metabolic activity in the right hemispheric region of interest relative to the left.

For the recall grouping, the ANOVAs showed no significant main effects or interactions for the hemispherically averaged r/wb ratios, but there were significant effects for the laterality scores. The group × region interaction was significant for the frontal regions, $F(4,110) = 4.42$, $p < .01$. This was attributable to poor performers showing relatively higher left hemispheric activation in the inferior frontal (IF) region, $F(1,24) = 3.72$, $p = .016$. For the temporal regions, there was a main effect of grouping, $F(1,24) = 4.74$, $p < .01$, indicating relatively higher left hemispheric values in poor performers, and a group × region interaction, $F(4,88) = 4.39$, $p < .01$. The interaction indicated that this effect was more pronounced in the inferior temporal (IT), $F(1,24) = 8.27$, $p < .01$, midtemporal (MT), $F(1,24) = 3.53$, $p < .025$, and superior temporal (ST) regions, $F(1,24) = 3.92$, $p < .025$, than in the other two temporal regions.

Mean metabolic data for patients divided into groups on the basis of perseverations are given in Figure 3.

For the perseveration grouping, the only significant effects were in the laterality of temporal regions. There was a group × region interaction, $F(4,88) = 4.63$, $p < .01$, indicating that patients who produced many perseverations had relatively higher metabolic activity than patients with fewer perseverations in the left temporal pole (TP), $F(1,24) = 6.91$, $p < .001$.

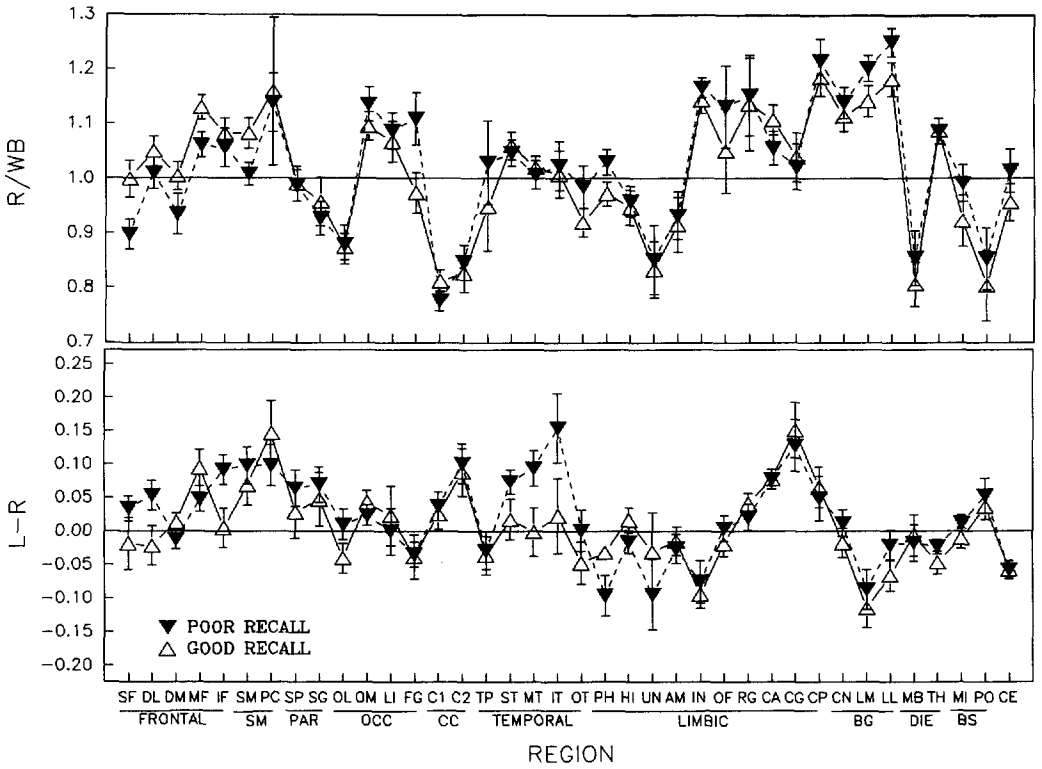

Figure 2. Mean (upper graph) and a laterality (lower graph) metabolic data for patients divided on the basis of their WMS total recall performance. Patients with strong recall are represented by the open triangles; patients with poor performance are represented by the filled triangles.

Correlations between Memory and Metabolic Variables

There were negative correlations between recall and metabolic laterality for inferior frontal ($r = -.288$, $p < .05$) and midtemporal ($r = -.366$, $p < .005$) regions, indicating that "poor" performers had higher left hemispheric activity in these regions. Perseverations were associated with mean metabolism in the anterior cingulate ($r = .173$, $p < .05$) and laterality in the temporal pole ($r = .286$, $p < .05$).

Post hoc analyses were performed to determine if the differences in metabolic patterns between "good" and "poor" performers were a result of clinical phenomenology. Chi-square analyses revealed no significant differences in the frequency of subjects described as "deficit" patients and those classified as "nondeficit" patients when subjects were subdivided on the basis of total recall performance, $\chi^2(1, N = 26) = 3.17$, NS, or perseverations, $\chi^2(1, N = 24) = .336$, NS.

Similarly, there were no differences between "good" and "poor" performers in age, gender, race, handedness, or parental education; however, patients with stronger performances in recall, but not perseverations, had significantly higher education than those subjects with more impaired performances [$t(24.0) = 2.66$, $p < .01$ and $t(26.0) = 3.44$, $p < .002$, respectively]. Analysis of metabolic patterns in patients with relatively preserved recall and those with worse recall using education as a covariate indicated persistent differences in mean sensory–motor CMRglu ($p < .05$) and hemispheric laterality in dorsal lateral prefrontal ($p < .02$), inferior frontal ($p < .04$), and midtemporal ($p < .02$) regions.

Discussion

Overall, the results of this study suggest that patients with more marked verbal memory impairment have relatively increased metabolism in several regions of the left hemisphere that are thought to mediate verbal memory, including inferior frontal and midtemporal regions, as well as some that do not. Although the pattern of mean metabolism differed somewhat depending on which memory dimension was considered, the pattern of laterality differences was similar along recall and perseveration domains.

The findings tend to parallel the results of comparisons between patients and healthy controls, which have shown

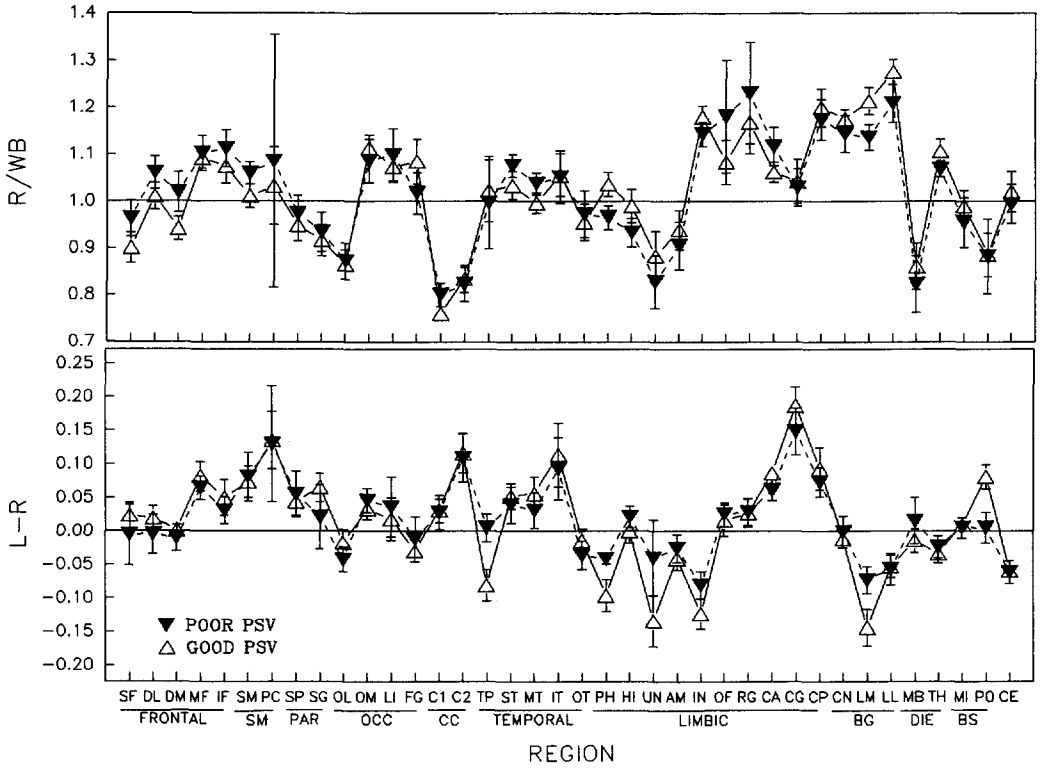

Figure 3. Mean (upper graph) and laterality (lower graph) CMRglu data for patients grouped based on the number of perseverations produced on the WMS. Patients who produced relatively few perseverations are represented by the open triangles; patients who gave many perseverations are represented by the filled triangles.

that patients with schizophrenia have higher left hemispheric metabolism in their midtemporal, superior temporal, and sensory–motor regions (Gur et al 1995b). These results, taken together, not only provide more evidence for the importance of frontal and temporal cortical regions in verbal memory, but are also consistent with the theory of left hemispheric overactivation in schizophrenia (Gur 1978).

The current study suggests how memory may be related to the pathophysiological basis of schizophrenia. Replication by other investigators who have also used FDG to study resting patients with a variety of neuropsychiatric disorders will be required to address the question of specificity.

One limitation of the present study is the sample size. Although it is one of the larger sample sizes in the current literature, the inclusion of additional patients would have maximized the number of subjects in high- and low-performance groups and allowed for more detailed analyses of possible differences in clinical symptomatology and the inclusion of other memory grouping variables. Given differences between men and women in severity of schizophrenia and sex differences in resting metabolism in healthy controls (Gur et al 1995a), it might be helpful to compare metabolic and cognitive relationships in male and female patients.

An additional limitation is the resolution of the PET scanner. It is possible that there is dysfunction in small groups of neurons in regions that are not currently resolved because of volume averaging.

Further studies might attempt to determine whether or not there are differences in memory or other specific cognitive processes in patients with schizophrenia with different clinical features using resting metabolic or cognitive activation cerebral blood flow paradigms. Some authors have used cognitive activation during the acquisition of PET cerebral blood flow data to assess functional systems involved in specific cognitive tasks in normals and to further understanding of abnormalities in schizophrenia. Citing a study by Volkow et al (1987) that reported significant correlations between blood flow and clinical symptomatology in schizophrenia patients performing a smooth pursuit eye tracking task, Jones et al (1991) noted that such cognitive activation studies may increase both the sensitivity and the specificity of PET techniques. These questions are relevant given the notion of the heterogeneity of schizophrenia. Although studies designed to integrate physiological, clinical, and behav-

ioral data are particularly difficult, in part because they require large sample sizes, the variable associations between memory performance and resting glucose metabolism reported in this study, together with other reports of successful cognitive activation paradigms, suggest that this work might yield promising results.

This research was supported by the National Institute of Health grants MH-42191, MH-43880, MH-48539, and 5-MO1RR0040. This work was part of a doctoral dissertation copyrighted in 1993 by LHM.

The authors wish to thank Teong Thew, B.S., Michael Ngu, Diane Sandefur, and Sean Riggin, C.N.M.T. for their assistance with this project.

References

American Psychiatric Association (1987): *Diagnostic and Statistical Manual of Mental Disorders,* 3rd ed rev. Washington, DC: American Psychiatric Press.

Bauman E (1971): Schizophrenic short-term memory: A deficit in subjective organization. *Can J Behav Sci* 3:55–65.

Blanchard JJ, Neale JM (1994): The neuropsychological signature of schizophrenia: Generalized or differential deficit? *Am J Psychiatry* 151:40–48.

Buchsbaum MS, Nuechterlein KH, Haier RJ, et al (1990): Glucose metabolic rate in normals and schizophrenics during the Continuous Performance Test assessed by positron emission tomography. *Br J Psychiatry* 156:216–227.

Calev A (1984): Recall and recognition in chronic nondemented schizophrenics: Use of matched tasks. *J Abnorm Psychology* 93:172–177.

Carpenter WT Jr, Heinrichs DW, Wagman AM (1988): Deficit and non-deficit forms of schizophrenia: The concept. *Am J Psychiatry 145:578–583.*

Chang LT (1978): A method for attenuation correction in radionuclide computed tomography. *IEEE Trans Nucl Sci* NS-25:638–693.

Gangarosa ME, Saykin AJ, Malamut BL, Gur RC (1988): New scoring systems for the Wechsler Memory Scale: Inter-rater reliability. *J Clin Exp Neuropsychology* 2:43.

Goldberg TE, Weinberger DR, Pliskin NH, Berman KF, Podd MH (1989): Recall memory deficit in schizophrenia. A possible manifestation of prefrontal dysfunction. *Schizophr Res* 2:251–257.

Gur RE (1978): Left hemisphere dysfunction and left hemisphere overactivation in schizophrenia. *J Abnorm Psychology* 87: 226–238.

Gur RE, Pearlson GD (1993): Neuroimaging in schizophrenia research. *Schizophr Bull* 19:337–353.

Gur RE, Mozley PD, Resnick SM, et al (1991): Relations among clinical scales in schizophrenia: Overlap and subtypes. *Am J Psychiatry* 148:472–478.

Gur RE, Mozley PD, Shtasel DL, et al (1994): Clinical subtypes of schizophrenia differ in brain and cerebrospinal fluid volume. *Am J Psychiatry* 151:343–350.

Gur RC, Harper Mozley L, Mozley PD, et al (1995a): Sex differences in regional cerebral glucose metabolism during a resting state. *Science* 267:528–531

Gur RE, Mozley PD, Resnick SM, Harper Mozley L, Shtasel DL, Gallacher F, Arnold SE, Karp JS, Alari A, Reivich M, Gur RC (1995b): Resting Cerebral glucose metabolism in first-episode and previously treated patients with shcizophrenia relates to clinical features. *Arch Gen Psychiatry* 52:657–667.

Harvey PD, Earle-Boyer EA, Wielgus MS, Levinson JC (1986): Encoding, memory, and thought disorder in schizophrenia and mania. *Schizophr Bull* 12:252–261.

Hoff AF, Riordan H, O'Donnell DW, Morris L. DeLisi LE (1992): Neuropsychological functioning of first-episode schizophreniform patients. *Am J Psychiatry* 149:898–903.

Jones AKP, Friston K, Dolan R (1991): Positron emission tomography as a research tool in the investigation of psychiatric and psychological disorders. *Balliere's Clin Endocrinol Metab* 5:187–203.

Karp JS, Muehllehner G, Mankoff DA, et al (1990): Continuous-slice PENN-PET: A positron tomograph with volume imaging capability. *J Nucl Med* 5:617–627.

Koh SD, Kayton L, Berry R (1973): Mnemonic organization in young nonpsychotic schizophrenics. *J Abnorm Psychol* 81: 299–310.

Koh SD, Kayton L, Peterson RA (1976): Affective encoding and subsequent remembering in schizophrenic young adults. *J Abnorm Psychol* 85:156–166.

Kolb B, Wishaw IQ (1983): Performance of schizophrenic patients on tests sensitive to left or right frontal, temporal, or parietal function in neurological patients. *J Nerv Ment Dis* 171:435–443.

Mozley PD, Gur RE, Shtasel DL, et al (1994): Magnetic resonance imaging in schizophrenia: II. Relationship to clinical measures. *Schizophr Res* 12:195–203.

Olkin I, Finn J (1990): Testing correlated correlations. *Psychol Bull* 108:330–333.

Prigatano GP (1978): Wechsler Memory Scale: A selective review of the literature. *J Clin Psychology* 34:816–832.

Resnick SM, Karp JS, Turetsky B, Gur RE (1993): Comparison of anatomically-defined versus physiologically-based regional localization: Effects on PET-FDG quantitation. *J Nucl Med* 34:2201–2207.

Russell EW (1975): A multiple scoring method for the assessment of complex memory functions. *J Consult Clin Psychology* 43:800–809.

Russell EW (1988): Renorming Russell's version of the Wechsler Memory Scale. *J Clin Neuropsychology* 10:235–249.

Saykin AJ, Gur RC, Gur RE, et al (1991): Neuropsychological function in schizophrenia: Selective impairment in memory and learning. *Arch Gen Psychiatry* 48:618–624.

Saykin AJ, Shtasel DL, Gur RE, Kester DB, Mozley LH, Gur RC (1992, May): Neuropsychology in schizophrenia: State or trait? Presented at the 145th Annual Meeting of the American Psychiatric Association, Washington, DC.

Shtasel DL, Gur RE, Gallacher F, Heimberg C, Cannon T, Gur RC (1992): Phenomenology and functioning in first-episode schizophrenia. *Schizophr Bull* 18:449–462.

Spitzer RL, Williams JB, Gibbon M (1987): *Instruction Manual for the Structured Clinical Interview for DSM-III-R (SCID).* New York: Biometrics Research Department, New York State Psychiatric Institute.

Talairach J, Tournoux P (1988): *Co-planar Stereotaxic Atlas of the Human Brain.* Stuttgart: Thieme.

Volkow ND, Wolf AP, Van Gelder P, et al (1987): Phenomenological correlates of metabolic activity in 18 patients with chronic schizophrenia. *Am J Psychiatry* 144:151–158.

Wechsler D (1945): A standardized memory scale for clinical use. *J Psychology* 19:87–95.

Wood FB, Flowers DL (1990): Hypofrontal vs. hypo-sylvian blood flow in schizophrenia. *Schizophr Bull* 16:413–424.

Wysocki JJ, Sweet JJ (1985): Identification of brain-damaged, schizophrenic, and normal medical patients using a brief neuropsychological screening battery. *Int J Clin Neuropsychology* 7:40–44.

Yurgelun-Todd DA, Waternaux CS (1991): Cognitive deficits underlying verbal memory function in schizophrenic patients and controls. *Schizophr Res* 4:396–397.