

# Anterior Cingulate Metabolism Correlates with Stroop Errors in Paranoid Schizophrenia Patients

Thomas E. Nordahl, M.D., Ph.D., Cameron S. Carter, M.D., Ruth E. Salo, Ph.D., Louis Kraft, M.D., Juliana Baldo, Ph.D., Shahriar Salamat, M.D., Ph.D., Lynn Robertson, Ph.D., and Natalia Kusubov, M.T. (ASCP)

Using [O-15]-H<sub>2</sub>O PET Carter et al. (1997) reported that medicated patients with schizophrenia performing computerized single trial Stroop (1935) showed a reduction in the anterior cingulate activation response to the more attention demanding, incongruent Stroop condition. In that study, both patients and controls also showed a direct correlation between anterior cingulate activation and errors committed during incongruent trials of the task. In this study we follow up with an examination of paranoid schizophrenia outpatients and controls with very high resolution positron emission tomography (PET) and the longer half-life tracer [F-18]-fluorinated deoxyglucose (FDG) (Valk et al. 1990). All subjects (10 controls and 9 paranoid schizophrenia patients) were studied with FDG-PET while performing a computerized trial-by-trial version of the Stroop task during the uptake phase of the tracer (Carter et al. 1992). Results: As in previous studies using

the single trial Stroop, patients were able to perform the task but made more color-naming errors during incongruent trials than controls. The patients in the present study showed a trend towards increased metabolic activity in the right anterior cingulate cortex. In the patient group, but not in controls, the anterior cingulate glucose metabolic rate correlated positively with the total incongruent trial errors. Conclusion: These results are consistent with the hypothesis that the anterior cingulate plays a performance-monitoring role during human cognition. This study does not rule out a reduction in error sensitivity in this region of the brain in schizophrenia, as other studies have suggested, however the data show that in unmedicated patients with the paranoid subtype this function is preserved to some extent.

[*Neuropsychopharmacology* 25:139–148, 2001]

© 2001 American College of Neuropsychopharmacology.  
Published by Elsevier Science Inc.

From the Center for Functional Imaging (TEN, NK, RES), Lawrence Berkeley National Laboratory, University of California, Berkeley; Department of Psychiatry (TEN, RES, LK), University of California, Davis; Department of Psychology (LR), University of California, Berkeley; Department of Psychiatry (CSC), University Pittsburgh Medical Center, Western Psychiatric Institute and Clinic, Pittsburgh, PA; Department of Surgical Pathology (SS), Clinical Science Center, University of Wisconsin, Madison, WI; VA Northern California Health Care Systems (JB), Martinez, CA 94553; Department of Veterans Administration Medical Center (LR), Martinez, California 94553

Address correspondence to: Thomas E. Nordahl, Center for Functional Imaging, 55-121, Lawrence Berkeley National Laboratory, 1 Cyclotron Road, Berkeley, CA 94720. Email: tenordahl@ucdavis.edu

Received May 4, 2000; revised September 12, 2000; accepted October 26, 2000.

KEY WORDS: PET; Regional glucose metabolism; Anterior cingulate; Stroop task; Noradrenergic; Dopaminergic

In an [O-15]-H<sub>2</sub>O PET study of medicated inpatients with schizophrenia performing trial-by-trial Stroop task, one of the co-authors noted that the patients demonstrated more task errors when naming the color-incongruent stimuli. Furthermore, for both the patient and control group, there was a direct correlation between both anterior cingulate and hippocampal blood flow activation and the total number of incongruent trial Stroop errors (Carter et al. 1997). However, despite having a normal correlational pattern, the patients ab-

normally activated the anterior cingulate cortex. Carter et al. (1997) then interpreted their correlational findings as consistent with the notion that the anterior cingulate has a significant role in the monitoring of errors during the performance of cognitive tasks such as Stroop (see also Kiehl et al. 2000 and Carter et al. 1998).

In the present study we investigated high-functioning medication-withdrawn paranoid schizophrenia outpatients and controls with the highest resolution PET tomograph available [PET-600]. We employed the longer acting tracer [F-18]-fluorodeoxyglucose (FDG) to measure metabolic activity during the performance of a trial-by-trial Stroop task (Valk et al. 1990; Nordahl et al. 1996; Carter et al. 1993). In addition, we tested the relationship between both the anterior cingulate and hippocampal regional glucose metabolism with the errors committed during the color-incongruent trials.

## METHODS

### Subject Selection

Nine unmedicated patients with paranoid schizophrenia (7 males and 2 females; mean age  $37.6 \pm 8.3$  years; and 10 normal controls (8 males and 2 females; mean age  $32.3 \pm 9.9$  years; 1 left-handed) were studied with PET and the tracer FDG during the performance of a Stroop task (see Tables 1 and 2). The data from a tenth patient were not included in the analysis, as the patient had an error rate that exceeded 50% on the Stroop task. Excessive error rates in this patient were made in both neutral and incongruent conditions.

The patients' Clinical Global Impression (CGI) ranged from 2 to 4 and averaged  $3.2 \pm 0.8$ . No differences in age were noted between patients and controls ( $F(1,17) = 2.52, p = .23$ ). Patients were evaluated with a

**Table 2.** Demographic Characteristics of the Experimental Subjects.

Clinical Comparison	Paranoid Schizophrenia	Controls
N	9	10
Age (SD)	37.6 (8.3)	32.3 (9.9)
Age Range	25–53	25–53
Gender (Males/Females)	7/2	8/2
Education (SD)*	12.1 (4.0)	15.9 (2.2)
Parental Education	13.4 (3.0)	13.5 (3.7)
Handedness (Right/Left)	9/0	9/1
Days Off Medication**	14.5 (2.9)	
Years of Illness	14.6 (9.3)	

\*Patients and controls did not differ on any demographic variable except for personal education  $F = 6.4, p = 0.02$ . \*\*These figures apply to all subjects but one who had not received antipsychotic treatment in over 10 years.

physical examination and a modified SCID for DSM-III-R. Normal controls were evaluated with a semi-structured interview and physical examination. Exclusionary criteria included: history of substance dependence, history of substance abuse in the previous year, history of significant head trauma, any significant neurological abnormality or systemic illness. Normal volunteers were also required to have no personal nor any first-degree history of an Axis I psychiatric disorder other than caffeine or nicotine abuse. One patient had not taken his antipsychotic medication, haloperidol, in over 10 years. The remaining patients had been off their oral antipsychotic medication for a mean of  $14.5 \pm 2.9$  (mean  $\pm$  SD) days (range: 11–21 days). Most of the patients enrolled in this study participated in experimental drug treatment protocols following the completion of their imaging study.

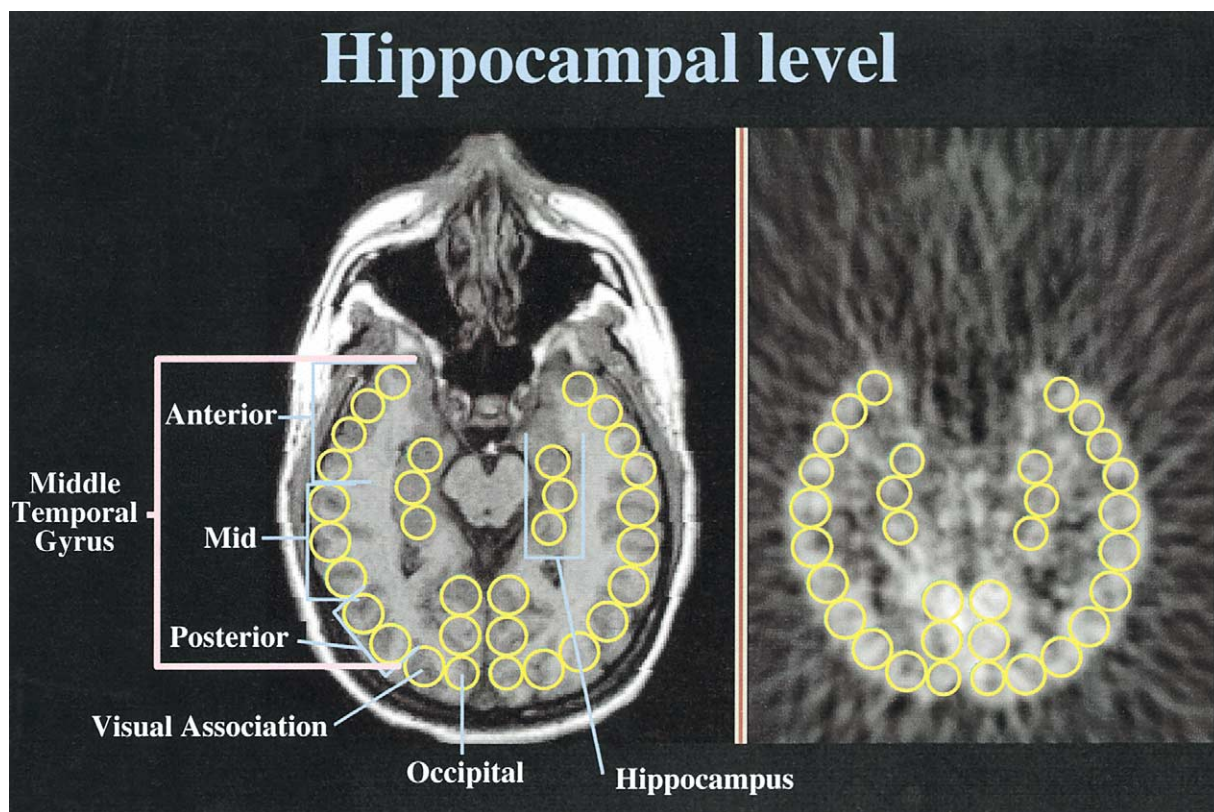
### PET/MRI Procedure

PET imaging was performed on the PET-600, a single-slice tomograph with a 2.6-mm full-width half-maximum in plane resolution and 6 mm axial resolution (Derenzo et al. 1988; Valk et al. 1990). Structural MRI images were acquired on a 0.5 Tesla MRI, and these images were initially used to assist in the acquisition of PET slices and then subsequently used to aid in placement of circular regions of interest (ROIs) (see Figures 1, 2, 3, 4). Initially, a mid-sagittal slice was obtained using spin echo technique with settings: TE = 33 ms and TR = 0.4 sec. The image contained  $256 \times 256$  pixels and resulted in a 1-mm  $\times$  1-mm resolution image. Following this, a study using gradient recall echo with Rf spoiling was performed to create a 3D volume involving  $256 \times 256 \times 96$  pixels, 1 mm  $\times$  1 mm  $\times$  2 mm voxel resolution, and which had a TE = 14.3, TR = 30 ms, and RF flip angle = 50 degrees.

**Table 1.** Patient Demographics.

Age/Sex	Years ill	Days off meds	BPRS-TOT	BPRS+	CGI
53/M	33	14	14	6	4
41/M	10	13	7	2	2
34/M	14	14	6	0	2
25/M	9	21	16	3	4
44/M	20	*	N/A	N/A	3
29/F	2.75	14	14	6	4
38/M	13	11	25	8	3
40/M	9	15	28	10	4
34/F	25	14	22	9	3
37.6(8.3)	14.8(8.8)	14.4(2.7)	17.4(8.0)	6.1(3.8)	3.3(0.8)

\*Patient off medication greater than 10 years. CGI represents Clinical Global Impression. The Brief Psychiatric Rating Scale (BPRS) is scaled with 0 as the minimal value. BPRS+ indicates 4 items: Conceptual Disorganization Suspiciousness, Hallucinatory Behavior, and Unusual Thought. The expressions in the bottom row represent mean(SD).



**Figure 1.** Circular ROIs are displayed on a hippocampal slice level emission image (right) and on the corresponding MRI image (left). The radii of the hippocampal ROIs are each 6.25 mm whereas the radii of the temporal cortical ROIs are 7.5mm.

Following MRI acquisition, the brain was rendered using VIDA imaging software system (see Klein et al. 1997). Four MRI slices were selected. These included: a slice running parallel through the long axis of the temporal lobe and passing through the hippocampus (Figure 1. Hippocampal Slice); a second slice running parallel to the first and sampling superior temporal gyrus (Figure 2. Superior Temporal Slice); a third slice parallel to the temporal lobe slices and passing through the striatum and thalamus (Figure 3. Striatal Slice); and a fourth slice parallel to the temporal lobe slices and passing through the mid-prefrontal cortex (Figure 4. Mid-Prefrontal Slice). Each of these four slices was projected to a rendered image of the head in order to determine landmarks for the PET images to be acquired. The mid-prefrontal slice was generally taken 2 cm above the striatal slice. The striatal slice was typically 2.5 cm above the hippocampal slice and 1.2 cm above the superior temporal lobe slice.

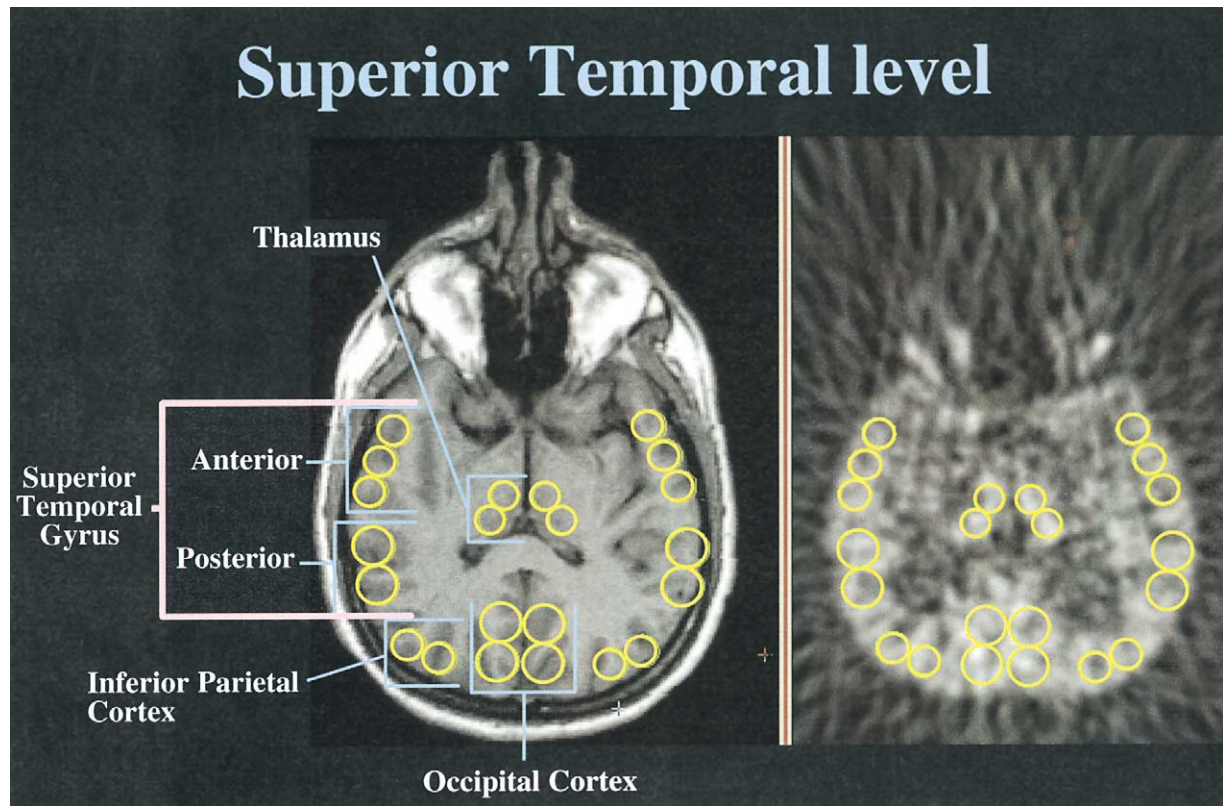
Following the MRI, the PET study was performed. The PET study was performed with the subjects having their eyes open and ears unoccluded in a dimly lit room. Prior to PET study, an arterial catheter was inserted into the left radial artery for determination of the tracer uptake curve. During the initial 30 minutes of tracer uptake, the subjects were sitting in a chair, facing an Everex color monitor, which displayed the Stroop task.

Several seconds after beginning arterial blood sampling, approximately 10 mCi of FDG were injected into a right antecubital vein. Subjects engaged in a Stroop word-color task for roughly the first 20 minutes of uptake (see below). At 30 minutes following injection, the subject voided and was positioned in the PET scanner with the gantry of the scanner placed at an angle and position which was determined by landmarks on the rendered MRI image of the head associated with the hippocampal slice. This approximated the slice selection in our earlier work (Jagust et al. 1993; Nordahl et al. 1996).

Following placement in the PET tomograph, the four parallel slice acquisitions were obtained as described above sequentially with each slice containing at least 10 minutes of data and approximately  $1 \times 10^6$  coincidence events. Prior to obtaining emission data, a transmission scan was performed at each level to correct for photon attenuation.

### **Stroop Task**

Stimuli were presented on an Everex color monitor with presentation of stimuli controlled by an Everex 386si microcomputer. Stroop stimuli were color words presented in one of four colors: red, green, blue, or yellow. Stimuli consisted of 144 trials of the incongruent case (each of four color names presented printed in the



**Figure 2.** Circular ROIs are displayed on a superior temporal slice emission image (right) and on the corresponding MRI image (left). The radii of the occipital and posterior temporal ROIs are 7.54mm. The radii of the thalamic, anterior temporal and inferior parietal ROIs are all 6.25mm.

ink of the three remaining colors) and 144 trials of the neutral case (series of "XXXX" in one of the four colors). Verbal response latency was measured with a voice-operated relay interfaced with the computer and monitored through the game port. The subject's response was registered via a switch triggered by the voice-operated relay; this response terminated the stimulus. The stimulus duration was 2 seconds, and the inter-trial interval (ITI) was 1.5 seconds. Prior to the FDG uptake phase, subjects were instructed in the task and were administered 14 practice trials. For each subject the Stroop interference was calculated by subtracting the mean reaction time for voice onset to the neutral Stroop stimuli from the mean reaction time to the incongruent stimuli.

### DATA ANALYSIS

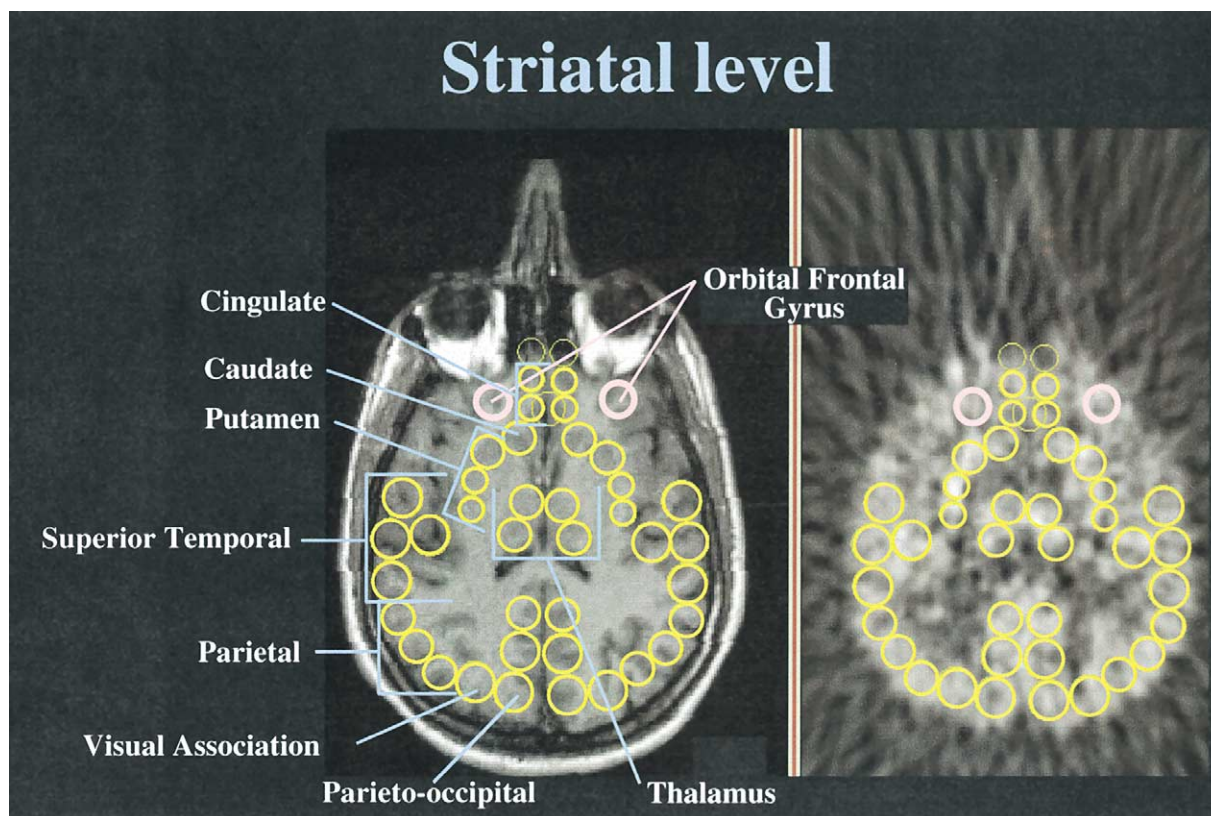
Glucose metabolic rates were calculated in cortical and subcortical regions of interest (ROIs) in the four slices acquired. First, the four PET slices acquired were aligned with their corresponding MRI slice utilizing a SUN SPARC station and the VIDA program. For each of the four PET slices, there was an initial estimate of the corresponding MRI slice from the method of selection of the

PET slice. Then, utilizing the VIDA program, we manipulated the initial MRI slice estimate into a final MRI slice corresponding to each of the four PET slices. We were able to move the slices using the three translational directions as well as rotate using the three basic angular rotations. Placement of the circles on each of the four MRI slices registered to a PET slice was then done in a semi-automatic fashion and blind to diagnosis (see Nordahl et al. 1996). The regional cerebral glucose metabolic rates (rCMRglcs) of the circular ROIs were obtained by using the arterial input function and the operational equation (Phelps et al. 1979; Reivich et al. 1985; Sokoloff et al. 1977), with rate constants  $k_1 = 0.161$ ,  $k_2 = 0.168$ ,  $k_3 = 0.098$ , determined for normal controls using the PET-600 in an earlier experiment (Jagust et al. 1991) and the rate constant  $k_4 = 0.0068$  determined by Phelps et al. (1979).

For each of the four slices sampled, the circular ROIs were averaged to evaluate rCMRglc in larger cortical or subcortical regions. Circle diameters were chosen to "cover" apparent cortical and subcortical gray matter on the PET image of the subjects. A standard atlas (Matsui and Hirano 1978) was used to label the ROIs (see Figures 1, 2, 3, 4).

Our targeted regions of interest (ROI) for the investigation of Stroop error relationship were the anterior cingulate (also contain sampling of medial prefrontal





**Figure 3.** Circular ROIs are displayed on a striatal slice emission image (right) and on the corresponding MRI image (left). The radii of the superior temporal, visual association, and posterior parieto-occipital cortex ROIs are all 7.5mm. The radii of the thalamic, parietal, orbital frontal, caudate, and anterior putamen ROIs are all 6.25mm. The radii of the cingulate and posterior putamen ROI are 5mm.

cortex) and the hippocampus (also contain sampling from amygdala, and parahippocampal gyrus). We determined an estimate of the whole brain or global metabolic as the volume-weighted average of the sampled cortical regions on the four brain slices. By regional metabolic rate it is meant the quotient of the absolute glucose metabolic rate of a region by the average cortical glucose metabolic rate (see e.g. Cohen et al. 1992). This transformation was designed to minimize the effects of individual variation in global glucose metabolism upon regional comparisons (Clark et al. 1985).

## RESULTS

### Task Performance

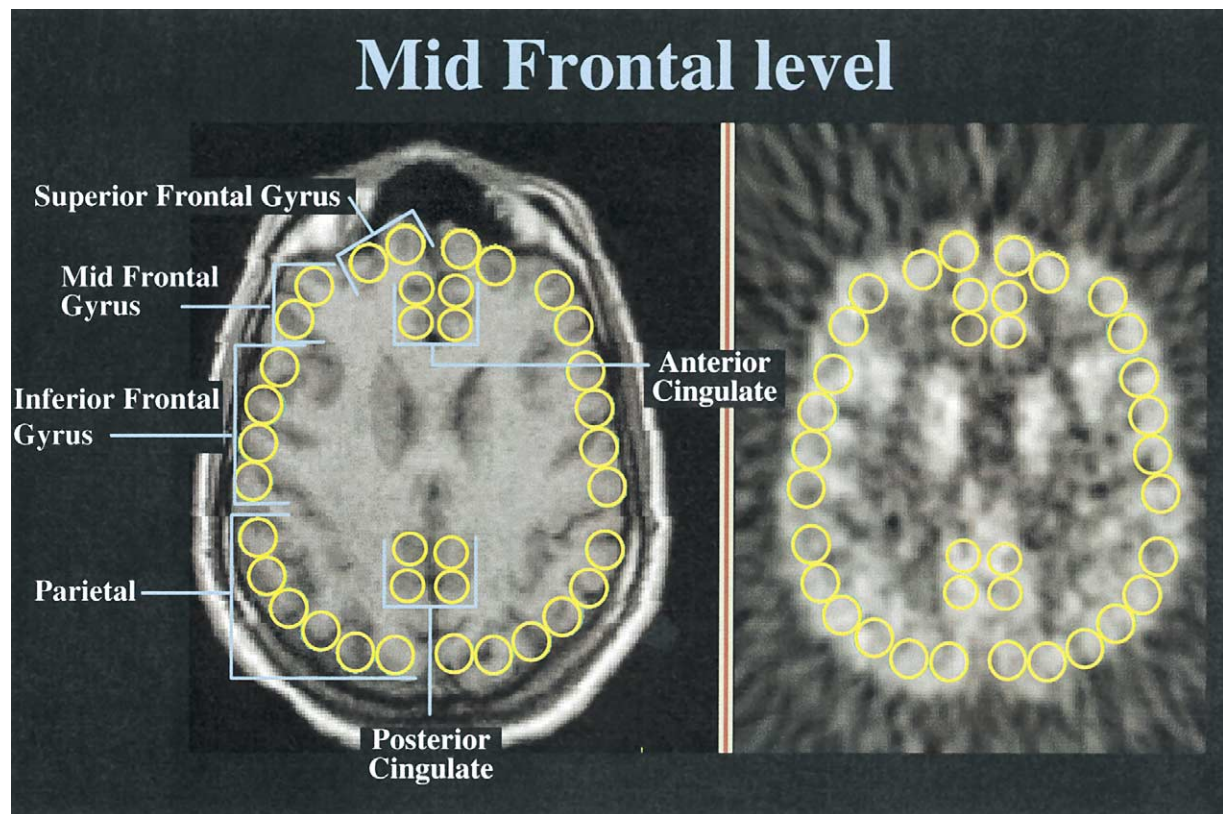
**Reaction Time Analysis.** The patients did not show significantly greater Stroop interference, as measured by the difference in mean reaction times for color-incongruent and neutral stimuli (Pts =  $173.7 \pm 135.4$ , Ctrl =  $129.1 \pm 53.8$ ,  $F(1,17) < 1$ ). However, both neutral reaction times [RTs] and incongruent RTs were slower for patients: Neutral RTs: [Pts =  $899.0 \pm 167.1$  msec, Ctrl =  $750.3 \pm 124.4$  msec;  $F(1,17) = 4.91$ ,  $p = .04$ , two-tailed] and Incongruent RTs: [Pts =  $1072.7 \pm 241.8$ , Ctrl =  $879.4 \pm 147.3$   $F(1,17) = 4.54$ ,  $p = .05$ , two-tailed].

**Error Analysis.** The overall error rates were relatively low (13.2% for patients and 5.2% for controls), which confirms that the subjects understood the task and were performing as instructed. Error rates for the patients during the incongruent trials were higher than that for the control subjects (Pts = 16%, Ctrl = 6%) [ $F(1,17) = 7.19$ ,  $p = .02$ , two-tailed].

**Speed-Accuracy Trade-off.** Pearson's correlation coefficients between reaction times and error rates for color-incongruent stimuli were calculated for the whole group: [ $R = +0.755$ ,  $p = .0002$ ], for the control subjects: [ $R = +0.395$ ,  $p = .26$ ], and for the patients with schizophrenia: [ $R = +0.766$ ,  $p = .016$ ]. The correlational analyses showed, if anything, evidence toward improved accuracy in association with faster speed for the patients with schizophrenia. Hence, the higher frequency of errors observed in the patients with schizophrenia was not simply due to a speed/accuracy trade-off.

### Regional Glucose Metabolism

The patients showed evidence of a higher right anterior cingulate metabolism [Pts =  $1.002 \pm 0.086$ , Ctrl =  $0.918 \pm 0.097$ ,  $F(1,17) = 3.98$ ,  $p = .06$ , two-tailed], but no evidence of a left anterior cingulate metabolic abnormality.



**Figure 4.** Circular ROIs are displayed on a mid frontal slice emission image (right) and on the corresponding MRI image (left). The radii of the frontal gyri, posterior parietal cortex ROIs are all 6.25. The radii of the anterior and posterior cingulate ROI are all 5mm.

malty (see Table 3). On an unplanned basis, and as there is some evidence of abnormal limbic metabolic asymmetry in schizophrenia (Gur 1999), we compared the anterior cingulate metabolic asymmetry quotient,  $(R-L)/(R+L)$ , between patients and controls and found asymmetry differences ([Pts =  $0.122 \pm 0.227$ , Ctrl =  $-0.122 \pm 0.229$ ;  $F(1,17) = 5.43$ ,  $p = .03$ , two-tailed]). There was no evidence of a hippocampal glucose metabolic abnormality (Table 3).

### Regional Metabolism Correlation with Task

**Table 3.** Glucose Metabolic Rates.

Brain region	mean $\pm$ SD (pt)	mean $\pm$ SD (ctrl)	F	p
L anterior cingulate	$0.939 \pm 0.089$	$0.978 \pm 0.133$	0.06	0.46
R anterior cingulate	$1.002 \pm 0.086$	$0.918 \pm 0.097$	3.98	0.06†
L hippocampus	$0.789 \pm 0.077$	$0.801 \pm 0.066$	0.13	0.73
R hippocampus	$0.776 \pm 0.071$	$0.781 \pm 0.071$	0.02	0.89
$(R-L)/(R+L)$ Cingulate	$0.122 \pm 0.227$	$-0.122 \pm 0.229$	5.43	0.03*

All statistical tests were two-tailed. The asterisk represents significance at the .05 level and the † represents a trend toward significance.

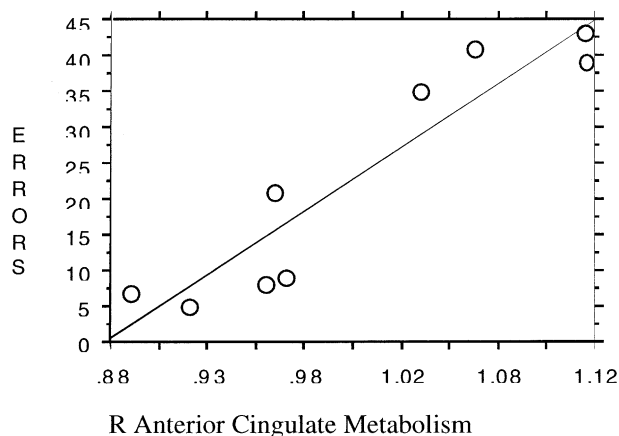
### Performance

The Pearson's product moment correlation coefficients, calculated between errors in the color-incongruent condition and right anterior cingulate glucose metabolism, were highly significant: [ $r = +0.934$ ,  $p = .0002$ , two-tailed] for the patient group (see Table 4 and Figure 5). If we had utilized the left plus right anterior cingulate in the above correlational analysis, the correlation

**Table 4.** Correlation Between Regional Glucose Metabolic Rates and Color-Incongruent Trial Errors.

Region	R	p
Patients		
R anterior cingulate	0.934	0.0002*
(R+L) anterior cingulate	0.824	0.006*
R Hippocampus	0.281	0.46
L Hippocampus	0.30	0.94
Controls		
(R+L) anterior cingulate	.271	0.45
R Hippocampus	.375	0.29
L Hippocampus	.480	0.16

All statistical tests were two-tailed. The asterisk represents significance at the .05 level.



**Figure 5.** This figure demonstrates the correlation between the right anterior cingulate metabolic rates and the color-incongruent Stroop errors.

would have been only modestly weaker: [ $r = +0.824$ ;  $p = .0002$ , two-tailed] for the patients. Inclusion of the tenth patient, who made excessive errors, would have still given a significantly positive correlation [ $r = +0.745$ ,  $p = .01$ ]. For the control subjects no evidence of a significant correlation was noted between errors in the color-incongruent condition and anterior cingulate glucose metabolism [ $r = 0.271$ ,  $p = .45$ , two-tailed]. No evidence of a correlation existed between hippocampal metabolism and errors in the color-incongruent condition for either the control or patient group (Table 4).

## DISCUSSION

Anterior cingulate glucose metabolic abnormalities were noted in the patients, with the patients showing evidence of higher regional metabolic rate on the right compared with controls. Further, the patients made more errors during color-incongruent trials than did controls. Finally, planned analyses revealed a very strong positive correlation between anterior cingulate glucose metabolism and color-incongruent trial errors for the patient group, but not for the control group. No such relationship was noted for hippocampal metabolic rates. RTs of patients were generally slower than controls on the cognitive task, but there was no evidence of a speed accuracy trade-off for the patients. In addition, no group differences in Stroop RT interference emerged between the patients with schizophrenia and the controls, consistent with other studies that have employed the single-trial version of the Stroop task (Carter et al. 1992; Salo et al. 1996; Taylor et al. 1996). In the discussion that follows we shall discuss the significance of the correlational linkage between the anterior cingulate metabolism and color-incongruent errors.

### Anterior Cingulate-Incongruent Trial Error Linkage

A decade of ERP studies have associated the anterior cingulate cortex with error detection (Falkenstein et al. 1991; Gehring et al. 1990). More recent event-related fMRI studies have confirmed that this region does indeed show increased activity during incorrect responses (Carter et al. 1998, Kiehl et al. 2000). Carter et al. (1998) proposed a refined theory of performance monitoring by the anterior cingulate cortex (ACC), that rather than monitoring errors *per se* it detects high levels of response competition. Within this model errors are considered to reflect high states of response competition, as activity associated with the incorrect response competes with activation of the correct response during ongoing stimulus evaluation during and immediately after execution of the error. It has been hypothesized that a disturbance in the function of the anterior cingulate cortex is related to impaired cognition and disorganization in schizophrenia, and initial studies using ERP (Kopp and Rist 1999; Mathalon et al. 2000) and fMRI (Carter et al. 1999) appear to support this hypothesis, by showing reduced error-related activity in this brain region. Carter et al. (1997) showed reduced activation associated with response competition in a heterogeneous, chronic medicated group of patients, while the correlation with errors, in the face of an increased error rate, was preserved. The present study also showed a correlation with errors and ACC metabolic rate in a homogeneous group of unmedicated patients with paranoid schizophrenia. The absence of such a correlation in controls could be interpreted as reflecting a decreased range of errors in this group. It is important to note that the present study was not an activation study *per se*, that is there was no contrast between cognitive conditions. Rather, while committing increased numbers of errors, schizophrenia patients' ACC metabolic rate was highest in subjects making the greatest numbers of color-incongruent trial errors. This could either indicate that higher ACC metabolism was associated with more disorganization (suggested by Liddle et al. 1992) or that the errors themselves were driving metabolic activity, as suggested by the ERP studies and event related fMRI studies cited above.

The present results cannot directly speak to the hypothesis that performance monitoring by the anterior cingulate cortex is impaired in schizophrenia. Increased activity associated with increased error rates could reflect either an intact system, or one that is impaired compared with normals but nonetheless still responsive to some degree to errors. In addition, to the degree that impaired performance monitoring would be associated with impaired modulation of executive functions and disorganization (Carter et al. 1999), the paranoid patients in the current study would be the least likely of any group of schizophrenia patients to show such an

impairment. It would be important for future studies to examine unmedicated patients with a range of symptomatology using event-related imaging methods to address the degree to which impaired performance monitoring by the anterior cingulate cortex is relevant to cognitive dysfunction in schizophrenia.

The anterior cingulate function during the Stroop task, whether it involves primarily error monitoring or it plays a role in response competition, may well require the involvement of the noradrenergic system, as the noradrenergic system is involved in processing novel stimuli (Clark et al. 1989; Foote and Bloom 1979; Watabe et al. 1982). It is thus of potential interest and perhaps surprising that stimulation of the locus coeruleus, with concomitant increased release of cortical norepinephrine, has been associated with lower anterior cingulate glucose metabolism in rats (Abraham et al. 1979). Relatively lower anterior cingulate metabolism was noted in our better performing patients and the metabolic rates of these better-performing patients were identical to the normal control mean. Interestingly, a number of studies of schizophrenia and paranoid schizophrenia have found evidence of central noradrenergic abnormality (Brambilla et al. 1994; Breier 1994; Farley et al. 1978; Litman et al. 1996; Van Kammen and Antelman 1984). Abnormalities in anterior cingulate metabolism may reflect relative inability to appropriately activate the noradrenergic system. However, Dolan et al. (1995) observed that the dopamine agonist, apomorphine, enhanced cognitive activation of the anterior cingulate in patients with schizophrenia who were not receiving antipsychotic medication.

### Anterior Cingulate Function Differences

The anterior cingulate findings in the present study differed from those in the Carter et al. (1997) study and due to our discrete sampling we were unable to obtain extensive coverage of the cingulate cortex. In this study the anterior cingulate glucose metabolic values showed evidence of being abnormally high, whereas the Carter et al. (1997) study reported abnormally low anterior cingulate activation in their patients with schizophrenia. This difference may be related to subtype differences, treatment differences, or PET resolution differences. More will be said about resolution differences below. Finally, it should be pointed out that the [O-15]-H<sub>2</sub>O-PET blood-flow study of Carter et al. (1997) involved a subtraction of a baseline study from an activated study. Thus, an abnormality in an [O-15]-H<sub>2</sub>O-PET activation study of patients performing a task could be accounted for in part by baseline difference as well as by task-related differences with the control population. If, in the Carter et al. (1997) study, the patients had a substantially elevated baseline, then the difference between the baseline and the activated study, the so-called activation, may appear lower.

Evidence from the literature does not readily suggest that the baseline [O-15]-H<sub>2</sub>O study would have been substantially elevated. Tamminga et al. (1992) found abnormally low anterior cingulate glucose metabolism in unmediated schizophrenia patients studied at rest while Haznedar et al. (1997) found decreased anterior cingulate glucose metabolism in unmedicated patients studied while performing a cognitive task. This might suggest that an [O-15]-H<sub>2</sub>O-PET study of the anterior cingulate would have also been abnormally low in patients with schizophrenia whether they were studied at rest or performing a certain cognitive task. However, the anterior cingulate metabolism in the Tamminga et al. (1992) study may have been different if their patients had been medicated as was the case in the Carter et al. (1997) study, or all outpatient paranoid subtype as was the case in this present study. In addition, the anterior cingulate metabolic measurement in the present study due to its higher in-plane resolution will include less contribution from the medial prefrontal cortex and adjacent white matter due to partial volume errors than the Tamminga et al. (1992) study or the Haznedar et al. (1997) study. On a per volume basis the resolution of the PET-600 used in this study is roughly five times finer than these studies cited which allows for the opportunity to sample separately the left and right cingulate. The presence of greater partial volume errors in the other cited studies could significantly contribute to their apparent cingulate metabolic rates.

Hence, the finding of an abnormally high rather than an abnormally low anterior cingulate metabolism in this FDG-PET study may be accounted for in part by the diagnostic subtype or clinical state differences, treatment differences, and tomograph resolution differences with the other schizophrenia studies investigating the anterior cingulate. Because of the long period of the cognitive task, 20 minutes versus a 1–2 minute(s) in the [O-15]-H<sub>2</sub>O experiment, the “activation” associated with this FDG-PET study may have also included efforts to automate the test. The presence of the strong correlation of the anterior cingulate glucose metabolism with the incongruent errors for the paranoid schizophrenia patients in this present study suggests that a significant part of the variance of the anterior cingulate metabolic rate was task-related.

### CONCLUSION

This study gives further evidence of functional abnormalities in the anterior cingulate for patients with schizophrenia, in particular for patients having paranoid subtype. The strong correlation between color-incongruent trial Stroop errors and anterior cingulate metabolism is consistent with the anterior cingulate having an involvement in the monitoring of errors



(Carter et al. 1997). Given that the design of the present study included a homogeneous group of paranoid patients, additional, more targeted studies are needed to determine the relationship between abnormalities in the performance monitoring function of the ACC and impaired cognition in schizophrenia. Further, investigation of the role of central monoamine function on the relationship between anterior cingulate metabolism and the incongruent trial monitoring of performance would be of great interest.

## ACKNOWLEDGMENTS

We are indebted to the suggestions of Dr. Robert M. Cohen. We are also indebted to Dr. Thomas F. Budinger, the chemists Dr. Henry Van Brocklin and Dr. James O'Neil, and Staff of the Center for Functional Imaging, Lawrence Berkeley National Laboratory where the study was performed. This work was funded in part by UCD Medical Scholar Research Fellowship to Dr. Kraft and MH 46990 to Dr. Nordahl. This work was supported by the Director, Office of Science, Office of Biological and Environmental Research, Medical Science Division of the U.S. Department of Energy under contract No. DE-ACO3-76SF00098.

## REFERENCES

- Abraham WC, Delanoy RL, Dunn AJ, Zornetzer SF (1979): Locus coeruleus stimulation decreases deoxyglucose uptake in ipsilateral cerebral cortex. *Brain Res* 172:387–392
- Barch D (1999): The anterior cingulate and response conflict. In Tamminga C (ed), *Images in Neuroscience*. Am J Psychiatry 156:1849
- Bench CJ, Frith CD, Grasby PM, Friston KJ, Paulesu E, Frackowiak RSJ, Dolan RJ (1993): Investigations of the functional anatomy of attention using the Stroop test. *Neuropsychologia* 31:907–922
- Brambilla F, Marini S, Saito A, Fassone G, Picardi A, Neruzzi D, Pancher D (1994): Noradrenergic and dopaminergic interrelation in schizophrenia. 53:231–242
- Breier A (1994): Clozapine and noradrenergic function: Support for a novel hypothesis for superior efficacy. *J Clin Psychiatry Suppl* B:122–125
- Breier A, Wolkowitz OM, Roy A, Potter WZ, Pickar D (1990): Plasma norepinephrine in chronic schizophrenia. *Am J Psychiatry* 147:1467–1470
- Carter CS, Barch DM, MacDonald AM, Noll D, Stenger VA, Cohen JD (1999): Anterior cingulate cortex and cognitive disability in schizophrenia: an event-related fMRI study. *Schizophrenia Research* 36:219
- Carter CS, Braver TS, Barch DM, Botvinick M, Noll D, Cohen JD (1998): Anterior cingulate cortex, error detection, and the on line monitoring of performance. *Science* 280(5364):747–749
- Carter CS, Mintun M, Nichols T, Cohen JD (1997): Anterior cingulate gyrus dysfunction and selective attention deficits in schizophrenia [O-15]-H<sub>2</sub>O PET study during single-trial Stroop task performance. *Am J Psychiatry* 154:1670–1675
- Carter CS, Robertson LC, Nordahl TE (1992): Abnormal processing of irrelevant information in chronic schizophrenia: selective enhancement of Stroop facilitation. *Psychiatry Research* 41:137–146
- Carter CS, Robertson LC, Nordahl TE, O'Shara-Celaya LJ, Chaderjian MC (1993): Abnormal processing of irrelevant information in schizophrenia: The role of illness subtype. *Psychiatry Res* 48:17–26
- Clark CR, Geffen GM, Geffen LB (1989): Catecholamines and the covert orientation of attention in humans. *Neuropsychologia* 27:131–139
- Clark D, Carson R, Kessler R, Margolin R, Buchsbaum M, Delisi L, King C, Cohen RM (1985): Alternate statistical models for the examination of clinical PET/FDG data. *J Cereb Blood Flow Metab* 5:142–150
- Cohen RM, Semple WE, Gross M, King AC, Nordahl TE (1992): Metabolic brain pattern of sustained auditory discrimination. *Experimental Brain Res* 92:165–172
- Derenzo SE, Huesman RH, Cahoon JL, Geyer AB, Moses WW, Uber DC, Vuletic T, Budinger TF (1988): A positron tomograph with 600 BGO crystals and 2.6 mm resolution. *IEEE Trans Nucl Sci* 35:659–664
- Dolan RJ, Fletcher P, Frith CD, Friston KJ, Frackowiak RSJ, Grasby PM (1995): Dopaminergic modulation of impaired cognitive activation in the anterior cingulate cortex in schizophrenia. *Nature* 378:180–182
- Falkenstein M, Hohnsbein J, Hoorman J, Blanke L (1991): Effects of crossmodal divided attention on late ERP components: II. Error processing in choice reaction tasks. *Electroencephalography and Clinical Neurophysiology* 78:447–455
- Farley IJ, Price KS, McCullough E, Deck JH, Hordynski W, Hornykiewicz O (1978): Norepinephrine in chronic paranoid schizophrenia: Above normal levels in limbic forebrain. *Science* 200:456–458
- Footo SL, Bloom FE (1979): Activity of norepinephrine containing locus coeruleus neurons in the unanesthetized squirrel monkey. In Usdin E, Kopin IJ, Barchas J (eds), *Catecholamines: Basic and Clinical Frontiers*, Vol. 1. New York, Pergamon Press, pp 625–657
- Gehring WJ, Coles MGH, Meyer DE (1990): The error-related negativity: An event-related potential accompanying errors. *Psychophysiology* 27(4A Suppl):S34
- Gur RE (1999): Is schizophrenia a lateralized brain disorder? Editor's Introduction, *Schizophrenia Bulletin* 25:7–9
- Haznedar MM, Buchsbaum MS, Luu C, Hazlett EA, Siegal BV, Lohr J, Wu J, Haier RJ, Bunney WE (1997): Decreased anterior cingulate gyrus metabolic rate in schizophrenia. *American Journal of Psychiatry* 154:682–684
- Jagust WJ, Seab JP, Huesman RH, Valk PE, Mathis CA, Reed BR, Coxson PG, Budinger TF (1991): Diminished glucose transport in Alzheimer's disease: Dynamic PET studies. *J Cereb Blood Flow Metab* 11:323–330
- Jagust WJ, Eberling JL, Richardson BR, Reed BR, Baker MG, Nordahl TE, Budinger TF (1993): The cortical topography of temporal lobe hypometabolism in early Alzheimer's disease. *Brain Res* 629:189–198

- Kiehl KA, Liddle PF, Hopfinger JB (2000): Error processing and the rostral anterior cingulate: An event-related MRI study. *Psychophysiology* 37:216–223
- Kopp B, Rist F (1999): An event-related brain potential substrate of disturbed response monitoring in paranoid schizophrenic patients. *Journal of Abnormal Psychology* 108(2):337–346
- Klein GJ, Teng X, Jagust WJ, Eberling JL, Acharya A, Reutter BW, Huesman RH (1997): A methodology for specifying PET VOIs using multimodality techniques. *IEEE Transactions on Medical Imaging* 16:405–415
- Liddle PF, Friston KJ, Frith CD, Hirsch SR, Jones T, Frackowiak RSJ (1992): Patterns of cerebral bloodflow in schizophrenia. *Br J Psychiatry* 160:179–186
- Litman RE, Su TP, Potter WZ, Hong WW, Pickar D (1996): Idazoxan and response to typical neuroleptics in treatment-resistant schizophrenia—Comparison with the atypical neuroleptic clozapine. *Br J Psychiatry* 168:571–579
- Mathalon DH, Fedor M, Faustman WO, Askari N, Ford JM (2000): Self monitoring abnormalities in schizophrenia: an event related potential study. *Proceeding of the Annual Meeting of the Society for Cognitive Neuroscience* 111.
- Matsui T, Hirano A (1978): *An Atlas of the Human Brain for Computerized Tomography*. New York, Igaku-Shoin Medical Publishers
- Nordahl TE, Kusubov N, Carter C, Salamat S, Cummings AM, O'Shoro-Celaya L, Eberling J, Robertson L, Huesman RH, Jagust W, Budinger TF (1996): Temporal lobe metabolic differences in medication-free outpatients with schizophrenia via the PET-600. *Neuropsychopharmacology* 15:541–554
- Pardo JV, Pardo PJ, Janer KW, Raichle ME (1990): The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. *Proceedings NAS* 87:256–259
- Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L, Kuhl DE (1979): Tomographic measurement of local cerebral glucose metabolic rate in humans with [F-18] 2-fluoro-2-deoxy-D-glucose: Validation of method. *Ann Neurol* 6:371–388
- Reivich M, Alavi A, Fowler J, Russell J, Arnett C, MacGregor RR, Shiue CY, Atkins H, Anand A, Dann R, Greenberg JH (1985): Glucose metabolic rate kinetic model parameter determination in humans: The lumped constant and rate constants for [F-18]-fluorodeoxyglucose. *J Cereb Blood Flow Metab* 5:179–192
- Salo R, Robertson LC, Nordahl TE (1996): Normal sustained effects of selective attention are absent in schizophrenic patients withdrawn from medication. *Psychiatry Research* 62:121–130
- Sokoloff L, Reivich M, Kennedy C, Des Rosiers MH, Patlak CS, Pettigrew KD, Sakurada O, Shinohara M (1977): The [C-14] deoxyglucose method for the measurement of local cerebral glucose utilization: Theory, procedure, and normal values in the conscious and anesthetized albino rat. *J Neurochem* 28:897–916
- Spitzer RL, Williams JBW, Gibbon M, First MD (1989): *Structured Clinical Interview for DSM-III-R*. Biometrics Research Division. New York State Psychiatric Institute
- Stroop JR (1935): Studies of interference in serial verbal reactions. *J Exp Psychol* 18:643–662
- Tamminga CA, Thaker GK, Buchanan R, Kirkpatrick B, Alphs LD, Chase TN, Carpenter WT (1992): Limbic system abnormalities identified in schizophrenia using position emission tomography with fluorodeoxyglucose and neocortical alterations with deficit syndrome. *Arch Gen Psychiatry* 49:522–530
- Taylor SF, Kornblum S, Tandon R (1996): Facilitation and interference of selective attention in schizophrenia. *Journal of Psychiatric Research* 30:251–259
- Valk PE, Jagust WJ, Derenzo SE, Huesman RH, Geyer AB, Budinger TF (1990): Clinical evaluation of a high resolution (2.6 mm) positron emission tomograph. *Radiology* 196:783–790
- Van Kammen DP, Antelman S (1984): Impaired noradrenergic transmission in schizophrenia? *Life Sci* 34:1403–1413
- Watabe K, Nakai K, Kasamatsu T (1982): Visual afferents to norepinephrine-containing neurons in cat locus coeruleus. *Exp Brain Res* 48:66–80