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Glucose Metabolic Rate in Normals and Schizophrenics During the Continuous Performance Test Assessed by Positron Emission Tomography

MONTE S. BUCHSBAUM, KEITH H. NUECHTERLEIN, RICHARD J. HAIER, JOSEPH WU, NANCY SICOTTE, ERIN HAZLETT, ROBERT ASARNOW, STEPHEN POTKIN and STEVEN GUICH

Local cerebral uptake of glucose labelled with fluorine-18 was measured by positron emission tomography in 13 patients with schizophrenia and 37 right-handed volunteers. Patients received no medication for a minimum of 31 days and a mean of 30 weeks. The subjects were administered the labelled deoxyglucose just after the beginning of a 32-minute sequence of blurred numbers as visual stimuli for the Continuous Performance Test. In normal controls, task performance was associated with increases in glucose metabolic rate in the right frontal and right temporoparietal regions; occipital rates were unchanged. Patients with schizophrenia showed both absolutely and relatively reduced metabolic rates in the frontal cortex and in the temporoparietal regions compared with normal controls.

In a pioneering study, Ingvar & Franzen (1974) imaged human cerebral blood flow with xenon-133 in patients with schizophrenia and controls. In normal resting subjects there were relatively high flows in the frontal lobes and lower flows in temporal and occipital regions; schizophrenics tended to lose this normal hyperfrontal pattern. Statistical analyses revealed that neither frontal nor occipital flow rates in themselves showed significant differences between groups, but that a frontal:occipital ratio did reach significance. Ingvar introduced the term 'hypofrontality' to describe this pattern.

Such ratio comparisons are a standard feature of much research in the psychophysiology of schizophrenia. Since individual baseline cerebral blood flows differ greatly, like EEG, heart rate, or other autonomic measures, ratios between data obtained at two different scalp locations were used to reveal this effect.

We decided to replicate the 1974 blood-flow studies with labelled fluorodeoxyglucose (FDG) and positron emission tomography (PET), using a small series of patients resting with their eyes closed. This series (Buchsbaum *et al*, 1982) revealed, like the 1974 data, a relatively diminished frontal:occipital ratio in patients with schizophrenia. This also occurred when patients were receiving brief electric shocks to their right forearm (Buchsbaum *et al*, 1984).

Six other PET studies of schizophrenia have been reviewed by Buchsbaum & Haier (1987). In general, these studies have tended to show that patients with schizophrenia had lower frontal:occipital ratios than normals, although it was not confirmed to a statistically significant extent in all six. Studies of cerebral blood flow by seven other groups also have tended to confirm the original Ingvar & Franzen finding (see Buchsbaum & Haier (1987) for a detailed review). However, both PET and blood-flow studies have been variable in the extent to which the hypofrontal differences are manifest. In some cases, while schizophrenics had lower ratios, these ratios were still above 1.00, leading to the term 'relative hypofrontality'.

One important source of variation that has been suggested (Buchsbaum *et al*, 1984; Weinberger *et al*, 1986) is the difference in psychological state during FDG uptake. Given the sensitivity of both cerebral blood flow and FDG uptake to task demands, posterior activation with visual stimulation, implied demands of 'resting', ambient sensory stimulation in the PET room, and other uncontrolled sensory and perceptual input might well influence the pattern of cerebral activity in different ways in patients and normals. To control this source of variation, we selected somatosensory stimulation for our second PET study (Buchsbaum *et al*, 1984). Pain stimulation had been reported to increase blood flow in the frontal lobe in man (Ingvar *et al*, 1976) and animals (Tsubokawa *et al*, 1981), and to reveal diminished pain sensitivity in patients with schizophrenia (Davis *et al*, 1979*a*,*b*; Buchsbaum *et al*, 1986). Pain stimulation during FDG uptake continued to reveal statistically significant differences in relative frontal/occipital metabolic rate. However, it did not alter frontal:occipital ratios from the resting state in normals (Buchsbaum *et al*, 1983). Thus, while perhaps useful for controlling sensory conditions and thus reducing variance, the shock condition did not

specifically activate the brain regions targeted for study (although the 'rest' condition might not be optimal for comparison).

For our third study, we selected the Continuous Performance Test (CPT) because this task has shown particular sensitivity to schizophrenic performance deficit. The CPT is a visual vigilance task that involves monitoring a series of briefly presented stimuli (usually numbers or letters) that appear rapidly one after the other and pressing a button each time a pre-designated letter or number is presented. Adult chronic schizophrenic patients score significantly lower than chronic alcoholics or normal subjects, and schizophrenic in-patients score lower than in-patients with either schizoaffective disorder or major affective disorder (Walker, 1981). However, this abnormally low CPT target detection rate (the *d'* score) characterises 40–50% rather than all schizophrenic in-patients (Orzack & Kornetsky, 1966; Walker & Shaye, 1982). Furthermore, these poor CPT performers are more likely to have family history of schizophrenia (Walker & Shaye, 1982) or serious mental illness (Orzack & Kornetsky, 1971) than schizophrenic patients who are good CPT performers.

Low levels of CPT target discrimination also characterise persons who would be predicted to be at heightened risk for schizophrenic disorder (Rutschmann *et al*, 1977; Erlenmeyer-Kimling & Cornblatt, 1978; Nuechterlein, 1983). The relative sensitivity of the CPT to attentional impairment among children at heightened risk for schizophrenia is also suggested by the finding that the CPT *d'* score produced significant differences between children or schizophrenic mothers and representative normal children, whereas measures from cross-modal reaction time and incidental learning tasks did not (Nuechterlein *et al*, 1982).

Deficits in target detection rate and false alarm rate have been demonstrated in both stable, post-psychotic schizophrenic out-patients on antipsychotic medication (Asarnow & MacCrimmon, 1978) and remitted schizophrenic patients off medication and functioning at their pre-morbid level (Wohlberg & Kornetsky, 1973). Thus, cross-sectional studies at pre-morbid, psychotic, and post-psychotic points suggest that some persons prone to schizophrenia might manifest CPT deficits throughout their life course.

Recently, an auditory discrimination task, not dissimilar to the visual CPT in subject performance, was used during FDG uptake in normals and patients with schizophrenia (Cohen *et al*, 1987). A correlation between metabolic rate in middle pre-frontal cortex and accuracy of performance was found in normal subjects. Further, decreased metabolic rates in pre-frontal cortex of schizophrenics were found, even among those patients with performance in the normal range. This report is consistent with our earlier finding of frontal reductions in schizophrenia, and supports our selection of the CPT as an appropriate task for PET study.

Two comparison groups of normal controls were planned: one doing the task with the same instructions as the schizophrenics, and one completely uninstructed but watching the stimuli passively. This contrast was added to allow identification of brain regions activated by the cognitive aspects of the vigilance task.

Method

Subjects

Thirteen patients with schizophrenia (11 men, 2 women, mean age 28 ± 6.7 years) were recruited from the clinical and research programmes of the University of California at Irvine (UCI) and Los Angeles (UCLA), and do not overlap with earlier samples. Eleven were right handed and two were left handed. Patients were off all psychoactive medication for a minimum of 31 days and a mean of 30 weeks. For long-acting, injectable, antipsychotic medication, the minimum period off medication was eight weeks. All patients were in good physical health and none had noteworthy abnormalities on physical examination or as found on laboratory tests. Patients with a history of seizure disorder, major head trauma, or substance abuse were excluded. Psychiatric interviews and assessments of the patients were carried out at UCLA independently of PET laboratory procedures in the week before the scan. The diagnostic work-up included the Present State Examination (PSE; Wing *et al*, 1974) modified to allow use of DSM–III criteria, the expanded version of the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962; Lukoff *et al*, 1986), and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1982). The mean BPRS score (sum of first 18 items) was 33 (s.d. = 10). The mean SANS score (sum of all but the subjective and global ratings) was 30 (s.d. = 10). Mean educational level was 12.8 years. Patients received the CPT task at the interview as well as during the glucose uptake period.

The normal control group for this study consisted of 37 right-handed volunteers. Subjects were screened for health just as the patients were, by physical examination, medical history, laboratory measures, and psychiatric interview at UCI. The BPRS and SANS were not done. Eighteen subjects, the CPT task group (14 men, 4 women, mean age 26.2 ± 8.1 years), received the degraded-stimulus CPT (Nuechterlein *et al*, 1983). Their mean educational level was 14.7 years. A group of 19 subjects, the no-task group (9 men, 10 women, mean age 35.5 ± 13.8 years), received identical stimuli but were told only to use the flashes as a fixation point. The CPT task group was age- and sex-matched to the schizophrenics for comparison.

Task

Single digits (0–9) were presented for 40 ms at a rate of one every two seconds. Subjects were told to press a button using their right hand each time that they detected the digit 0 and that it was equally important to respond to zeros and not respond to non-zeros. Targets were presented irregularly with a probability of occurrence of 0.25. Stimuli were presented silently by rear projection on a 24 cm × 24 cm screen, with a Kodak carousel slide projector fitted with an Ilex No. 4 Synchro-Electronic Shutter and blurred to a degree that makes digits barely recognisable (such that a 2.8 diopter correction is required to refocus clearly). The subject's eyes were 1.2 m from the rear projection screen.

Positron emission tomography

Changes in regional brain activity were imaged as glucose metabolic rate using sterile, pyrogen-free ^{18}F-2-deoxyglucose, prepared at the Crocker Nuclear Laboratory, University of California, Davis. Batches containing 90–100 mCi of ^{18}F-2-deoxyglucose dissolved in 0.9% isotonic saline were synthesised from ^{18}F made in a 2-h bombardment, by the ^{20}Ne(d,a)^{18}F reaction using a 27.5 MeV external deuteron beam (20 μÅ) from the 76-inch isochronous cyclotron. Radiochemical purity and pyrogen testing were performed before injection of the ^{18}F-2-deoxyglucose using high-performance liquid chromatography on a varian 5000 and a Limulus amoebocyte lysate gelation test, respectively. The US Pharmacopeia sterility test was performed on the ^{18}F-2-deoxyglucose after administration due to the 14-day incubation time. All quality-assurance procedures confirmed the ^{18}F-2-deoxyglucose to be within specifications and of pharmaceutical quality.

Before PET scanning, an individually molded, thermosetting plastic head holder was made for each subject, to minimise head movement. The same head holder was used for magnetic resonance imaging (MRI).

For the PET procedure, subjects were seated in a darkened isolation room. An intravenous line of 0.9% saline drip was inserted into the subject's left arm for blood sampling and another one into the right arm for injection of the labelled glucose. The left arm was wrapped in a hot pack for arteriolisation of venous blood. The left arm was extended through a slit in a black curtain two metres high, so as to screen blood sampling activity. Both patients and controls who were administered the CPT during uptake were instructed just before injection time and were given a trial run of the CPT to ensure their understanding of the task. Two to three minutes before the ^{18}F-2-deoxyglucose injection (4–5 mCi), room lights were extinguished and visual stimuli were begun; the stimuli continued for 32–37 minutes after injection of the radionuclide. Subjects were not spoken to during uptake, and all remained quiet and co-operative. Subjects were continuously observed to ensure that they were following instructions. After 30–35 minutes of FDG uptake, the subject was transferred to the adjacent scanning room. Nine planes (CTI NeuroECAT) at 10 mm increments and parallel to the canthomeatal line (CM) were done between 45 and 100 minutes after FDG injection. Scans were performed with both shadow and septa shields in, a configuration with measured in-plane resolution of 7.6 mm and 10.9 mm resolution in the z-dimension (axial). A calculated attenuation correction and smoothing filter were used. The scanner was calibrated each scan day, with a cylindrical phantom, and compared with well-counter data.

Scan slice processing and selection

Scans were transformed to glucose metabolic rate according to the model of Sokoloff (1977) and constants from Phelps *et al* (1979) were used for consistency with earlier studies. Three slices were selected exactly following our previously described technique (Buchsbaum *et al*, 1982, 1984). The slices were outlined with a boundary-finding algorithm, and a 2-cm-thick ring of cortex identified as in Fig. 1. Eight values (four anteroposterior sectors for each hemisphere) were obtained from each slice. Values were expressed as ratio data to control for individual differences in overall level (sector mean : whole-slice mean).

Statistical analysis

The first analysis focused on comparison of CPT task and CPT no-task normal groups. Second, for a direct comparison with our previous schizophrenia studies (Buchsbaum *et al*, 1982, 1984), we contrasted the normal control CPT task group with the patient group. In this report, we chose to match exactly the PET image cortex peel approach of our two earlier studies at the National Institute of Mental Health (NIMH). Thus, the PET slices

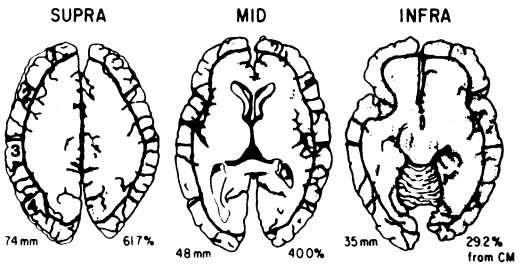

FIG. 1 Three slice levels used in the analysis of the cortical surface. PET images are selected to match these levels and then a computer algorithm is applied to delineate the four cortical sectors on each hemisphere numbered R1–R4 for the right and L1–L4 for the left in anteroposterior sequence. In most individuals, the sectors are largely composed as follows. The supraventricular slice comprises (a) superior and middle frontal gyrus, (b) inferior frontal, pre-central and post-central gyrus, (c) parietal lobe, supramarginal and angular gyrus, and (d) occipital pole. The midventricular slice comprises (a) middle frontal and some superior frontal gyrus, (b) pre-central gyrus, insula and some superior temporal gyrus, (c) middle and inferior temporal gyrus (in some individuals, some parietal lobe may be included), and (d) occipital pole. The infraventricular slice comprises (a) inferior frontal gyrus and some middle frontal gyrus, (b) tip of temporal lobe and some superior and middle temporal gyrus, (c) middle temporal gyrus, and (d) inferior occipital pole.

were identified for level matching with the photographic atlas of Matsui & Hirano (1978), and the method developed at NIMH (Buchsbaum *et al*, 1982, 1984) for extracting the cortical peel was applied (Fig. 1). This same method also has been adopted by Jernigan *et al* (1985) and Sheppard *et al* (1983).

The *a priori* hypothesis that the frontal cortex of normals would show increases in relative metabolic rate in the CPT task group was examined first using *t*-tests. Where individual area ratio values previously have been reported to show differences between normals and schizophrenics with *t*-tests, we have used one-tailed *t*-tests for glucose increases with task. This was followed by: (a) four-way analysis of variance (ANOVA, BMDP 2V; Dixon, 1982) with independent groups (task, no-task, or controls task, schizophrenics task) as one dimension and repeated measures for slice level (supra-, mid- and infraventricular), hemisphere (left, right) and sector (anterior to posterior) using conservative or Huyhn–Feldt adjusted degrees of freedom; (b) ANOVA on simple interactions where three-way or higher interactions were found; (c) *t*-tests on collapsed means following significant interactions; and (d) *t*-tests on all cells, identified as exploratory analyses.

The same statistical approach was used to compare controls and schizophrenics for a replication of earlier methods. First, where we have previously reported *t*-tests as significant, we used one-tailed *t*-tests in replication. Then, we computed a four-way ANOVA with diagnostic group as an independent dimension (normals and schizophrenics both doing the CPT) and with slice level (supra-, mid- and infraventricular), hemisphere (right, left) and anteroposterior cortical position (sectors numbered 1 through 4 from front to back), as repeated-measures dimensions. Previous studies would be confirmed by a significant diagnostic group by anteroposterior sector interaction, indicating a different pattern of sector means from front to back in the two groups.

Results

Frontal lobe metabolic rate change with task in normal subjects

The measure most comparable with the blood-flow studies of Ingvar & Franzen (1974) and Weinberger *et al* (1986) is the mean across the three slice levels for the frontal lobe,

TABLE I

Activation by task within normal subjects: relative glucose use (mean/whole-slice mean) at supraventricular, midventricular, and infraventricular levels

	Controls			
	CPT		*CPT no task*	
	Left	*Right*	*Left*	*Right*
Supra-, mid- and infra-slice levels combined				
Anterior	1.11 ± 0.04	1.15 ± 0.05	1.10 ± 0.06	1.12[1] ± 0.05
Midanterior	1.04 ± 0.05	1.14 ± 0.05	1.05 ± 0.04	1.10[2] ± 0.04
Midposterior	0.96 ± 0.06	1.06 ± 0.06	0.96 ± 0.04	1.00[2] ± 0.07
Posterior	1.00 ± 0.05	1.04 ± 0.05	1.00 ± 0.05	1.04 ± 0.06
Supraventricular				
Anterior	1.07 ± 0.09	1.13 ± 0.10	1.06 ± 0.09	1.08 ± 0.07
Midanterior	1.07 ± 0.08	1.16 ± 0.08	1.05 ± 0.08	1.10[2] ± 0.08
Midposterior	0.97 ± 0.07	1.05 ± 0.08	0.95 ± 0.07	1.00[2] ± 0.07
Posterior	1.07 ± 0.10	1.13 ± 0.12	1.08 ± 0.08	1.10 ± 0.10
Midventricular				
Anterior	1.10 ± 0.04	1.12 ± 0.05	1.08 ± 0.07	1.10 ± 0.05
Midanterior	1.10 ± 0.05	1.21 ± 0.06	1.11 ± 0.05	1.17[2] ± 0.05
Midposterior	0.95 ± 0.10	1.06 ± 0.06	0.97 ± 0.07	1.00[2] ± 0.09
Posterior	0.93 ± 0.08	0.98 ± 0.07	0.93 ± 0.08	1.00 ± 0.05
Infraventricular				
Anterior	1.16 ± 0.07	1.21 ± 0.06	1.15 ± 0.08	1.18 ± 0.08
Midanterior	0.94 ± 0.05	1.06 ± 0.08	0.98 ± 0.08	1.05 ± 0.08
Midposterior	0.98 ± 0.04	1.07 ± 0.06	0.97 ± 0.04	1.00[2] ± 0.10
Posterior	0.99 ± 0.08	1.02 ± 0.06	0.99 ± 0.09	1.01 ± 0.08

ANOVA summary: task by level by hemisphere by anteroposterior sector interaction, not significant. Main effect of task, $F = 10.38$, d.f. = 1,35, $P = 0.0028$. Level effect: $F = 4.89$, d.f. = 1.48, 51.70, $P = 0.019$ (Huyhn–Feldt adjusted d.f.). Hemisphere effect: $F = 68.08$, d.f. = 1,35, $P = 0.000$. Sector effect: $F = 57.44$, d.f. = 2.69, 94.20, $P = 0.000$. Task by hemisphere interaction: $F = 6.46$, d.f. = 1,35, $P = 0.0156$. Task by hemisphere by sector, trend effect, $F = 4.47$, d.f. = 1,35, $P = 0.04$. Level by hemisphere by sector, $F = 2.71$, d.f. = 4,157, $P = 0.02$. Other interactions not significant. Effect of age covariance; main effect of task $F = 5.54$, $P = 0.025$.

1. Significantly different from CPT no-task group by *t*-test, one-tailed, $P < 0.05$.
2. Significantly different from CPT no-task group by *t*-test, two-tailed, $P < 0.05$.

because these investigators similarly collapsed data across blood-flow detectors. For each sector (see Fig. 1), we calculated relative metabolic rate (sector/whole-slice mean). Significantly higher relative metabolic rate was observed with task for the right frontal lobe, sector R1 (mean = 1.15, s.d. = 0.05), than for the no-task control visual stimulation (mean = 1.12, s.d. = 0.05); this was confirmed by *t*-test ($t = 1.83$, $P < 0.05$, one-tailed; see also top of Table I). Higher rates were also observed for right posterior frontal cortex (R2) at the supraventricular level (Table I).

This pattern of higher right frontal and right parietal relative metabolic rates when normal subjects performed the task was also confirmed in our specified sequence of analysis, with the four-way ANOVA (Tables I and II). Because each sector metabolic rate is divided by whole-slice mean, a significant main effect of task reflects an increase in the cortical : non-cortical ratio, and a task by hemisphere interaction indicates a general right hemisphere increase with task performance (Table II). The task by hemisphere by sector trend effect (Table I) is associated with the larger right posterior frontal (R2) and parietal/temporal (R3) metabolic rates seen with task than with control stimulation. Simple interaction ANOVA on the right and left hemisphere separately revealed a trend effect (anteroposterior position by task group, $P = 0.06$) for the right side, but no significant interaction on the left.

With *t*-tests collapsed across levels, sectors R2 and R3 (see Fig. 1, containing parietal lobe at the supraventricular level and temporal lobe at the mid- and infraventricular level) reach significant levels for task activation for the right hemisphere (Table I). Simple interaction ANOVA on the three levels (supra-, mid-, and infraventricular; presented because of the appearance of similar analyses in other reports and our analyses of differences between controls and patients) revealed significant task and hemisphere by task interactions at the supraventricular level, anteroposterior position by task by hemisphere interactions at the midventricular level, and task by hemisphere and anteroposterior position by task interactions at the infraventricular level ($P < 0.05$, d.f. = 1,35, for task by hemisphere, and d.f. = 2.4, 81, for anteroposterior position by task, Huynh–Feldt correction). Lastly, exploratory *t*-tests on the 12 left-sided sectors showed no significant differences between them on task activation.

Task performance and relative metabolic rate

We explored the relationship in the controls between CPT task performance (d') and relative metabolic rate for each cortical sector by calculating correlation coefficients. The right midposterior sector on the midventricular slice reached 0.56 ($P < 0.05$) indicating that individuals with relatively higher metabolic rates in this area performed better. No other sector value reached $P < 0.05$.

TABLE II

Hemispheric activation by task within normal groups: glucose use (sector/whole-slice mean)

	Left	*Right*
CPT task	1.03 ± 0.08	1.10 ± 0.07
No task	1.03 ± 0.07	1.07 ± 0.07

ANOVA, task by hemisphere interaction, $F = 6.46$, d.f. = 1,35, $P = 0.016$.

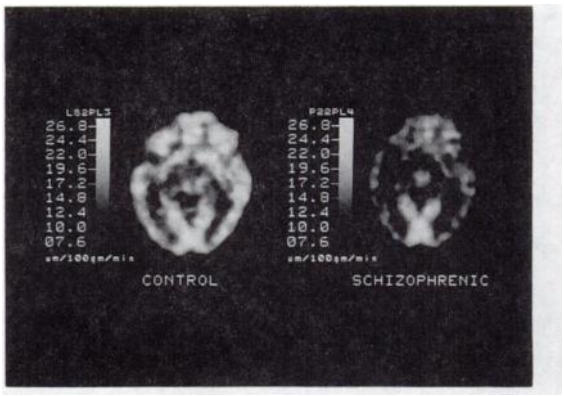

FIG. 2 Typical infraventricular level PET scan in normal control and patient with schizophrenia. Scale is μmol glucose/100 g brain/min and represented as slice maximum to slice minimum in nine steps of grey. Both subjects have frontal lobes appearing on the slice below this one, so that decrease in metabolic rate cannot be due entirely to partial-volume effects. Individual differences in slice appearance are illustrated by this pair.

Differences between patients with schizophrenia and normal controls

Patients showed lower activity in the frontal region than normal controls as assessed by both relative and absolute metabolic rates. Typical PET scans are shown in Fig. 2.

Analyses were carried out in parallel with the comparisons in normals examining the task effects. For the frontal lobe collapsed across the three slices, patients with schizophrenia had lower relative metabolic rates than controls in the right (1.10 v. 1.15) and left (1.07 v. 1.11) anterior sectors ($P < 0.025$, one-tailed). Next, the four-way ANOVA confirmed a significant group by anteroposterior sector interaction (Table III) as well as a group by hemisphere by anteroposterior sector interaction, and a group by level by hemisphere by sector interaction (Fig. 3 and Table IV).

TABLE III

Differences between schizophrenics and normals during degraded-stimulus CPT: group × sector interaction for relative glucose use (sector/whole-slice mean)

Cortex sector	*Controls (n = 18)*	*Schizophrenics (n = 13)*
1	1.13 ± 0.05	1.08 ± 0.04
2	1.09 ± 0.09	1.09 ± 0.09
3	1.01 ± 0.05	1.01 ± 0.03
4	1.00 ± 0.05	1.04 ± 0.07

ANOVA group by sector interaction, $F = 3.61$, d.f. = 2.98, 86.39, $P = 0.0167$.

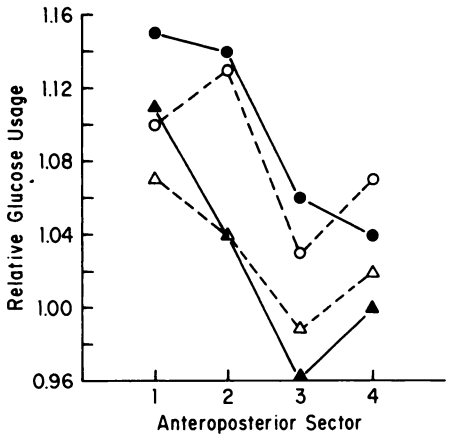

FIG. 3 Relative glucose metabolic rate from front (1) to back (4) across scan levels. There is a diminished difference between right and left hemispheres in schizophrenics, especially for sector 3. (●——● normal, right; ○- - -○ schizophrenic, right; ▲——▲ normal, left; ▵- - -▵ schizophrenic, left.)

Next, simple interactions were examined, with three-way ANOVA on right- and left-sided data separately. Group by anteroposterior sector interactions were confirmed for both sides separately ($P=0.01$ for the right, $P=0.029$ for the left), but the pattern of activity across sectors is somewhat different. Both hemispheres show less increase in activity in schizophrenic patients than normal subjects from the posterior to the anterior sectors; but the patients show less difference between right and left in the temporoparietal sector (Fig. 3). A supplementary ANOVA omitting the two left-handed schizophrenics confirmed the same laterality effects and showed an additional four-way interaction ($F=2.89$, d.f. = 6, 102; $P=0.01$).

Hypofrontality ratios

The relative hypofrontality reported in our earlier studies is more robust at mid- and infraventricular levels in the current data. Analyses were carried out on front:back (sector L1:L4 and R1:R4) ratios (Table V), using the frontal:occipital ratio of 1.05 as a cut-off score, found to be a useful criterion in our 1982 and 1984 studies. For the infraventricular slice, we identified 7 of 13 schizophrenics

TABLE IV

Differences between schizophrenics and normals during degraded-stimulus CPT: relative glucose use (sector mean/whole-slice mean) at supraventricular, midventricular, and infraventricular levels

	Controls		*Schizophrenics*	
	Left	*Right*	*Left*	*Right*
Supra, mid and infra levels combined				
Anterior	1.11 ± 0.04	1.15 ± 0.05	1.07[2] ± 0.06	1.10[2] ± 0.07
Midanterior	1.04 ± 0.05	1.14 ± 0.05	1.04 ± 0.03	1.13 ± 0.04
Midposterior	0.96 ± 0.06	1.06 ± 0.06	0.99 ± 0.05	1.03 ± 0.05
Posterior	1.00 ± 0.05	1.04 ± 0.05	1.02 ± 0.06	1.07 ± 0.04
Supraventricular				
Anterior	1.07 ± 0.09	1.13 ± 0.10	1.04 ± 0.05	1.09 ± 0.08
Midanterior	1.07 ± 0.08	1.16 ± 0.08	1.09 ± 0.07	1.17 ± 0.07
Midposterior	0.97 ± 0.07	1.05 ± 0.08	1.00 ± 0.07	1.06 ± 0.06
Posterior	1.07 ± 0.10	1.13 ± 0.12	1.08 ± 0.09	1.12 ± 0.07
Midventricular				
Anterior	1.10 ± 0.04	1.12 ± 0.05	1.05[1] ± 0.10	1.06[2] ± 0.09
Midanterior	1.10 ± 0.05	1.21 ± 0.06	1.10 ± 0.05	1.19 ± 0.05
Midposterior	0.95 ± 0.10	1.06 ± 0.06	1.02[2] ± 0.05	1.02 ± 0.06
Posterior	0.93 ± 0.08	0.98 ± 0.07	0.92 ± 0.07	1.01 ± 0.06
Infraventricular				
Anterior	1.16 ± 0.07	1.21 ± 0.06	1.12[1] ± 0.06	1.14[2] ± 0.07
Midanterior	0.94 ± 0.05	1.06 ± 0.08	0.94 ± 0.05	1.03 ± 0.07
Midposterior	0.98 ± 0.04	1.07 ± 0.06	0.96 ± 0.08	1.00[2] ± 0.08
Posterior	0.99 ± 0.08	1.02 ± 0.06	1.06[2] ± 0.07	1.08[2] ± 0.06

ANOVA summary: group by level by hemisphere by anteroposterior sector interaction, $F=2.37$, d.f. = 6, 174, $P=0.0313$ (Huyhn–Feldt adjusted d.f. used). Main effect of group, not significant. Level effect: $F=11.49$, d.f. = 1.46, 42.44, $P=0.0004$. Hemisphere effect: $F=55.48$, d.f. = 1, 29, $P=0.000$. Sector effect: $F=32.31$, d.f. = 2.97, 86.39, $P=.000$. Group by sector interaction: $F=3.61$, d.f. = 2.98, 86.39, $P=0.0167$. Group by hemisphere by sector interaction, $F=3.41$, d.f. = 2.90, 83.96, $P=0.023$. Other interactions are NS.

1. Significantly different from normal control group by *t*-test, one-tailed, $P<0.05$.
2. Significantly different from normal control group by *t*-test, two-tailed, $P<0.05$.

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TABLE V
Differences between schizophrenics and normals during degraded-stimulus CPT: frontal:occipital ratios

	Controls			Schizophrenics		
	Left	*Right*	*Combined*	*Left*	*Right*	*Combined*
Supraventricular	1.00	1.00	1.00	0.97	0.97	0.97
Midventricular	1.19	1.15	1.17	1.14	1.05**	1.10*
Infraventricular	1.18	1.18	1.18	1.06**	1.07***	1.07***

One-tailed *t*-tests contrasting controls and schizophrenics: *$P<0.025$, **$P<0.01$, ***$P<0.0025$.

as hypofrontal but only 1 of 17 normals. Thus, we obtain a sensitivity of 53% and a specificity of 94%.

Absolute metabolic rates

Metabolic rate (μmol glucose/100 g brain/min) was lower in the frontal region of patients with schizophrenia than normal controls (Table VI). Patients had significantly lower metabolic rates in the R1 sector collapsed across levels as well as lower metabolic rates in the R1, L1, R2, and L2 sectors at mid- and infraventricular levels. R3 and R4 sectors were not different. ANOVA confirmed an anteroposterior sector by group interaction; this can be seen by examining the mean values for levels combined and hemispheres combined (schizophrenic values in top right-hand corner of Table VI). Here schizophrenics showed a gradient of only 0.7 μmol from front to back (18.3–17.6), whereas normals showed a gradient of 2.2 μmol (21.7–19.5); this represents a reduction of anteroposterior gradient to only 32% of normal in the patients. The entire pattern of regional metabolism is actually different between the groups, as confirmed by the significant four-way interaction. Note that overall glucose metabolic rate across all locations was not significantly different between normals (20.4) and patients (17.9; $P=0.18$, see footnote to Table VI).

TABLE VI
Glucose metabolic rate (μmol/100 g/min) during degraded-stimulus CPT

	Controls						Schizophrenics					
	Left		*Right*		*Combined*		*Left*		*Right*		*Combined*	
	mean	*s.d.*	*mean*	*s.d.*	*mean*	*s.d.*	*mean*	*s.d.*	*mean*	*s.d.*	*mean*	*s.d.*
Levels combined												
Anterior	21.3	6.5	22.1	6.7	21.7	6.6	18.1*	4.4	18.5*	4.4	18.3	4.4
Midanterior	19.9	5.2	22.0	6.3	21.0	5.9	17.7	3.8	19.2	3.8	18.5	3.8
Midposterior	18.4	5.6	20.4	6.4	19.4	6.0	16.7	3.8	17.3	3.7	17.0	3.7
Posterior	19.0	5.7	19.9	5.9	19.5	5.7	17.1	3.1	18.0	3.1	17.6	3.1
Combined	19.7	5.8	21.1	6.3	20.4	6.0	17.4	3.8	18.3	3.7	17.9	3.7
Supraventricular												
Anterior	20.9	10.1	21.9	10.3	21.4	10.2	19.4	5.1	20.3	5.5	19.8	5.3
Midanterior	21.0	9.9	22.7	10.7	21.4	10.3	20.3	5.3	22.0	5.3	21.2	5.3
Midposterior	19.3	10.0	21.0	11.0	20.2	10.5	18.6	4.6	19.8	5.0	19.2	4.7
Posterior	20.9	9.8	21.9	10.1	21.4	10.0	20.1	4.7	20.9	4.4	20.5	4.5
Combined	20.5	9.9	21.9	10.4	21.2	10.1	19.6	4.8	20.8	4.9	20.2	4.8
Midventricular												
Anterior	22.6	6.1	23.0	6.2	22.8	6.1	18.0***	5.0	19.0***	4.5	18.0	4.7
Midanterior	22.4	5.4	24.9	6.4	23.7	5.9	18.7**	3.7	20.2**	3.9	19.5	3.7
Midposterior	19.1	4.8	21.6	5.6	20.4	5.1	17.2	3.8	17.2**	3.3	17.2	3.5
Posterior	18.8	5.1	19.9	5.5	19.3	5.2	15.4**	2.9	17.0	3.3	16.2	3.0
Combined	20.7	5.2	22.4	5.8	21.6	5.5	17.3	3.7	18.1	3.6	17.7	3.7
Infraventricular												
Anterior	20.4	5.1	21.4	5.5	20.9	5.3	16.9***	3.7	17.3***	3.8	17.0	3.7
Midanterior	16.2	3.2	18.4	4.2	17.4	3.7	14.0	2.9	15.3**	3.2	14.7	3.0
Midposterior	16.9	3.8	18.7	4.4	17.8	4.1	14.3	3.5	15.0**	3.6	14.7	3.4
Posterior	17.2	4.3	17.8	4.3	17.5	4.3	15.7	2.6	16.1	2.7	15.9	2.6
Combined	17.7	4.0	19.1	4.5	18.4	4.2	15.2	3.1	15.9	3.1	15.6	3.1

ANOVA summary: group effect, $F=1.85$, $P=0.18$; level, $F=8.2$, d.f. = 2,58, $P=0.006$; level by group, $P=$ NS; hemisphere, $F=58$, $P<0.0001$; anteroposterior position, $F=39$, $P<0.0001$; group by anteroposterior sector, $F=3.33$, d.f. = 2,61, 75.7, $P=0.029$; group by hemisphere by anteroposterior sector, $P=0.0071$; group by level by hemisphere by anteroposterior sector, $P=0.017$ by Huyhn–Feldt. Ohter interactions, NS. *$P<0.05$, one-tailed; **$P<0.05$, two-tailed; ***$P<0.02$, one-tailed.

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Task performance and relative metabolic rate

Those normal subjects who performed best on the CPT tended to show relatively higher metabolic rates in the right temporoparietal region, but among schizophrenics this relationship was reversed. For schizophrenic patients, the correlation coefficient between relative metabolic rate in the R3 sector, midventricular level and d' score was -0.57 ($P<0.05$) in the patients, indicating that worse performance was associated with relatively higher levels; no other sector was significant (-0.50 at supraventricular level, -0.33 at infraventricular level). This was also the only sector to reach significance in normals ($r=0.56$) and the difference in correlation coefficients between normals and schizophrenics is also statistically significant (Fisher's z test, $P<0.05$). CPT performance was better in normals (mean d' score = 2.50; s.d. = 0.93) than in schizophrenics (mean = 2.16, s.d. = 0.85) but this difference was not significant.

Clinical correlations with relative metabolic rate

On an exploratory basis, we calculated correlation coefficients between the anteroposterior ratio (infraventricular level, R1 : R4) in the patients (chosen because it yielded the most robust group differences) and age ($r=-0.58$, $P<0.05$), age of onset ($r=-0.54$, NS), length of neuroleptic treatment ($r=0.34$, NS), BPRS positive symptoms ($r=0.43$, NS), SANS ($r=-0.08$, NS) and CPT d' ($r=0.03$, NS). Neither BRPS anxiety nor depression correlated significantly with the anteroposterior level for any of the three levels or hemispheric sides. The anxiety correlations were all positive (0.39, 0.43, 0.38) for the three levels, thus not supporting the suggestion that hypofrontality could be associated with increased patient anxiety.

Since age was a significant correlate of anteroposterior ratio, we entered age as a covariate in an ANOVA with anteroposterior ratios for left and right hemisphere at three levels, comparing normals and schizophrenics. A significant diagnostic group effect was confirmed ($F=9.24$, d.f. = 1,28, $P=0.005$). Age-adjusted infraventricular level ratios for the right hemisphere were 1.17 in normals and 1.07 in schizophrenics.

Discussion

There were three major findings: the relative increases in glucose metabolic rate with attentional task performance in normals in the right frontal and right temporoparietal regions, a replication of earlier findings of relative hypofrontality in patients with schizophrenia, and anatomical overlap between areas of the brain activated by the task and those differing between patients and controls.

Schizophrenia and neuroanatomical models of attention

Behavioural studies have emphasised that attention is not a unitary phenomenon, but instead refers to complex interactions between mental operations such as focusing on or engaging a target, sustaining the focus over time, encoding stimulus patterns, and disengaging and shifting the focus (Davies & Parasuraman, 1982; Posner & Presti, 1987; Mirsky & Duncan, 1989). This complexity is recognised in neuroanatomical models of attentional functioning, which posit the involvement of a network of interrelated brain areas. As summarised by Mesulam (1985) and Mirsky & Duncan (1989) the pre-frontal cortex supports planning and executive functions, including shifts of attentional focus, and is hypothesised to include a motor representation of extrapersonal space in the frontal eye fields and adjacent polymodal cortex. The inferior parietal lobule and superior temporal sulcus are a polymodal sensory convergence area that is hypothesised to serve as a sensory representation of extrapersonal space and to have an important role in focusing on a target stimulus. The cingulate cortex may play a role in motivational aspects of attention, including evaluation of relevance. Finally, the reticular activating system, including brainstem reticular formation and reticular thalamic nuclei, regulates attentional tone through ascending and descending pathways.

For the current analysis of cortical deficits in schizophrenia, the frontal and temporoparietal components of the attentional network are particularly important. Recent PET evidence (see review by Buchsbaum & Haier, 1987) and electrophysiological evidence (Strandburg *et al*, 1984; Buchsbaum *et al*, 1986) indicate that frontal areas are a prominent site of differences between schizophrenic patients and control subjects. The parietal cortex has also been a site of differences between schizophrenic patients and controls in topographic electrophysiological studies (Strandberg *et al*, 1984; Buchsbaum *et al*, 1986). In addition, many of the most commonly found neuropsychological impairments in adult schizophrenic patients and children at risk for schizophrenia, such as disturbances in visual search, visual/motor integration, graphaesthesia, right–left orientation, and fine motor co-ordination, may be mediated by pre-frontal and right parietal cortex (see Asarnow, 1982, for a review). Thus, our findings of relative increases in glucose metabolic rate in right frontal and temporoparietal cortex during performance of the degraded-stimulus CPT is consistent with current neuroanatomical models of attentional functioning. Furthermore, the lower metabolic rate of schizophrenic patients in frontal and right temporoparietal areas during the CPT can be understood in the context of these models.

Replication of previous studies

Our results in this study are generally consistent with the majority of reports of PET and regional cerebral blood flow. The current data match our 1982 and 1984 studies in revealing a difference in anteroposterior gradient tested by ANOVA, and a difference in frontal:occipital ratios tested by *t*-test. We have reported our data in this way to facilitate cross-study comparison, and to provide evidence for a specific regional pattern rather than global brain metabolic change. In our recent review (Buchsbaum & Haier, 1987) we summarised the right frontal: occipital ratio data from seven studies. This summary revealed significantly lower frontal:occipital ratios in schizophrenics than in normals in three studies (Buchsbaum *et al*, 1982; 1984; Farkas *et al*, 1984) and non-significantly lower ratios in the remaining four (Sheppard *et al*, 1983; Jernigan *et al*, 1985; Wolkin *et al*, 1985; Kling *et al*, 1986). Of the four studies published since then, Volkow *et al* (1987) and Cohen *et al* (1987) also found lower ratios in schizophrenics, Gur *et al* (1987) found normals and patients equal, and Early *et al* (1987) do not present data in tabular form to allow evaluation of the frontal:occipital ratio.

These studies differ widely in uptake conditions, size and location of the regions of interest, medication status of patients, demographic features, and sample size. Cross-study comparisons are difficult but not entirely uninstructive. A modest consistency appears, congruent with levels of type II statistical error inherent in these small samples; the work shows reduced frontal cerebral blood flow (see Buchsbaum & Haier, 1987), formulations of Ingvar (1979), Levin (1984), and Weinberger (1987) on the role of the frontal cortex in schizophrenia, and heterogeneity of schizophrenic diathesis (Buchsbaum & Rieder, 1979).

Magnitude of relative hypofrontality

The size of the effect can be assessed by examining the diminution of the normal anteroposterior gradient in patients, the relative relationship to one standard deviation in normals, and the comparable sensitivity and specificity in other biological marker studies. The size of the effect must also be considered in the context of the biological heterogeneity of patients with schizophrenia.

The decrease in normal anteroposterior gradient is in a range compatible with significant pathophysiology in about half the patients. The normal front–back gradient is 11% (1.15–1.04, right side, levels combined, Table IV) but only 3% (1.10–1.07) in patients, a reduction to a level only 27% of normal. Similar contrasts are seen in examining metabolic rate, where normals show a gradient of 2.2 μmol/100 g/min (22.1–19.9, right side, levels combined, Table VI) but patients show a gradient of 0.5 (18.5–18.0), a reduction to 23% of normal levels. The change in gradient from 2.2 to 0.5 is 1.7 μmol/100 g/min, which is 8% of the normal frontal metabolic rate. In comparison, cortical metabolic rate change with painful electric shock was 1.68 μmol, a change of 6% (Buchsbaum *et al*, 1983) and the difference between eyes closed and eyes open was 10% (Phelps *et al*, 1981).

The size of the effect for the right anterior:posterior ratio in standard units is 1.10 (1.18 in normals, 1.07 in patients, 0.10 standard deviation). This is in the same range as the other blood-flow and PET studies reviewed elsewhere (Buchsbaum & Haier, 1987) and in the range expected by statisticians for psychiatric studies (Bartko, 1990).

The sensitivity (53%) and specificity (94%) of the 1.05 anteroposterior gradient (the criterion established in our 1982 study) in this study is in the range of those reported for other biological tests in psychiatry (see review by Buchsbaum & Haier, 1987). For the 1984 data, we found 11 of 16 schizophrenics hypofrontal but only 7 of 19 controls; this is a sensitivity of 68% and a specificity of 63%. The current sensitivity parallels the findings that poor CPT performance characterises about half of schizophrenic in-patients (Orzack & Kornetsky, 1966; Walker & Shaye, 1982). Use of the CPT as the uptake task appeared to enhance the specificity without changing sensitivity, the change expected with a task more salient for schizophrenia. With heterogeneity among schizophrenics for the frontal lobe diathesis, a lack of improvement in sensitivity is not unexpected.

Hemispheric laterality

The metabolic rate of the whole right hemisphere cortical surface was higher than that of the left, and this difference was larger during active execution of the CPT task than during passive viewing. The difference was greatest at the mid- and infraventricular levels in the midanterior and midposterior segments, and least for the supraventricular level in the anterior and posterior segments (Table I). This higher-activity area is located on average in the superior and middle temporal gyrus and inferior anterior parietal lobe (Brodmann's areas 40, 41, 42, 22, 37, 27, part of 39).

Patients with schizophrenia in PET studies with controls who were more right than left active (all eyes closed) were relatively less right-activated than

controls in three studies (Buchsbaum *et al*, 1983; Jernigan *et al*, 1985; Wiesel *et al*, 1987) and equally right activated in two (Wiesel *et al*, 1985; Gur *et al*, 1987). However, patients in studies with controls who were more left activated than right (all eyes open) showed relatively greater right activation (Wolkin *et al*, 1985; Volkow *et al*, 1987; Kling *et al*, 1986 for low frontal region). These shifts are small, and not uniformly evaluated statistically in these reports. However, they suggest that schizophrenic patients may have different lateralisation patterns than controls, and that having them do a specific task during uptake may be crucial for exploring hemispheric contrasts.

The perceptually degraded nature of the stimuli presented during the CPT (Nuechterlein *et al*, 1983) may be a contributor to the greater metabolic rate in the right hemisphere. Beyond the overall demand for ongoing vigilance that characterises the CPT, the specific cognitive processes required for detection of the target in different versions of the task may vary. Degraded stimuli have been shown to yield a right hemisphere performance advantage in studies of normal subjects (Hellige, 1982; Moscovitch, 1979; Sergent, 1983). This superiority of right hemisphere processing for degraded stimuli has been interpreted as being due to the greater capacity of the right hemisphere to extract critical features of a degraded stimulus through a holistic mode of processing or, alternatively, to do more efficient processing of stimuli of reduced energy (Hellige, 1982; Sergent, 1983). However, the right hemisphere may have a larger role in regulating overall attentional tone than the left hemisphere (Mesulam, 1985). Thus, it is possible that right-sided differences are integral to the deficits in directed attention shown by schizophrenic patients or, alternatively, that the degraded-stimulus CPT emphasises right-sided differences due to the degraded nature of its stimuli.

Relative frontal lobe hypofunction and task

In studies which have evaluated frontal lobe function both in resting and in performing schizophrenics, contrasts with normals appear stronger during tasks. Our own current data show the whole frontal lobe both relatively and absolutely lower in schizophrenics during the CPT, while scans from schizophrenics resting with eyes closed (Buchsbaum *et al*, 1982) reached significance only on ratios and only at the supraventricular level. Cerebral blood flow during Wisconsin Card Sort Test showed stronger evidence of hypofrontality than during rest (Weinberger *et al*, 1986), although resting schizophrenics were significantly hypofrontal as well (confirmed by ANOVA; ratios of 1.12 in normals and 1.07 in schizophrenics appear in their fig. 4). Volkow *et al* (1987) also concluded that an eye tracking task enhanced group differences.

Performance deficit and brain imaging

Brain imaging data extend the widely observed finding that schizophrenics perform poorly on attentional tasks by identifying the neuroanatomical basis of normal performance and the deficit in schizophrenia. In normals we demonstrated increases in relative metabolic rate in frontal and right parietal and temporal regions with task performance in comparison to passive viewing of the visual stimuli. No task-related differences were observed in visual centres. Normals who performed relatively better had higher relative metabolism in the right parietal area. Patients with schizophrenia differed from normals in a pattern which suggested a differing organisation of task performance rather than merely passive viewing, a hypothesis difficult to reject on psychophysical data alone. While the patients showed lower right and left frontal metabolic rate, tendencies for left parietal and both left and right visual areas to be higher than normal (see Fig. 3 and compare Tables I and IV) suggest the activation of brain areas apparently less engaged by normals. Poor organisation of task performance and activation of less appropriate, efficient, or capable brain areas might be a consequence of diminished frontal lobe function. The pervasive finding of hypofrontality across several tasks and during resting states may be associated with impairment in executive functions of the frontal lobe. Its work, one step out of the direct operational chain for many tasks, might be expected to be more poorly correlated with performance scores than other task-specific brain regions, in this case the right temporoparietal area.

Alternatively, compensatory but not wholly restorative shifting of metabolic work from dysfunctional regions in frontal and right temporoparietal cortex to left temporoparietal and occipital cortex may occur in schizophrenia. The intriguing difference in correlations between task performance and metabolism, positive and significant in normals, negative and significant in patients, suggests right temporoparietal inefficiency in patients. A failure to use alternative cognitive strategies and shift degraded-stimulus CPT work to another cortical area in individuals with dysfunctional cortex in this region or failure to coordinate joint right parietal/right frontal information processing might yield such a result.

These findings, that regions of metabolism activated "during a well-defined cognitive task are

not completely co-extensive with the region associated with task performance in normal subjects", meet Matthysse's (1986) criteria for revealing new models of the schizophrenic process. Because tasks seem to shift areas of relative hypoactivation within the frontal cortex, as seen in our finding of maximal hypofrontality in superior levels with rest and in inferior levels during the CPT, detailed analysis of the frontal lobe with gyrus by gyrus statistical testing seems a critical next step.

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*Monte S. Buchsbaum, MD; Richard J. Haier, PhD; Joseph Wu, MD; Nancy Sicotte; Erin Hazlett; Stephen Potkin, MD; Steven Guich, *Department of Psychiatry & Human Behavior, University of California, Irvine, Medical Sciences I, Room D-404, Irvine, California 92717*; Keith H. Nuechterlein, PhD; Robert Asarnow, PhD, *Psychiatry & Biobehavioral Sciences, Neuropsychiatric Institute, University of California, Los Angeles, 1010 Westwood Boulevard, Los Angeles, California 90024, USA*

*Correspondence