

Conf- 820593--1

BNL 31442

Regional Glucose Metabolism Using PETT in Normal and
Psychiatric Populations

MASTER

BNL--31442

DE02 016752

Brodie, J.D.* , Wolf, A.P.+ , Volkow, N.* , Christman, D.R.+ ,
DeFina, P.* , DeLeon, M.* , Farkas, T.* , Ferris, S.H.* ,
Fowler, J.S.+ , Gomez-Mont, F.* , Jaeger, J.* , Russell, J.A.G.+ ,
Stamm, R.+ and Yonekura, Y.+

* New York University Medical Center, 550 First Ave., New York, NY 10016

+ Brookhaven National Laboratory, Upton, New York 11973

Acknowledgement

This research was supported in part by the Department of Energy, Office of Health and Environmental Research and Public Health Service Grant NS-15638. The authors thank Dr. A.B. Brill, Dr. B. Jones, Ms. A. A. Farrell and Ms. K. Karlstrom for their assistance.

DISCLAIMER

This work was prepared for the U.S. Government by the Brookhaven National Laboratory, Upton, New York, under contract number DE-AC02-76SF00090. The U.S. Government is authorized to reproduce and distribute reprints for government purposes not withstanding any copyright notation that may appear hereon. This work is not to be distributed outside the U.S. Government.

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED

229

INTRODUCTION

Psychiatry deals with abnormal behavior, but normality has been very difficult to define, given the wide range of variations in normal populations caused by the interaction of biological, cultural and social factors (Von Bertalanffy, 1968). Over the past 25 years, there has been increasing interest in the biological concomitants of mental illness. The primary focus of most studies has been on pathology, although a biochemical framework for non-pathological mental functioning has yet to be established in humans. Several years ago, we initiated a study of regional brain metabolism in a group of rigorously defined normal subjects, designed to provide a reference for other human investigations in the Brookhaven National Laboratory-New York University program. Thus far we have studied ^{18}F -2-deoxy-2-fluoro-D-glucose (^{18}FDG) metabolism in about 150 subjects including normals, schizophrenics, senile dementias, and primary affective disorders. The present paper presents some of the data analyzed to date.

MATERIAL AND METHODS

The normal population consisted of 20 males, aged 19 to 59. Inclusion in the study was determined by the absence of medical, neurological, and psychological pathology. Medical exclusions were: a history of severe head trauma, chronic hypertension, significant vascular disorders, diabetes mellitus, thyroid abnormalities and history of psychiatric illness.

Gross psychopathology was identified with the Structured Clinical Interview (SCI), an inventory of 179 yes or no items filled out by the examiner during a 20- to 30-minute interview. The SCI can also be scored for ten overlapping scales: anger, hostility, conceptual dysfunction,

fear, worry, incongruous behavior, incongruous ideation, lethargy, dejection, perceptual dysfunction, physical complaints, self depreciation, and sexual problems. Any significant score beyond the norms on any SCI component automatically excluded the candidate.

Neurologic and neurophysiologic screening included medical history and testing for intelligence (WAIS), anterograde memory (Randt-NYU Memory Test) (Randt, 1980), perceptual-motor function and structure (Bender Visual-Motor Gestalt Test), and handedness (Edinburgh Handedness Inventory (Oldfield, 1971). Subjects also underwent a comprehensive laboratory work-up, a brief neurological screening examination, a CT scan (to provide scans which could be correlated with PETT), a computerized EEG, and visual and auditory evoked potentials (John, Karmel, Corning, 1977).

The schizophrenia group included 13 volunteer white males aged 21 to 54, consensually diagnosed by two psychiatrists on the Research Diagnostic Criteria for schizophrenic disorders (Spitzer, Endicott, Robins, 1973). Schizophrenic candidates were screened for history or presence of significant medical illness and frank neurological disease, for use of drugs other than prescribed psychotropic medication, for laboratory abnormalities (on SMA-12, urinalysis, and thyroid function), and for drug and alcohol abuse. Psychopathology was determined by the Combined Instrument Schedule (CIS) which is a combination of three semi-structured interviews: the PSE (Wing, Cooper, Santonus, 1974) SADS (Endicott, Spitzer, 1978), and CMS (Cooper, Kendell, Gurland, 1969); by a diverse set of perceptual experiments designed to measure a broad spectrum of attention factors; and by a battery of detailed neuropsychological tests

for specific patterns of cognitive, linguistic, and behavioral dysfunction.

In the group of nine patients with affective disorders, five had a diagnosis of unipolar depression, based on RDC criteria, and were clinically depressed at the time of the run. The other four had a diagnosis of manic-depressive psychosis and were clinically manic when the scans were performed.

The senile dementia group consisted of 15 patients, mean age 73. Diagnosis was based on psychiatric, psychometric (Ferris, DeLeon, Wolf, 1980) and CT scan evaluation. A group of 14 elderly subjects, mean age 68, who failed to show pathology by the same diagnostic criteria served as the control group.

All subjects underwent a series of contiguous non-contrast CT-section scans, taken on a GE 8800 instrument at 10 mm intervals at an angle 0° from the canthomeatal (CM) reference line, to correspond to the angle of the positron emission scans. All showed visually normal CT-section scans, which were a requirement for the normal candidates only.

All PETT scans were performed on the PETT III at Brookhaven National Laboratory, using ^{18}F FDG as tracer. Patients fasted for two hours before the procedure. The metabolic images were derived using the extension to humans (Reivich, Kuhl, Wolf, 1979) of the Sokoloff method for deoxyglucose uptake (Sokoloff, Reivich, Kennedy, 1977). Samples for counting and glucose determination were obtained either by arterialization of venous blood through handwarming to 44°C or by direct radial artery cannulation. A venous catheter in the contralateral arm permitted injection of tracer without disturbing the patient. For the 30-minute uptake period, patients

were not touched unless necessary and silence was maintained except for the sounds of the computer and air conditioning fan.

Scanning was started 30-minutes after injection of tracer, with the average time per scan being from 8 to 14 minutes. Scans were analyzed at the "basal ganglia" (CM + 40-50 mm) and at the centrum semiovale (CM + 60-70 mm) level. A histogram was constructed by dividing each metabolic image into 20 levels of glucose metabolic activity in 0.4/100g/min increments. The distribution of the pixels within this histogram was then calculated for the different brain slices of the normal subjects. The range of metabolic activity with the highest number of pixels within a slice was obtained to determine the predominant level of activity in the group.

To obtain a preliminary estimate of the effect of handwarming (for blood arterialization), the location of the regions with highest metabolic activity was determined at the basal ganglia level of 15 normal subjects and 20 schizophrenics. The glucose metabolic activity was classified according to the histogram. The highest 0.4 mg range of glucose metabolism was determined for each subject, with individual pixel belonging to this category classified as belonging to the left hemisphere, the right hemisphere, or the midline area where the two hemispheres merge.

The relation between the anterior and the posterior regions of the brain was determined at the BG and CS levels for the first 11 normal and first 13 schizophrenic subjects. In the basal ganglia scan, the frontal lobe was defined posteriorly by a line bisecting the head of the caudate nucleus perpendicular to the interhemispheric fissure. The region of

interest (ROI) coursed anteriorly to avoid basal ganglia and the anterior horns of the lateral ventricles by approximately 1 to 2 mm on CT scan (about 1 PETT pixel or 0.43 mm in real brain). On the centrum semiovale scan, the posterior border of the frontal lobe was defined by the central sulcus and bypassed the ventricle anteriorly. A nonfrontal region, used for reference purposes in the data analysis, was defined for both levels as the entire area within the skull not included in the frontal region.

For the analysis of patients with senile dementia and their elderly controls, regions of interest in the BG scan included frontal cortex, temporal cortex and caudate nucleus. Correlations between glucose metabolism and cognitive impairment were determined using standardized tests of cortical functioning (Ferris, DeLeon, Wolf, 1980).

RESULTS

All normal subjects showed a unimodal pattern in distribution of pixels on the histogram. The metabolic range with the maximal number of pixels varied at different brain levels in relation to the amount of gray matter, white matter, and cerebrospinal fluid. Three subjects accounted for most of the dispersion. One had a pixel distribution at lower metabolic levels and two were skewed to higher metabolic levels. These deviations from the group pattern appear throughout most of the brain slices. A test-retest design would reveal whether the differences are state dependent or individually characteristic. Given the small number of subjects with deviant patterns, it was not possible to relate the finding to any of the other parameters measured (neurometrics, neuropsychological tests, age).

In 13 of the 20 normal subjects, a left-right asymmetry -- reflected as higher glucose metabolism on the right compared to the left side -- was detected, at the cortical area between the frontal part of the midline gray matter and the cortical area overlying the lateral aspect of the basal ganglia. In 15 of the 20, left-right asymmetry was noted at the temporal cortex of the BG level.

The significance of this finding is currently unclear (Mazziotta, Phelps, Miller, et al., 1981). It could reflect the effects on the brain of the arterialization procedure, which uses a handwarmer on the subject's left hand. Table I shows the location of the pixels with highest metabolic activity for both normal and schizophrenic subjects who underwent a handwarmer procedure and those who did not. Although the number of subjects are small, the higher metabolic activity does seem to occur in the right rather than the left hemisphere.

It has been reported that monaural, non-verbal auditory stimulation, regardless of side stimulated, results in a diffuse frontotemporal asymmetry as well as bilateral parietotemporal activation (Metter, Wasterlain, Kuhl, et al., 1981). Thus the mechanical noise of PETT III could account for the asymmetry. Part of this excess right sided activity may be due to the metabolic reflection of anxiety as reported by (Reivich, 1982). Finally, postmortem brain studies have shown the right frontal hemisphere to be wider than the left (Oldfield, 1971).

The global metabolic rate and the standard deviation at the BG level is summarized in Table 2 for normal, schizophrenic, depressed, and manic subjects. Preliminary results suggest a greater metabolic heterogeneity in the psychiatric population than in normal controls. This may reflect

problems in nosology, severity of illness, state variance, or other factors yet unrecognized. Certainly, these findings warrant cautious examination before pathognomonic features can be ascribed to PETT data. Comparison of the frontal-nonfrontal relationship between 11 normal subjects and 13 schizophrenics at the BG and CS levels suggests it is lower in the schizophrenics (Figure 1). Using covariance analysis with the "nonfrontal slice" as the covariate, this relative difference in frontal activity was significant at the .01 and .05 levels for the basal ganglia and centrum semiovale planes respectively. Although approximately half of the patients were on psychotropic medication at the time of the run, they showed no significantly different metabolic patterns with regard to whole plane of section or frontal-nonfrontal relationship than nonmedicated patients. There was no significant age difference between the two groups.

RCMRG was diminished at the BG levels in patients with dementia in all ROI's examined when compared with controls. Significant correlation was found between the quantitative decline in glucose metabolism and the degree of cognitive impairment (Ferris, DeLeon, Christman, et al., 1981). This change is consistent with the impairment of oxygen metabolism in a similar population (Frackowiak, Pozzilli, Legg, 1981).

A pair of monozygotic twins in the normal group proved to have identical values of neurometric and psychological evaluation. On brain scans, given three week apart, global metabolic rate at the BG and CS level respectively was 3.96 mg/100g/min and 3.76 mg/100g/min for one twin and 4.78 mg/100g/min and 4.67 mg/100g/min for the other. Although values were

different, distribution of grades of metabolic activity at the level of the high BG (CM6) and CS (CM7) were very similar (Figure 2).

DISCUSSION

The metabolic distribution was similar for most of the normal subjects. If this pattern proves to be consistent, it may be a useful parameter for comparison of psychiatric illnesses. Also noteworthy is the finding that similarities in glucose metabolism between the identical twins appeared at the level of their activity distribution rather than on the absolute values. Considering the similarity in all other variables examined, the difference in absolute activity probably represents state dependency but may be attributed to test-retest error.

The unimodal distribution of metabolic activity seen in the normal subjects may be due to an averaging effect secondary to the low resolution of PETT III, or it may reflect metabolic heterogeneity in white and gray matter as a whole (John, Karmel, Corning, 1977).

Comparison of metabolic activity in the younger (Kendell, 1979) versus the older (Ingvar, Schwartz, 1974) normal population revealed no significant differences in global absolute values or metabolic activity distribution.

On comparison of the cerebral metabolic activity between normal and psychiatric populations, we observed differences in both absolute values and patterns of activity. The diminution in the frontal-nonfrontal ratio in the schizophrenics seems to be fairly consistent. Future analysis on the PETT VI instrument should help determine whether this hypofrontality is due to diminution of glucose uptake in the gray matter, in the white

matter, or is a part of a larger distributed alteration in the pattern of glucose utilization. Although these findings may reflect a trait in schizophrenics, a provocative test-retest situation will probably be a more sensitive index of regional cerebral metabolic functioning in this illness. On the other hand, in our studies with Alzheimer's patient, a high correlation was found between degree of cognitive impairment and regional and subregional glucose metabolic rates (Ferris, DeLeon, Christman, 1981).

Because of the small number of subjects with primary affective disorders and their metabolic heterogeneity, no firm conclusions can be drawn at this time. In designing future PETT studies of the affective disorders, however, investigators should keep this heterogeneity in mind and obtain a reliable quantitative description of psychiatric symptom presentation.

Any attempt to find an anatomical focus for behavior or a pattern of behaviors that presents as a psychiatric syndrome presents a number of methodological and analytical problems. For example, the 30-minute glimpse of cerebral glucose metabolism afforded by a PETT study may not be representative. Most psychiatric patients, unless they have irreversible impairment, would not be expected always to be pathological, even in the midst of florid disease. It is difficult to control what is going on in the patient's brain during the study or the level of anxiety and its effects on the metabolic rate. Moreover, the effects of diet and fasting on stress and on regional metabolism itself have not been studied and are difficult to evaluate in the present context. We must depend on

verbalization of behavior. A patient may be able to tell the investigator he heard voices while in the machine but now were these voices reflected in his mental activity? Did they cause great anxiety? Or were they reflected at various times in the uptake of FDG or in metabolic rate changes of different degrees? If we were averaging over a 30-minute uptake and the patient had three minutes of intense mental activity early in the procedure, it might produce a different metabolic pattern than might be observed if it occurred later.

A number of other questions wait to be answered. To what extent are these images affected by utilization of alternative energy sources, for example. The amounts of aerobic versus anaerobic metabolism have never been assessed. There might even be regional metabolic preferences for energy sources other than glucose. Another tracer might reflect patterns of activity substantially at variance with those determined by the glucose method.

Furthermore, when attempting neuroanatomical localization of metabolic activity we will have to take into account that a defined anatomical area is not necessarily functionally homogeneous and that a given function may not be localized.

Perhaps the major problem in applying PETT technology to human behavior lies in the fact that we are dealing with a greater variance than might be reflected in any single biochemical alteration. We are looking for anatomic loci for feeling states or logical thoughts, factors that are not at issue with lower animals. Our search may be chimerical; it may be that the relationships of various mental processes, perhaps reflected by

metabolic activity, will turn out to be far more pertinent than the intrinsic metabolic activity in any given area. This is related to the unresolved issue of the localized versus the distributed fashion in which the human nervous system processes information (Luria, 1980) and it also addresses the distinction between functional differences (uncorrelated areas) as opposed to anatomical differences.

REFERENCES

- Von Bertalanffy L, (1968) General Systems Theory. Braziller, New York.
- Metter EJ, Wasterlain CG, Kuhl DE, et al. (1981) FDG Positron Emission Computed Tomography in a Study of Aphasia. *Ann. Neurol.* 10:173-83.
- Randt CT, et al. (1980) A Memory Test for Longitudinal Measurement of Mild to Moderate Deficits. *Clinical Neuropsychology* 2:184.
- Oldfield RC (1971) The Assessment and Analysis of Handedness. The Edinburgh Inventory. *Neuropsychologia* 9:97-113.
- John ER, Karmel, BZ, Corning WC, et al. (1977) Neurometrics. *Science* 196: 1393-1410.
- Spitzer RL, Endicott J, Robins E (1973) Research Diagnostic Criteria. New York State Department of Mental Hygiene, New York.
- Wing JK, Cooper JE and Sastonus N (1974) The Description and Classification of Psychiatric Symptoms: An Instructional Manual for the P.S.E. and CATE60 System. Cambridge University Press. London.
- Endicott J, Spitzer R (1978) A'diagnostic Interview: The Schedule for Affective Disorders and Schizophrenia. *J. Gen. Psychiatry* 35:837.
- Cooper JE, Kendell RE, Gurland BJ, et al. (1969) Combined Mental State. Cross National Study of Diagnosis of the Mental Disorders: Some Results from the First Comparative Investigation. *Suppl. Amer. J. of Psych.* 125:1-46.
- Ferris SH, DeLeon M, Wolf A, et al. (1980) Positron Emission Tomography in the Study of Aging and Dementia. *Neurobiology of Aging* 1: 127-131.
- Reivich M, Kuhl DE, Wolf A, et al. (1979) The ¹⁸F-Fluorodeoxyglucose Method for the Measurement of Local Cerebral Glucose Utilization in Man. *Circ. Res.* 44:127-137.

- Sokoloff L, Reivich M, Kennedy C, et al. (1977) The ^{14}C -Deoxyglucose Utilization: Theory, Procedure and Normal Values in Conscious and Anesthetized Albino Rat. J. Neurochem. 28:897-916.
- Mazziotta JC, Phelps ME, Miller J, et al. (1981) Tomographic Mapping of Human Cerebral Metabolism: Normal Unstimulated State. Neurology 31:503-516.
- Reivich M (1982) Local Cerebral Glucose Metabolism: Clinical and Physiologic Studies. Presented in International Symposium on Positron Emission Tomography of the Brain. Cologne, Germany, May 1982.
- Ferris SH, DeLeon MJ, Christman D, et al. (1981) Positron Emission Tomography Studies of Regional Brain Metabolism in Elderly Patients. In: Perris C, Struwe G, Janson B (eds) Biological Psychiatry. Elsevier/North Holland Biomedical Press, 280-283.
- Frackowiak RSJ, Pozzilli C, Legg NJ, et al. (1981) Regional Cerebral Oxygen Supply and Utilization in Dementia. Brain 104: 753-778.
- Kendell RE (1979) The Classification of Depressions: A Review of Contemporary Confusion. Brit. J. Psych. 129:15-28.
- Ingvar DH and Schwartz MS (1974) Blood Flow Patterns Induced in the Dominant Hemisphere by Speech and Reading. Brain 96, 274:88.
- Luria AR (1980) Higher Cortical Functions in Man. 2nd edition, Basic Books, New York.