A Method for Comparing Different Procedures of Estimating Regional Glucose Metabolism Using Fluorine-18-Fluorodeoxyglucose

Campbell M. Clark, Edward W. Grochowski, and Walter Ammann

Department of Psychiatry, TRIUMF PET Programme, and Department of Radiology, University of British Columbia, Vancouver, Canada

The purpose of this paper is to describe a method for determining whether a particular procedure for estimating regional metabolism using the deoxyglucose tracer analogue yields better data than another in terms of subsequent statistical analysis. The method is based on a simple model of regional cerebral glucose metabolism with three potential sources of metabolic variability, namely individual differences in cerebral metabolic rate, consistent regional differences and error. When the literature rate constants were compared to a dynamic procedure for estimating regional rate constants in patients with Huntington's Disease, the literature values were clearly superior in that the error component was approximately half (18.5 versus 39.3%). Although these results cannot be generalized to all procedures for estimating regional glucose metabolism, the method can be applied to determine if a particular procedure will be more sensitive than another to differences between groups.

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To date, a number of procedures have been suggested for the estimation of rate constants in the calculation of regional cerebral metabolism (rCMRglc) using the ^{18}F-deoxyglucose trace analogue (FDG) with PET. These procedures range from the commonly-used autoradiographic method using literature rate constants to dynamic estimates of regional rate constants using data from serial scans during the uptake phase (*1–5*). Thus far, the recognized advantages of the autoradiographic method are potentially greater axial sampling, shorter scan times and less sensitivity to errors in the measurement of the input function, as well as its relative simplicity, in terms of programming, data processing and disk storage. In contrast, the advantages of using dynamic rate constants have been theoretically greater accuracy in the estimation of true values of rCMRglc and for application in studies where the tissue is abnormal. However, the improvement in accuracy has only been considered from a mathematical perspective in terms of fitting the regional uptake curve or apparent reductions in regional metabolic variability. An alternate approach would be to compare different procedures in terms of a sensitivity in subsequent data analysis. For example, an estimate of rCMRglc may be considered as the summation of three components, namely, basal metabolic rate, consistent regional effect, and error. From a data analytic standpoint, the best procedure would maximize the regional effect and minimize the error component. With respect to this paper, it should be noted that the earlier studies estimating glucose metabolism using arterial/venous differences found considerable variability in normal basal rates of cerebral metabolism (*6–8*). Although this variability may be the result of small sample sizes as well as the small differences between the measures, these studies do provide an independent benchmark for the level of variability in individual brain metabolism.

In an earlier paper, Clark, Carson, Kessler et al. describe a statistical procedure for partitioning the metabolic variability derived from a number of subjects and regions into these three sources (*9*). The purpose of this study is to suggest and illustrate that this statistical procedure can be employed to determine whether one method for estimating rCMRglc yields better data than another method for the subsequent analysis of rCMRglc. Although the conclusions in terms of efficacy of a specific solution may not directly generalize to all PET centers due to, for example, inherent differences in scanner properties, a decision can be made regarding the best approach for a specific center when conducting clinical studies.

THE STATISTICAL MODEL

The basis for the statistical model is described in detail in Appendix 1. Using this model, measured rCMRglc may be partitioned into three components, namely individual differences in CMRglc or basal metabolic rate, consistent regional variations in rCMRglc and error.

The primary suggestion of this paper is that this model can be applied to two sets of data which only differ in the method employed to estimate rCMRglc. By comparing

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For reprints contact: C. M. Clark, PhD, Department of Psychiatry, 2255 Wesbrook Mall, Vancouver, B.C. V6T 2A1 Canada.

the partitioning of the total metabolic variability into these three potential sources of variability, the method which yields statistically better results can be determined. Specifically, 'better' may be defined as minimizing the error component while maximizing the region component. This statement is true whether one wishes to analyze absolute or relative rates. A second suggestion for subsequent statistical analysis is to ascribe variation unrelated to consistent regional variation to individual difference in CMRglc rather than error. This statement is true when the regional data are standardized using an estimate of average brain metabolism.

To illustrate this approach, two methods of calculating rCMRglc were compared using the same data set. The first was proposed by Hawkins, Phelps and Huang (*4*) and estimates rCMRglc using dynamic regional kinetic rate constants while the second was the standard autoradiographic method using literature values for the rate constants (*1*). Although Hawkins, Phelps, and Huang (*4*) developed this method for the specific case where literature rate constants were not appropriate (i.e., tumors), the question still arises whether this method or another would provide better statistical data in the general case.

METHODS

Subjects and PETT Procedures

Eight subjects with confirmed Huntington's disease were scanned using the UBC:TRIUMF PETT-VI scanner (average inplane resolution = 9.2 mm FWHM) (*10*). A bolus injection of 3–5 mCi of FDG was administered to each subject. The uptake scanning procedure was as follows: 8-30-sec scans (total time: 4 min), 5-60-sec scans (total time: 5 min), 5-120-sec scans (total time: 10 min), 4-300-sec scans (total time: 20 min) followed by one 15-min scan. Serially timed arterial blood sampling was done to conform to the following time sequence: eight within the first minute postinjection of FDG, (3–5 mCi); six in the second minute; three in the third, two in the fourth and fifth minutes, and one at 7.5, 10, 13, 16, 20, 30, 40, and 55 min. Arterial ^{18}F radioactivity in the plasma glucose, measured before the FDG injections and at intervals during the scan, was counted in a scintillation well-counter. Attenuation correction was done by transmission scan (^{68}Ge ring source) prior to the FDG injection. Initial head positioning was determined using a saggital reconstruction of the transmission scan. Head placement was maintained throughout the scanning procedure by means of an individually moulded plastic face mask.

Calculations of rCMRglc and Region of Interest (ROI) Placement

Initially, rCMRglc was calculated for the 15-min scan using Brooks' form of the four constant Sokoloff equation and literature values for the rate and lumped constant ($k_1 = 0.102$, $k_2 = 0.130$, $k_3 = 0.062$, $k_4 = 0.0068$, LC = 0.42) (*1*, *11*, *12*). Four slices from the seven-slice array for each subject were matched such that the same brain levels were represented. Sixteen ROIs were placed on these four slices to obtain estimates of frontal, parietal, occipital, temporal and caudate metabolism. To calculate dynamic rate constants these regions were transferred onto the uptake scans. As the spatial coordinates are almost identical (head movement being the only possible source of error) little if any error would be introduced for the comparison of the two methods. Moreover, for the dynamic rate method, head movement is always a possible source of error. Dynamic rate constants and subsequent estimates of rCMRglc were then calculated for the sixteen regions as suggested by Hawkins, Phelps and Huang (*4*). Given the overall scan time, only k_1, k_2 and k_3, as well as blood volume radioactivity were estimated, whereas k_4 was fixed at 0.0068.

These procedures yield two sets of rCMRglc estimates which are identical except for the rate constants estimation. Each of these data sets were then compared to determine which yielded better results according to the statistical model outlined above. In addition, the means for each region were compared and interregional correlations calculated. This analysis determines whether systematic differences in rCMRglc occur and whether the regional results are similar for each subject.

RESULTS

Before comparing the results of the two procedures, it is essential to know the goodness of fit between the regional count rate and the fitted rate constants over time for the dynamic method. Therefore, for each fitted line, correlation coefficients were calculated for each subject and region (i.e., 128 correlations). Not one of these correlations was below 0.9 and the majority (96%) were over 0.95. Visual analysis of the residuals suggested that the unaccounted for variability was normally distributed. These results suggest that as expected the data were well-fitted and no subject or region could be identified where the fits were poor.

The comparison of the two methods in terms of partitioning the total variability are given in Table 1. With respect to total variability the two methods were almost equivalent (133.3 versus 141.2 square units). However, when the two methods are compared in terms of percentage of total variability ascribed to each source, the two methods differed substantially. The most dramatic difference was the percentage of variability unaccounted for by the model (i.e., error). For the literature values, the percentage of unaccounted for variability was 18.5% of the total variability while for the dynamic estimates, this percentage was double or 39.3%. However, the two procedures were almost identical in terms of variability attrib-

TABLE 1
Partitioning of Variability in Literature and Dynamic Estimates

		Standard Rates		Dynamic Rates	
Source	df	SS	% of Var	SS	% of Var
Individual differences in CMRglc	7	74.0	55.6	64.1	38.3
Consistent regional pattern	15	34.5	25.9	31.6	22.4
Unaccounted for variation	105	24.8	18.5	55.5	39.3
Total	127	133.3		141.2	

uted to consistent regional patterns across subjects with the standard rate constants being slightly better (i.e., 25.9% versus 22.9%). In contrast, for the literature values, the variability ascribed to individual difference in basal cerebral metabolic rate was 55.6%, in comparison to 38.3% for the dynamic method. In summary, one may conclude the major difference between the two methods was whether variability was attributed to individual differences in metabolic rate or to error.

The second comparison of interest is whether the two methods provide different information with respect to rCMRglc. These data are summarized in Table 2. T-tests were done comparing the two methods for each region; no significant differences were found. However, when the rCMRglc values for each region were correlated using the Pearson product moment correlation (i.e., dynamic with literature value) the correlations ranged from 0.33 to 0.95. This finding suggests that for some regions (e.g., the caudates), the two methods are extremely similar in terms of individual estimates of rCMRglc while for others (e.g., left frontal, Slice 2, right frontal, Slice 1) the fit between the two methods is far more tenuous (i.e., $r \leq 0.42$). These low correlations indicate that on average the two methods yield similar results, but the metabolic rates for individual subjects do not map well onto each other.

DISCUSSION AND CONCLUSIONS

The primary purpose of this paper is to suggest a statistical method for determining whether different models for determining rate constants yield better results based on a simple model of rCMRglc. It should be noted, however, this method is appropriate only when there is no reason to suspect the presence of abnormal tissue. There are obvious cases where abnormal means different tissue (e.g., tumor) and hence, literature values are not appropriate. However, for the case where there is only atrophy or selective tissue loss (e.g., Huntington's disease), the tissue may be essentially normal. From a clinical perspective, it is important to know the limits of generalization of the literature values. By using Huntington's patients rather than normal controls, it is apparent that the literature values yield comparable data for these patients.

Specifically, the essential findings of these analyses are that the two methods were almost equivalent in terms of regional effects but that using standard or literature rate constants partitions a substantially greater amount of the variability into basal metabolic rate rather than error. This latter finding makes intuitive sense because the same rate constants are being applied across all regions and hence one would expect a greater scalar effect. With respect to a subsequent analysis of absolute rates of rCMRglc, the autoradiographic method may provide slightly better data as the consistent regional variation was slightly higher (25.9% versus 22.4%). More importantly, because the dynamic estimation of rate constants did not improve while consistent regional variation and error variance increased, one would conclude for this case where the data are standardized to an estimate of basal metabolism that literature values would provide data more sensitive to regional difference. For example, for these data, approximately 55.6% of the total variability would be removed by

TABLE 2
Mean, Standard Deviation, Correlations and t-values for Regional Estimates

			Standard		Dynamic			
Slice	Region		$\bar{X}$	SD	$\bar{X}$	SD	t	r
I	Frontal:	Medial	5.62	1.04	5.61	1.17	−0.01	0.64
		Right	5.94	0.82	5.96	0.81	0.05	0.42
		Left	5.64	0.94	6.00	0.98	0.76	0.92‡
	Parietal:	Medial	6.41	1.16	6.57	1.27	0.26	0.95¶
		Right	5.93	1.12	5.99	0.90	0.13	0.78*
		Left	6.00	1.21	6.14	0.99	0.25	0.83*
II	Frontal:	Medial	5.38	0.95	5.57	1.12	0.37	0.83†
		Right	5.54	0.83	5.85	0.95	0.69	0.67
		Left	5.20	0.88	5.10	0.96	−0.22	0.33
	Occipital		7.14	1.05	7.02	0.97	−0.24	0.93‡
		Right	5.69	0.86	6.01	0.92	0.72	0.93‡
		Left	5.31	0.92	5.10	1.19	−0.40	0.86†
III	Temporal:	Right	4.81	0.74	5.16	0.80	0.91	0.76*
		Left	5.37	0.72	5.61	0.75	0.67	0.65
IV	Caudate:	Right	5.55	0.78	5.94	1.04	0.87	0.90†
		Left	5.50	0.86	5.56	0.85	0.14	0.85†

*$p \leq 0.05$.
†$p \leq 0.01$.
‡$p \leq 0.001$.
¶$p \leq 0.0001$.

a standardization procedure if rCMRglc was estimated using literature values for rate constants. In comparison, a standardization procedure would only remove 38.3% of the total variability if dynamic rate constants are used. Although there is considerable debate concerning the correct method for standardization as well as specific caveats regarding valid interpretations of standardized data, it is clearly the most powerful technique for increasing sensitivity to regional difference in rCMRglc available at this time (*9, 13–16*).

Therefore, one may be placed in a scientific quandary in deciding whether to use dynamic or standard estimates of rate constants. Specifically, dynamic regional rate constants, in all probability, or at least theoretically, give more accurate estimates of true rCMRglc. Yet, in terms of subsequent data analysis, this method is less likely to identify regional differences. Given the rationale for the development of the PET/FDG methodology was to identify meaningful regional differences in either clinical populations or activated normal subjects, there are compelling practical reasons for employing the method most likely to highlight these regional differences. Besides the statistical advantages, the practical advantages of the autoradiographic method are shorter scan times, simpler computer programming and data storage, potentially greater axial sampling and less sensitivity to errors of measurement in the input function. In addition, depending upon the patient population, specific clinical confounds are lessened. For example, in the current study, patient head placement was maintained by means of a plastic face mask. However, if movement did occur between the uptake and the long scans, this movement would clearly affect the estimates of rCMRglc using the dynamic method. This potential confound does not occur with the autoradiographic method. However, the question still remains whether these findings are true for other methods of estimating rCMRglc, other scanners and populations.

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APPENDIX

The Statistical Model

Intuitively, the simplest arithmetic characterization of measured rCMRglc is:

$$rCMRglc_{ij} = CMRglc_i + Reg_j + e,$$

where $CMRglc_i$ is individual i's basal metabolic rate, Reg is region effect for region j, e is error associated with the estimate. As discussed, $CMRglc_i$ has been shown to vary considerably across individuals while Reg is assumed to constant value reflecting the particular metabolic characteristics of the region. This value may be the result of density of neural packing, type of neurons, or functional state. Error (e) in the individual case may arise from the scanner characteristics, attenuation correction or the method of calculating rCMRglc. Over a group of subjects and a number of regions the total metabolic variability (or sum of squares total, SS_{TOT}) is:

$$SS_{TOT} = SS_{CMRi} + SS_{REGj} + SS_{error},$$

where SS_{CMR} is the amount of systematic variability (i.e., basal metabolic rate for the individual) which can be attributed to variations in CMRglc among the subjects 1 to i.

SS_{REG} is amount of consistent variability (i.e., similar for all subjects) which can be ascribed to regions 1 to j.

SS_{error} is variability which cannot be accounted for by the individual differences in basal metabolism or consistent regional variations.

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