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Letters

CT in Brain Density Determination

The paper by Cala et al. in the January/February *AJNR* [1] presents very interesting material but leaves some important questions on methodology and data analysis unanswered. Since CT data on normal volunteers are valuable, I hope the authors can clarify these points and perhaps extend their analysis.

1A. When a subjective analysis of material is done, the evaluators should be blind to the variable in question to avoid conscious or unconscious bias. Did the authors perform the grading for atrophy without knowledge of the age of the subjects whose images they were grading?

1B. Was the gray/white matter difference obtained from the difference between the mean gray and white values for the entire group or by summing the differences for each subject? In theory these should give the same result, but if gray and white matter values were not both obtained on every subject, they could be different.

It is very disturbing that the authors found a gray/white difference of half that found by Arimitsu et al. [2], despite the fact they used their technique and the same model scanner at the same nominal generator settings. They suggest that the difference might have occurred because the subjects studied by Arimitsu et al. were older. This seems highly unlikely since neither the authors nor Arimitsu et al. found a variation of the gray/white matter difference with age. A more likely explanation must be sought in technical factors or methodology. Gray/white matter CT value differences are atomic number dependent and therefore very sensitive to changes in the effective energy of the x-ray beam [3].

2A. The authors reported that the mean value for a water phantom in their scanner varied from −3 to −4 with a standard deviation of ±3–4 Hounsfield units (H). I trust that the standard deviation was of the pixel variation on an individual scan, not of the mean over an ensemble of scans. If the latter, their water value varied over a range of greater than −9 to +3 H (±2 standard deviation). Such a degree of variation would be excessive and would make their CT values dubious. If they had such variation, did it also occur from day to day or from scan to scan? If the latter, then their difference values would have been affected.

2B. Was their beam ever checked for effective energy?

2C. Was the packing material used around the head different from the plastic granules used by Arimitsu et al.?

2D. Did their scanner use the same type wedges?

2E. The illustrations seem to show that the side on the observer's right was consistently darker than that on the left. Was there any systematic section nonuniformity on their scanner?

3A. If there is no physical explanation for this discrepancy, the most likely explanation is that the two groups took their samples in different locations. Arimitsu et al. did not provide an illustration showing the location of their samples but their data showed that the average values varied depending on location. Because of subtle spectral shift artifacts, values can be elevated depending on their proximity to the skull. From figure 1D, I would expect the white matter value at location III to be higher than that from location II, which would be the opposite of that found by Arimitsu et al. If the authors could provide a table indicating the average values found in each of the six areas measured, separated by gender it would help us evaluate these differences.

3B. The authors found no change in gray or white matter values with age. In a recent study [4], we found a linear decrease in the CT values in the centrum semiovale with age in 123 normal subjects, aged 23–88 years. There are three reasons that might account for this discrepancy. The authors averaged white matter values from three separate areas which may have overwhelmed any relationship in the centrum semiovale alone. We found that the CT values were negatively correlated with the size of the skull, possibly related to spectral shift artifacts, and that removing the effect of this variable enhanced the age relationship. Finally, the authors age range was limited to 15–40 years which may not be sufficient to demonstrate the age effect. I would urge the authors to reanalyze their data using the CT values for the white matter of the centrum semiovale only. If they can obtain a measure of skull size on level 4A (total intracranial pixels would be best but an internal diameter would suffice) and do a regression analysis for the CT value with size, size squared, and age as the independent variables, they could evaluate our findings in their subjects.

Lastly, some general comments. Quantitative studies using CT values are fraught with difficulty [5]. Arimitsu et al. attempted to use the gray/white matter difference as an internal check to avoid some of these problems. Unfortunately, they obtained values from different sections. Since adequacy and thickness of packing, skull size, and skull thickness vary from section to section, there is no reason to believe that the gray/white difference they obtained would have any greater usefulness than their absolute values. Cala et al. have fallen into the same conceptual trap.

The concept of an overall brain "density" which the authors used to compare results with Reese et al. is invalid for many of the reasons discussed above. Different scanners have different bone artifacts which will vary from patient to patient and section to

section. An overall value which includes fluid, partially volumed bone and calcifications, artifactually elevated soft tissue, etc. is exceedingly difficult to interpret.

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Reply

We thank Dr. Zatz for his interest in our paper and will try to settle his anxieties by providing the following information.

1A. The observer grading the images for atrophy was "blind" to the age of the subjects.

1B. The gray/white matter difference was obtained separately for each subject.

As for differences noted when comparing the work of Arimitsu et al., we accept the suggestion that we may have chosen different areas for analysis.

2A. The mean value of the water phantom varied from −3 to −4 Hounsfield units (H) with a standard deviation of 3–4 H (on normal accuracy and 60 sec scan). These values were obtained during regular routine quality control checks, using the full field of the scanner and a number of 7 × 7 pixel rectangles in various parts of the scanner field. Therefore, the values reported for standard deviation were from pixel variations on individual phantom scans and not from the mean of an ensemble of scans. The value sometimes varied over a week, which was the reason for the regular weekly check and the application of a wedge correction applied by the engineer if the standard deviation was excessive. If the standard deviation was not correctable by wedge correction, the x-ray tube was considered failing; replacement always corrected the defect.

2B. The effective energy of the beam was not checked by half-value layer measurements. Future work on the new tubes supplied to the EMI CT 1010 by General Electric Company will include a regular measurement of half-value layer attenuation.

2C. The packing material was the same as that used by Arimitsu et al. and was supplied with the machine by the manufacturer.

2D. The wedges were also supplied by the manufacturer.

2E. The illustration showing one half darker than the other is an unfortunate photographic reproduction fault. There was no systematic slice nonuniformity on the original pictures.

There would seem to be no physical explanation for the discrepancy between the two studies so perhaps we took our blocks from different locations. Without an illustration with which to compare it is difficult to be certain.

3A. Our data did not vary depending on location or gender (see table 1). The gray matter values were all obtained from the same section so the differences due to different skull thickness between sections did not apply. As 1W was also obtained from this section, the gray/white matter difference was minimally affected by using different sections for the other white matter sites. In addition 2W and 3W had essentially the same value as 1W at the 0.001 level. If 1W is compared to the mean of the three gray matter sites on the same slice, the gray/white matter difference is not significantly different from the gray matter total/white matter total difference.

TABLE 1: **Values of Gray/White Matter Density**

	White Matter			Gray Matter		
	1	2	3	1	2	3
Females:						
No.	43	41	41	43	43	43
Mean	30.36	28.85	30.40	33.79	32.99	32.44
Standard deviation	4.45	3.69	3.24	3.47	3.81	3.17
Males:						
No.	49	50	49	50	50	50
Mean	28.76	29.39	31.17	34.02	33.02	32.97
Standard deviation	3.61*	3.75	4.36*	3.66	3.35	3.12
Total:						
No.	92	91	90	93	93	93
Mean	29.51	29.15	30.82	33.91	33.01	32.73
Standard deviation	4.08	3.72*	3.89*	3.55	3.55	3.14

* Statistically different at the 0.01 level. No means were statistically different at 0.001 level.

3B. No statistically significant change in the density of white matter was observed up to age 40 years. 2W (centrum semiovale) did not decrease with age and as the mean was essentially the same as for 1W and 3W, the arduous task of measuring the internal cranial diameter of 115 subjects was not performed.

We have examined figure 10 of Zatz's reference [4] and agree that the downward slope of the graph is significant at the 0.001 level when taken to age 80 years. However, up to age 60 years there is no significant downward slope - nor is there up to age 40 years. Zatz's data and ours agree for the age group we have both examined. Therefore, the subjects over age 60 years have created the statistically significant trend. It would be very relevant to know what medical criteria were used to include these subjects in the normal series. It is a finding which is of interest and warrants further investigation in its own right. Furthermore, Zatz found a trend with age with one slice only (centrum semiovale) out of seven, which lowers the significance of this finding substantially as there are no obvious grounds for supposing a trend should occur in one of the white matter sites.

We agreed that comparisons between different installations can be very difficult and this must apply to the Syntex System 60 head scanner used by Zatz as it does to the old Mark I EMI head scanner used by Reese et al. However, in the comparison we used, we excluded for the purpose of the figure, all high Hounsfield units (>60) and all low Hounsfield units (<15). Most bone artefacts were eliminated as the sections analysed for white and gray matter were cranial to those displaying the petrous bones, roofs of orbits, etc.

The overall value for brain density is considered valid as most subjects would have similar soft tissues in the scalp (except perhaps for the muscle bulk associated with the temporalis muscles) and therefore the histogram presentation is still considered an acceptable method of comparing the two sets of results. Physiological calcification in the pineal and choroid plexuses is so small compared

to the total surface area of the scan slice that any averaging phenomenon would not be of any magnitude.

We thank B. Murphy, The Raine Unit of Medical Statistics, University of Western Australia, for his independent viewing of Zatz's figure 10.

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Local Cerebral Blood Flow Measurements

We read with interest the paper, "Local cerebral blood flow measured by CT after stable xenon inhalation" [1] which appeared in the August 1980 *AJR* and the May/June 1980 issue of *AJNR*. We disagree with a number of statements made in this article and question others.

The authors state in the abstract that "local cerebral blood flow measurements are possible with a single 1 min scan." We believe this statement should be qualified. An estimate of blood flow may be based on one datum point requiring at least two scans (a baseline and an enhanced image) only if blood:brain partition coefficients (λ) are assumed known. However, this approach ignores an important advantage of the "xenon methodology". Partition coefficients can be derived when additional enhanced images are acquired when equilibrium is generally reached within 4 min in tissue with fast flow but it may require 30 min or more in tissue with slow flow (normal or diseased) [2]. We emphasize that all "direct" and "indirect" methods require estimates (measured or approximated) of xenon concentration in both arterial blood and tissue at equilibrium. There are other methodologies which do not require scanning at equilibrium, however, they do require multiscanning during buildup and multivariable analysis to obtain estimates for both flow rate (k) and partition coefficient (λ). These techniques are not possible with a single scan and the derived estimates improve significantly with additional scans [3].

The authors emphasize their perference of using "slow" scans (about 60 sec) for blood flow studies. We believe slow machines can be used but special consideration should be given to the effect of relatively poor temporal resolution. The use of midscan as the effective scan time results in systematic errors that depend on scan time (t) and flow rate constants (k) (Spital R, personal communication). These errors may be significant during the rapid buildup phase (first minute) in tissue with rapid flow. We believe that the in vivo autoradiographic technique is not the best or the most precise. Its major advantage lies in its simplicity since it requires few computations. It has been shown that other techniques yield better estimates (small errors) of flow [3].

We fail to understand how enhancements of about 18 CT units in gray matter as shown in figure 2 and an error of $\pm$ 1 CT unit on both baseline and enhanced scans, yield errors of under 5% of blood flow (table 3). In addition, we cannot comprehend how errors of derived flow based on estimates of both blood:brain partition coefficient (λ_i) and flow rate constant (k_i), $F_i = \lambda_i k_i$, can be less than the error of partition coefficient alone (table 3).

We also question a number of statements made in the article concerning the results shown in figure 7. The low blood flow estimates based on a scan performed within the first minute of xenon inhalation may be due to a number of factors:

A. If the expired gas is monitored but true end-tidal values are not used for iteration of the convolution integral (equation 6), the xenon buildup rate in arterial blood is overestimated and flow may be significantly underestimated.

B. The error in using midscan as effective scan time is more pronounced in the first minute during rapid buildup.

We agree with the authors that scanning during the first minute of xenon inhalation should not be recommended due to the limited enhancement and the significant increase in the errors of estimated blood flow. This is particularly true when the in vivo autoradiographic technique is used.

We concur with the authors that cerebral blood flow decreases under anesthesia. Table 5 indicates a decrease of about 40% in fast flow and a somewhat lesser decrease in slow flow. On the other hand, figure 7 shows a dramatic decrease of about a factor of three in flow. When the in vivo autoradiography method is used, tissue volumes intermixed with small quantities (10%–20%) of tissue with slow flow (white matter or other), will demonstrate a similar flow pattern, namely, a decrease in estimated flow with time. We think this effect should be seriously considered before attributing the dramatic decrease in estimated flow solely to anesthesia.

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Reply

The comments of Gur and Shabason have been noted and we thank them for their interest in our paper. We agree that at least one (and preferably two or three) steady state (noncontrast) brain scans measured in Hounsfield units (H) must be obtained before local cerebral blood flow measurements can be calculated from ΔH changes from single 1 min scans during stable xenon inhalation by the in vivo autoradiograhic or any other method. Local cerebral blood flow values can only be calculated with accuracy if the $L\lambda$ has been measured at saturation. These questions are discussed on pages 216–220 of our paper. For example, on page 218 we state: "The ΔH units for each region of interest during saturation for each of two brain sections, recorded concurrently 4 mm apart, were measured by examining volumes as small as 0.04 cm^3 (4 voxels). At 1 min intervals, the Hounsfield units were reproducible with low standard deviations and computed blood flow values showed statistically significant reproducibility. Thus, minute-to-minute flow values were obtained." The article also explained how $L\lambda$ is measured after 10 min inhalation, that regions of low flow need extrapolation of $L\lambda$ to infinity or to tissue equilibrium, and stressed the importance of this measurement. We also discussed and gave results of other measuring methods from serial scans during buildup or washout phases based on modifications of the Fick principle. In later publications we have confirmed that $L\lambda$ undergoes changes in