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Invited Commentary: Senile Dementia

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Invited Commentary: Senile Dementia

The authors have obviously done a great deal of excellent and creative work in examining subjective analysis of gray-white matter discriminability and its correlation with severity of senile dementia. This aspect of the paper is well done, well documented, and presented in such a manner that the reader could replicate the study or begin to use it clinically on an already known demented population. However, the results are preliminary because there are no age-matched normal controls. Further the following comments on particular details seem appropriate.

1. Arimitsu et al. [1] found less difference between the CT values for gray and white matter in patients under 15 years of age than in older patients, which they suggested might be due to a higher attenuation value for white matter in their younger subjects. Since they also found that the calvarium was thinner in these young subjects they could not eliminate the possibility that the difference was due to radiographic spectral changes. George et al. may want to comment on this potential explanation for their observations.

2. The objective linear measurements of ventricular size and sulcal width (10 of them) are not fully presented, either in raw data form, summarized form, or in correlational form with cognitive measures. This limits the usefulness of this information. In addition, it would be useful to know if the ventricular/brain ratios at the frontal horns would have been altered, if bone windows had been used in measuring brain width [2].

3. The methodology used in obtaining the CT number information, "three four-pixel samples" at the centrum semiovale and high convexity levels in white and cortical gray matter is inadequately described. It is unclear if equal samples were taken in the left and right hemispheres, and if they were at exactly the same location and slice level in all subjects. We have observed changes in CT numbers of 2–8 H in white matter on the same centrum semiovale slice, depending on where the sample (150 pixels) was taken—frontal area, middle area, or parietal area (all away from bone).

4. Further, the authors examined gray and white CT values only at the centrum semiovale and high convexity slices. Previous research has shown that increased CT numbers are routinely observed near the apex [3]. One reason they found a correlation between increasing gray and white CT values at the centrum semiovale in high convexity slices and increasing ventricular size may be that these larger ventricles extended higher and forced the observers to examine even higher slices (closer to apex) than would normally be done in patients having normal-sized ventricles.

5. In aphasia stroke patients where semiautomated computer programs were used to analyze the infarct and ventricle size [4], a wide range in hemisphere size was observed—6,000 pixels (or less) to 11,000 pixels per slice, depending on the slice level [5]. It would be useful to know the mean size (standard deviation and range) of the slices examined at: (1) centrum semiovale and (2) high convexity. The high convexity slice in figure 2C appears to be much larger, for example, than the high convexity slice shown in figures 1C and 3C. The Naeser, Gebhardt, and Levine study with dementia cases found it necessary to control for slice size at the centrum semiovale level and CT numbers were examined *only* on slices of 6,900–9,000 pixels [6]. Lower white matter CT numbers (less than 40 H in 150 pixel samples) were observed in the dementia cases as compared to age-matched nondementia cases. The difference in dementia/nondementia cases was not observed at high convexity (5,000 pixels or less) or below the centrum semiovale level (greater than 10,000 pixels). Hence, it would be important to know the slice size range used in this study to obtain the gray and white matter CT number samples at both the centrum semiovale and high convexity levels.

6. The important issue of the relation between CT numbers in gray and white matter and aging and/or dementia needs to be studied further. Naeser et al. [6] observed *decreased* CT numbers in white matter and mixed gray and white matter at the centrum semiovale slice level in 21 presenile and senile dementia cases versus seven age-matched nondementia cases. Zatz et al. [7] recently examined 123 normal aging subjects, ages 23–88 years, with semiautomated computer programs and observed that with increasing age, there was a *decrease* in CT values in white matter in the slice just above the ventricles. The precent fluid volume and cranial size had no effect on this observation. These two studies [6, 7] in both dementia cases and normal aging reported a *decrease* in CT numbers at the supraventricular level in white matter. Each used semiautomated computer programs to analyze the CT information [4] and each study examined tissue samples which were at least 150 pixels in size. These appear to contradict the observation of *increased* CT values in gray and white matter in more severely demented cases in the present study. It is possible such differences were observed in part because of differences in the number of pixels per sample studied—that is, 4 pixel samples in the present study, and 150 pixel samples in the other two studies [6, 7].

Szoke et al. [8] recently observed that compact myelin isolates from *aged* rat brain showed a large increase in the ratio of unsaturated/saturated long chain glycolipid fatty acids compared to isolates from mature or older animals. If this instability in myelin were also observed in aged human or dementia brains, it is possible the change would be observed in white matter CT values (although the direction of change is not known at this time). Penn et al. [9] already observed a 20% *increase* in brain tissue CT numbers in

infants during the first 20 weeks after birth. In infants, this increase is believed to be due to a combination of decrease in water content of the brain (increase in attenuation values) and increase in lipid concentration (decrease in attenuation values). Future adult dementia studies using the methodology employed in the infant study where biochemical and histologic information *combined* with CT attenuation value information would provide increased understanding of CT attenuation values in dementia.

7. The present study states there was a significant correlation between left hemisphere CT values and the cognitive measures. However, nine of 11 of the chosen cognitive measures were verbal tasks (probably left hemisphere tasks) and only two of these 11 tasks (Guild Designs and Digit Symbol Substitution Test) can be considered nonverbal tasks (probably right hemisphere tasks) [10]. Thus, the correlations for left versus right hemisphere CT values and cognitive measures would be more valid if a more equal number of verbal *and* nonverbal tasks were included.

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Author's Response

Our intent is to report the observation that CT gray and white matter differentiation is visually diminished or lost in senile dementia. A definitive explanation for this phenomenon is not apparent at this time. We are currently exploring the issue of parenchymal changes in senile dementia with a more elaborate study including quantitative methods using a newer generation G.E. 8800 scanner, in a larger patient population with age- and gender-matched normal controls.

The commentary by Naeser et al. is weighted heavily on the issue of CT numbers and especially on the question of whether CT attenuation values go up or down in dementia (item 6). This emphasis undoubtedly reflects their investigative interests, but is somewhat at variance with the thrust of our own report. We do not know definitely whether CT numbers go up or down; provisionally, they seem to be going up with increasing dementia. In their article, Dr. Naeser and coworkers, on the other hand, reported that the CT numbers of 14 presenile and seven senile dementia patients were significantly lower than six presenile and one elderly normal controls. We believe the following issues are relevant to this seeming contradiction and must be addressed in order to adequately interpret the results.

1. All senile and most (10 of 14) presenile dementia patients in the Naeser et al. group exhibited cortical atrophy—all normal controls did not.

2. Their illustrations (figs. 1 and 6) of CT number sampling suggest the inclusion of sulci in addition to gray and white matter. Therefore, the lower CT number values in the impaired group may in part reflect sampling of coexistent dilated sulci.

3. Region of interest sampling methods are typically associated with wide variation; small shifts in cursor position can profoundly alter mean CT values. In the Naeser et al. article, the cursor in figure 7, for example, incorporates within the region of interest a small focus of high attenuation. A minor repositioning of the cursor would very likely produce a significantly lower mean CT value, possibly falling within the impaired range.

4. Whole slice CT values of dementia patients in all cases were lower than whole slice values of the normal controls. Since the whole slice mean CT value method avoids the various pitfalls inherent in cursor positioning, such a method is potentially of clinical usefulness. However, it must be shown that the presence or absence of sulcal dilatation is not a primary determinant of mean CT values; otherwise, whole slice averaging may only reflect a quantitation of the degree of cortical atrophy.

5. The populations of their study and our own are not comparable. The series of Dr. Naeser and coworkers included seven senile dementia patients and one elderly normal control, a sample too small to permit conclusions about or comparisons of CT attenuation changes in senile dementia.

For these reasons, we believe that the issue of the direction of attenuation changes in senile dementia is as yet

TABLE 5: **Correlation Coefficients between CT Linear Measures and Cognitive Measures**

Cognitive Measures	Linear Measures					
	B/B′	C	E/E′	F	G	OMVA
Paragraph 1	NS	NS	NS	NS	NS	NS
Paragraph 2	−0.50†	NS	−0.68†	−0.65†	−0.63†	−0.44*
Paired associates 1	−0.38*	−0.49†	−0.50†	−0.50†	−0.38*	−0.50†
Paired associates 2	NS	NS	−0.35*	NS	NS	NS
Designs	−0.48*	NS	−0.66†	−0.52†	−0.46*	NS
WAIS vocabulary	−0.40*	−0.40*	−0.60†	−0.55†	−0.60†	−0.39*
Digits forward	−0.35*	NS	−0.64†	NS	−0.46*	−0.55†
Digits backward	−0.50†	NS	−0.53†	−0.49*	−0.54†	−0.51†
DSST	−0.52*	−0.46*	−0.73†	−0.58†	−0.60†	−0.52†
MSQ	0.45*	0.59†	−0.75†	0.60†	0.54*	0.69†
GDS	0.48*	NS	−0.70†	0.53†	0.60†	0.52†

Note.—Correlation coefficients were all nonsignificant for linear measures A/A′ (bifrontal ratio), H (left sylvian), and I (right sylvian); they were nonsignificant for the following linear measures with these exceptions: D (third to sylvian), DDST = −0.43* and J (sum of sulci), MSQ = 0.45*. B/B′ = bicaudate ratio, C = width of third ventricle, E/E′ = width of bodies ratio, F = left frontal horn oblique, G = right frontal horn oblique, OMVA = maximal ventricular area, WAIS = Wechsler Adult Intelligence Scale, DSST = Digit Symbol Substitution Test, MSQ = Mental Status Questionnaire, GDS = Global Deterioration Scale, NS = nonsignificant correlation.

* $p < 0.05$.

† $p < 0.01$.

unsettled. Naeser et al. asked for more information on the linear measurements and their relation to cognitive function (item 2). The patients ($n = 26$) comprised 17 females and nine males with a mean age of 70.7 ± 5.3 years; all were right handed. The correlation coefficients for 11 of the linear measures are shown in table 5. Note that the width of the third ventricle (C) correlated significantly ($p < 0.05$) with four of the 11 cognitive measures (range, 0.40–0.59) and that the ratio (E/E') of the width of the bodies of the lateral ventricles (E) to the width of the brain (E') correlated significantly ($p < 0.01$) with 10 of the 11 cognitive measures (range, 0.35–0.75).

With reference to the selection of gray and white matter samples for measurement (item 3), only two brain levels were used for the purpose of obtaining pilot data. The high convexity level was selected because of the high percentage of cognitive measure correlations that was obtained with the ratings of gray-white matter discriminability. The centrum semiovale level was picked because we believed that reliable sampling of white matter numbers would be most easily achieved at this level. The first slice above the ventricular system was designated as the *centrum semiovale level.* The cut immediately above the centrum semiovale level was invariably designated the *high convexity cut.* The four pixel samples were derived by use of the cursor from regions that were subjectively assessed to clearly represent white matter; gray matter samples were similarly derived from medial cortex. Areas of sampling were selected almost invariably from midhemisphere levels. Equal numbers of four pixel samples were derived from the same slice for each hemisphere, that is, three gray samples and three white samples for each hemisphere. A relatively small (four pixel) sample size was chosen in an effort to obtain homogeneous sampling of gray matter. Despite the small sample size, measures of gray matter CT numbers are less likely to be homogeneous than samples of white matter derived from central white tissues, due to the essentially unavoidable averaging of contiguous white matter and adjacent sulci.

Subsequently, we have also noted that CT numbers may vary considerably among frontal, midhemispheric, and occipital areas. Therefore, in our current study, we structured CT sampling on a regional basis to include values separately from frontal, temporal, and parietal regions.

The suggestion that increasing ventricular size may have influenced the level at which centrum semiovale CT numbers were sampled is intriguing (item 4). Centrum semiovale samples were indeed obtained from the first slice above the ventricular system; therefore, in patients with larger ventricles, samples may well have been taken nearer to the vertex than in patients with smaller ventricles. This may also explain why the high convexity slice in figure 2C in a patient with normal ventricles is somewhat larger than the high convexity slices in figures 1C and 3C, which are both of patients with larger ventricles.

Standardization of sites in CT sampling procedures has also been of concern to us (item 5). In subsequent studies, we are defining brain levels separately for men and women by determining the distance of a particular slice to a fixed landmark, for example, the base of the skull. We are also evaluating the use of the relatively fixed foramen of Monro and the pineal as internal landmarks. The concept of using slice size as an indicator of brain level is interesting, but presupposes that all brains are of the same size and shape and that all skulls are of uniform thickness and shape. It remains to be shown that slice size, which in essence defines skull and not brain size, is a reliable predictor of brain level. It may be more practical to simply use the distance from a fixed level, for example, the base of the skull or possibly the foramen of Monro, as an indicator of brain level rather than the size of the cranium as proposed. The accuracy of both methods is affected by variations in brain size and shape, but the former method is not subject to the additional confounding influence of skull shape and size.

With reference to their final comments (item 7) the cognitive test battery used in the present study was predominantly weighted with verbal and probably left hemisphere tests. Nevertheless, it is of interest that CT number measures taken from the left hemisphere should be better associated with left hemisphere tasks than measures taken from the right hemisphere given the generally held assumption that Alzheimer disease is bilateral and diffuse. Our data do suggest that further investigation using regionalized CT and neuropsychologic evaluations of senile dementia would be desirable.