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C R Jack, Jr

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Commentary

Medial Temporal Lobe Volumetrics in Traumatic Brain Injury

Clifford R. Jack, Jr, *Department of Diagnostic Radiology, the Mayo Clinic, Rochester, Minn*

In this issue of *AJNR*, Bigler et al (1) describe magnetic resonance (MR)-based volume measurements of the hippocampal formation and the temporal horn in a group of control subjects 16 to 65 years of age, and in a group of subjects who have had head trauma. The article is divided into two parts. The first is a descriptive study of these volumes in healthy subjects, and the associations between age, sex, and head size. The second part is a separate study in which these volume measurements in subjects who have had a traumatic brain injury are compared with those in control subjects.

In recent years, a great deal of interest in quantitative MR-based measurements of the medial temporal lobe has arisen. There are several reasons for this. First, the neuroanatomic substrate of declarative memory is centered in medial temporal lobe limbic areas, with the hippocampal formation and entorhinal cortex as particularly critical structures in this pathway (2). Second, unlike computed tomography, MR is capable of reliably producing high-quality images of the medial temporal region with precise delineation of the naturally occurring neuroanatomic boundaries of several of the key structures of the medial temporal lobe limbic system, particularly the hippocampal formation (3). And third, medial temporal lobe limbic areas are the primary site of at least two fairly common diseases—Alzheimer disease and medial temporal lobe–onset epilepsy (4, 5). Anatomic abnormalities of the hippocampus have also been implicated in schizophrenia (6). Bigler et al have extended applications of quantitative MR imaging of the medial temporal lobe to persons who have had a traumatic brain injury. They found a number of interesting associations, including some that might be quite useful in predicting cognitive outcome after traumatic brain injury.

In order to maximize the precision of MR-based quantitative medial temporal lobe measurements, attention must be given to the three primary elements of image-based quantitation (7): (*a*) the pulse sequence parameters used when acquiring the MR images themselves, (*b*) the technical details of image processing, including segmentation and region of interest delineation, and (*c*) the boundary criteria used to define the neuroanatomic structures of interest. Several different MR techniques have been used by different investigators performing quantitative studies of the medial temporal lobe—T1-weighted spin-echo, T1-weighted three-dimensional volumetric, and fast spin-echo imaging (8–12). The images have been acquired in the coronal, oblique coronal, axial, and sagittal plane. Methods of image segmentation used to define the regions of interest include image tracing with a manual interactive device most commonly, stereologic techniques, and automated methods (13–15). Bigler et al introduce a new approach for volume measurements of the hippocampus and temporal horn: feature space segmentation. Feature space techniques have been used by a number of investigators for measurement of global/hemispheric brain and cerebrospinal fluid volume, and also measurement of the volumetric burden of multiple sclerosis plaques, but have not been used to my knowledge for hippocampal volume measurements (16–19).

With the authors' approach, a dual fast spin-echo pulse sequence is acquired with contiguous 3-mm coronal sections through the hippocampus and temporal horn. Image segmentation is done in two steps. First, a feature space algorithm (k-nearest neighbor) is run which segments each image pixel into cerebrospinal fluid, gray matter, or white matter categories. This step is not sufficient, however, to segment the hippocampal formation and temporal horn from adjacent structures fully. Because the cerebrospinal fluid in the temporal horn is contiguous with that in the choroidal

Address reprint requests to Clifford R. Jack, Jr, MD, Department of Diagnostic Radiology, the Mayo Clinic, 200 First St SW, Rochester, MN 55905.
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fissure, which in turn is contiguous with the cerebrospinal fluid in the cisterna ambiens, the medial boundary of the temporal horn must be established by manual interactive tracing. The same is true of the medial boundary of the hippocampal formation, which is contiguous with the gray matter ribbon of the parahippocampal gyrus (20, 21). The judgment of an operator with expertise in neuroanatomy is also necessary to establish the anterior and posterior boundary of the hippocampus, and also to segment manually the hippocampal head from the overlying amygdala. Thus, it is not clear that the feature space segmentation approach outlined by Bigler et al is less time consuming or more precise than manual tracing, which is the more traditional approach to anatomic segmentation in this region because in both instances an extensive amount of input is required by an operator with neuroanatomic expertise to define anatomic boundaries. Appropriately, Bigler et al have evaluated the test-retest reproducibility of their method, and have calculated reliability coefficients. As indicated in a prior editorial (22), it is difficult to compare the reproducibility of the authors' technique with that reported for other techniques, because no standardized method for calculating and reporting test-retest reproducibility of continuous quantitative radiologic variables has been established in our field.

Although one of the chief aims of the authors' work is to create a normative database, it should be understood by the reader that the absolute age-specific hippocampal and temporal horn volumes reported are valid only for the particular method of volumetric analysis that the authors use. For example, if different anatomic boundary criteria were selected for the hippocampus, or a different image processing algorithm were used, then the hippocampal and temporal horn volumes obtained would be different from those reported here (23). Any site that wishes to undertake a program in volumetric analysis therefore needs to establish its own normative volumetric database, which will be specific for the technique that they use. A normative volumetric reference point is absolutely essential if the objective is to quantify cerebral atrophy (whether global or regional) associated with a particular disease process. Because cerebral atrophy is a negative phenomenon, it must be characterized as a loss of tissue relative to age- and sex-specific values in control subjects. Volumetric values in the patient population can then be expressed as *z* scores relative to the control population as Bigler et al have appropriately done (24).

One of the major findings in healthy subjects reported in this study is a lack of atrophy over the age span examined; that is, hippocampal volumes did *not* decline with age, and temporal horn volumes did not increase with age. These findings are at odds with the clinical experience of most neuroradiologists, which would indicate that cerebral atrophy is associated with aging. Autopsy studies have confirmed a loss of brain weight and volume with increasing age (25, 26). A number of imaging studies (computed tomography and MR) have also found that cerebral atrophy is a feature of normal aging (27–31).

How can this experience be reconciled with the data that the authors report? One possible explanation may be the age range the authors studied, 16 to 65 years. Groups studying epilepsy have measured hippocampal volumes in healthy young and middle-aged adults (approximately 18 years to late 40s), and no volume loss with increasing age is found in this age range (32–34). The healthy controls in studies of Alzheimer disease, on the other hand, have been in the 60-to-90-year range and a linear loss of hippocampal volume is usually found (35). The data derived from pooling these two different sources of normal hippocampal volumes would imply that hippocampal volumes remain fairly constant from late adolescence through middle age and begin to decline as one approaches older age (ie, over 65). If indeed the "normal brain volume"-versus-age plot plateaus in adolescence and middle age, and then reaches a "knee" with a decline after 65 years of age, it is conceivable that the sampling scheme of Bigler et al, which ends in the 55-to-65-year group, might reside entirely on the plateau and miss the decline seen in persons in their 70s, 80s, and 90s. The authors acknowledge this, and this would seem to be a rational explanation for the their finding of no age-associated atrophy.

A second possible explanation for the authors' findings rests with the definition of healthy controls. In many studies of normal aging, a control subject is defined as a person who is functioning normally in society, who is not known to have any disease process that would impair cognition, and who performs in the "normal" range on formal cognitive testing (36). It is

widely acknowledged, however, that declines in many cognitive domains occur with aging. This has led to the practice of "age norming" standard neurocognitive tests to account for the observed decline in so-called healthy subjects (37–39). However, the notion that cognition declines and the brain atrophies as a normal feature of aging is controversial. For example, DeCarli et al (40) have described a group of "super normal" individuals who display no age-related decline in temporal lobe volume, and no decline in cognitive function with advancing age. DeCarli et al (40) have raised the possibility that the presence of conditions that increase in prevalence with age, such as hypertension (or the cumulative effect of long-term poorly controlled hypertension on the central nervous system) might account for the increased prevalence of cerebral atrophy and cognitive decline in "healthy" elderly persons, if healthy is defined simply as adequately functioning in society and not demented (40–42). Little information is given about methods of recruiting the control subjects in the study of Bigler et al, but some apparently were university faculty members. A speculative explanation for the absence of age-related cerebral atrophy in this study may be that the elderly persons recruited were university faculty members who were functioning at a high level into their 60s, and therefore might be "super normal" subjects.

Another important finding in the control subjects reported by Bigler et al is the lack of correlation between hippocampal and temporal horn volumes. This could be interpreted as confirmation of the clinical experience of most neuroradiologists, which is that the person-to-person variability normally found in the size of the temporal horns is substantially greater than the variability normally found in brain parenchymal volume (in this case hippocampal volume). The authors' data support this notion. The normalized volumes in their Table 3 indicate that the standard deviation of hippocampal volume as a percentage of total hippocampal volume (ie, the coefficient of variation) is about 10%. On the other hand, the coefficient of variation for the temporal horn is four times greater than this at about 40%.

The data provided on the patients with traumatic brain injury are most interesting. Traumatic brain injury produces hippocampal atrophy and temporal horn enlargement. However, the mechanism by which this occurs is unknown. Are these two radiologic findings the manifestation of hippocampal and temporal lobe deafferentation secondary to generalized cortical cell loss, a manifestation of direct mechanical injury to the temporal lobe at the time of trauma, or perhaps, calcium-mediated excitotoxic or ischemia-related cell death in the period immediately following head trauma? The authors' observation of brain atrophy (hippocampal atrophy and ventricular enlargement) in patients who have had a head injury is consistent with the experience of most practicing radiologists (at least in the setting of severe closed head injury). On the other hand, the authors' finding that the ventricular system is larger in patients scanned less than 100 days after trauma than in patients scanned after 100 days after trauma is difficult to explain, other than by invoking the presence of noncommunicating hydrocephalus caused by traumatic subarachnoid hemorrhage in the early group, which later resolves. The most interesting finding, however, from the perspective of the clinical utility of this technique is the apparent power to predict long-term cognitive outcome that is vested in volume measurements of the hippocampus and temporal horn when these measurements are made 4 to 7 months after injury. If this finding is confirmed in subsequent studies, then volumetric measures of the hippocampus and temporal horn might assume an important role in the clinical management of head injury.

Rigorously conducted volumetric analyses require great attention to details of image acquisition, image processing, neuroanatomic boundary definitions, and appropriate analyses of the data. The entire process is time consuming and complicated; nevertheless, by virtue of our training in neuroanatomy and imaging physics, neuroradiologists are ideally positioned to play a pivotal role in population-based volumetric studies.

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