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HIPPOCAMPAL VOLUME AND SHAPE ANALYSIS IN AN OLDER ADULT POPULATION

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Abstract

This report presents a manual segmentation protocol for the hippocampus that yields a reliable and comprehensive measure of volume, a goal that has proven difficult with prior methods. Key features of this method include alignment of the images in the long axis of the hippocampus and the use of a three-dimensional image visualization function to disambiguate anterior and posterior hippocampal boundaries. We describe procedures for hippocampal volumetry and shape analysis, provide inter- and intra-rater reliability data, and examine correlates of hippocampal volume in a sample of healthy older adults. Participants were 40 healthy older adults with no significant cognitive complaints, no evidence of mild cognitive impairment or dementia, and no other neurological or psychiatric disorder. Using a 1.5 T GE Signa scanner, three-dimensional spoiled gradient recalled acquisition in a steady state (SPGR) sequences were acquired for each participant. Images were resampled into 1 mm isotropic voxels, and realigned along the interhemispheric fissure in the axial and coronal planes, and the long axis of the hippocampus in the sagittal plane. Using the BRAINS program (Andreasen et al., 1993), the boundaries of the hippocampus were visualized in the three orthogonal views, and boundary demarcations were transferred to the coronal plane for tracing. Hippocampal volumes were calculated after adjusting for intracranial volume (ICV). Intra- and inter-rater reliabilities, measured using the intraclass correlation coefficient, exceeded .94 for both the left and right hippocampus. Total ICV-adjusted volumes were 3.48 (± 0.43) cc for the left hippocampus and 3.68 (± 0.42) for the right. There were no significant hippocampal volume differences between males and females ($p > .05$). In addition to providing a comprehensive volumetric measurement of the hippocampus, the refinements included in our tracing protocol permit analysis of changes in hippocampal shape. Shape analyses may yield novel information about structural brain changes in aging and dementia that are not reflected in volumetric measurements alone. These and other novel directions in research on hippocampal function and dysfunction will be facilitated by the use of reliable, comprehensive, and consistent segmentation and measurement methods.

Keywords

Boundaries; Hippocampus; Shape; Volume

INTRODUCTION

Medial temporal lobe structures, including the hippocampus, are critical for episodic memory. Effects of normal aging on hippocampal structural integrity are somewhat controversial (Bigler, Blatter, & Andersob, 2002; Raz, Rodrigue, Head, Kennedy, & Acker, 2004), but Alzheimer's disease (AD) is associated with medial temporal atrophy and episodic memory dysfunction even early in the course of the illness (Jack, Petersen, O'Brien, & Tangalos, 1992; Johnson, Saykin, Flashman, & Riordan, 1998; Killiany, Moss, Albert, Sandor, Tieman, & Jolesz, 1993; Laakso et al., 1995; Scheltens et al., 1992). Magnetic resonance imaging (MRI) is an important tool for examining the size and shape of the hippocampus in normal aging, AD, and mild cognitive impairment (MCI) (Jack et al., 2002; Laakso, Hallikainen, & Soininen, 2000; Laakso et al., 1995; Small, Tsai, DeLaPaz, Mayeux, & Stern, 2002), as well as other neuropsychiatric disorders (Meisenzahl & Schlosser, 2001) such as schizophrenia (Bogerts et al., 1993; Chance, Esiri, & Crow, 2002; Csernansky et al., 1998; Joyal et al., 2003; Kalus et al., 2004; Nelson, Saykin, Flashman, & Riordan, 1998; Shenton, Gerig, McCarley, Szekey, & Kikinis, 2002; Torres, Flashman, O'Leary, Swayze, & Andreasen, 1997) and temporal lobe epilepsy (Cendes et al., 1993; Jack, 1994; Scott, DeKosky, & Scheff, 1991; Sims & Williams, 1990; Soininen et al., 1994; Watson et al., 1992).

The majority of hippocampal volumetry studies in aging and AD have employed an MR field strength of 1.5 Tesla, and derived volumes using coronal slices varying from 1.5 mm to 3.1 mm in thickness. Volume acquisition has been calculated using a variety of programs and locally developed software, but time-intensive, individualized manual tracing has been the primary method for deriving hippocampal volumes. There now exists a body of literature with varying methods for measuring the hippocampus, and other medial temporal lobe structures such as the amygdala, entorhinal cortex, temporal horn, perirhinal cortex, and temporo-polar cortex, or a combination of the above (Bonilha, Kobayashi, Cendes, & Li, 2003; Convit et al., 1999; Golomb et al., 1993; Goncharova, Dickerson, Stoub, & deToledo-Morrell, 2001; Honeycutt & Smith, 1995; Honeycutt et al., 1998; Insausti et al., 1998; Mu, Xie, Wen, Weng, & Shuyun, 1999; Naidich, Valavanis, & Kubik, 1995; Pantel et al., 2000).

Different hippocampal volumetry methods result in different volume measurements. For example, Hasboun et al. (1996) compared three scan acquisition and reformatting protocols and obtained different, though correlated, hippocampal volumes with each. The authors noted that three-dimensional processing of scan data helped with visualizing ambiguous boundaries, such as those between the hippocampus and the amygdala. Analyzing hippocampal volume in the plane perpendicular to the long axis was encouraged. Overall, they emphasized the importance of using one protocol throughout a given study to eliminate method-related variance.

Our laboratory has developed a protocol for reliably segmenting the entire hippocampus using the software program BRAINS (Brain Research: Analysis of Images, Networks, and Systems; <http://www.psychiatry.uiowa.edu/mhcrc/IPL-pages/BRAINS.htm>), developed by the University of Iowa Mental Health Clinical Research Center Imaging Processing Lab (Andreasen et al., 1993). The BRAINS program allows simultaneous visualization and boundary demarcation in any of the three orthogonal views (Figure 1). It also includes a "telegraphing" function in which demarcations made in any view are automatically

displayed in the others. This permits boundaries to be defined where best visualized and transferred to the tracing view. Other software packages are available to support similar analyses (e.g., Analyze, <http://www.mayo.edu/bir/Software/Analyze/Analyze1NEW.html> and Slicer 3D <http://www.slicer.org/index.html>).

Our neuroanatomic approach largely follows the guidelines of Jack (1994) and Watson et al. (1992), while incorporating refinements in defining the posterior extent and anteromedial aspect of the hippocampus (Andreasen et al., 1993; Torres et al., 1997). Previous hippocampal tracing methods often excluded part of the posterior portion of the hippocampal tail. In these previous approaches, the posterior extent was defined by the coronal slice where the crus of the fornix was first seen in full profile (Bogerts et al., 1993; Jack, 1994; Laakso et al., 2000; Lemieux, Liu, & Duncan, 2000; Mu et al., 1999). This meant that the final 2–5 mm of the hippocampal tail, representing approximately 5–10% of the volume of the hippocampal formation, was ignored in order to obtain a reliable measurement. Our protocol involves tracing in the plane of the long axis of the hippocampus, where the hippocampal tail is better viewed than in the more common anterior commissure – posterior commissure (AC–PC) plane. Advances in MRI resolution and image contrast now permit inclusion of the most posterior section of the tail, particularly using three-dimensional processing capabilities such as those available in the BRAINS program. In addition, whereas our hippocampal tracing method distinguishes between the anterior boundary of the hippocampus and the amygdala, others have combined these two structures (Bogerts et al., 1993; Lehericy et al., 1994; Shenton et al., 1992). To eliminate boundary overlap, we often trace key medial temporal lobe structures simultaneously (i.e., hippocampus, amygdala, and entorhinal cortex). In addition to more comprehensive volumetric measurements, these methodological refinements enable us to examine changes in hippocampal shape for the structure as a whole. Shape analyses may yield novel information about structural brain changes in aging and dementia that are not reflected in volumetric measurements alone. In this paper we describe our protocol for hippocampal volumetry (see Appendix) and shape analysis, provide inter- and intra-rater reliability data, and examine demographic and neuropsychological correlates of hippocampal volume measurements in a sample of healthy older adults.

METHOD

Participants

A total of 40 healthy control participants (age 70.6 ± 5.1 years, 28 females) from the Memory and Aging Study at Dartmouth Medical School were included in this analysis. The Memory and Aging Study cohort is described in detail in our prior reports (Saykin et al., 2004; Saykin et al., 2006). Participants provided written informed consent according to procedures approved by the Dartmouth Medical School Committee for the Protection of Human Subjects. Control participants were recruited mainly through public lectures and advertisements. Screening and assessment procedures included a comprehensive telephone interview, medical chart review, and neuropsychological and geropsychiatric evaluations. In addition, demographic and self-report questionnaires were completed by the participants and their collaterals. Exclusion criteria included significant cognitive complaints, MCI or dementia, other relevant medical, psychiatric or neurological conditions, a history of head trauma with loss of consciousness lasting more than 5 minutes, a current or past history of substance abuse or dependence, left-handedness, and factors contra-indicating MRI.

MR Image Acquisition

Scans were acquired using a 1.5 T GE Signa LX scanner and a multi-axial local gradient head coil system (Medical Advances, Inc., Milwaukee, WI, USA). A three-dimensional

spoiled gradient recalled acquisition in a steady state (SPGR) sequence was acquired for volumetric analysis (TR = 25, TE = 3 or min, flip angle = 40, NEX = 1, and slice thickness = 1.5 mm without gaps, yielding 124 contiguous slices with a 24-cm field of view and 256 × 256 matrix with 0.9375-mm in-plane resolution). SPGR scan acquisition time was approximately 10 minutes. In addition, a fast spin echo T2-weighted scan (TR = 3000, TE = 96, 3-mm contiguous axial slices) was acquired and reviewed along with the SPGR scan by a Board-certified neuroradiologist to rule out incidental findings.

Image Transfer and Preprocessing

Each SPGR scan was transferred via ethernet from the MRI Center in Radiology to a Silicon Graphics Octane workstation (IRIX 6.5) in the Brain Imaging Laboratory. Images were prepared for use by resampling into 1-mm isotropic voxels. Scans were realigned along the interhemispheric fissure in the axial and coronal planes and then the long axis of the hippocampus in the sagittal plane.

Hippocampal Tracing

Using the BRAINS program (Andreasen et al., 1993), the boundaries of the hippocampus were visualized in the three orthogonal views. The “telegraphing” function was used to transfer boundary demarcations obtained in the axial and sagittal views to the coronal view, on which the traces were completed and volumetric measurements derived. We included in the hippocampal formation (HF): the hippocampus proper, dentate gyrus, subicular complex, alveus, and fimbria (Duvernoy, 1988). Our hippocampal boundary definitions and guidelines are described in detail in the Appendix.

Volumetric Correction

Total intracranial volume (ICV) was obtained by tracing the total brain area, including the cortex, cerebellum, brainstem, and cerebrospinal fluid (CSF), on every other slice of the original SPGR coronal series yielding traces at contiguous 3-mm intervals. All hippocampal volumes were adjusted for ICV using linear regression (Mathalon, Sullivan, Rawles, & Pfefferbaum, 1993).

Reliability Measures

One rater, blinded to diagnostic and demographic data, traced the SPGR scans. Six scans were used to examine intra- and inter-rater reliability, and were traced independently by a second rater. Each pair of reliability traces was completed within a 2-week period.

Shape Analysis

There are numerous methods that can be applied to analysis of the shape of brain structures (Bookstein, 1997; Dryden & Mardia, 1998; Gerig, Styner, Shenton, & Lieberman, 2001; Saykin et al., 2003; Saykin et al., 2001; Shenton et al., 2002; Thompson et al., 2004). In the present report, shape analyses were performed using the left and right hippocampal traces, obtained as described above and in the Appendix. A three-dimensional binary image was reconstructed from each series of two-dimensional slice-by-slice hippocampal segmentations, with voxel values corresponding to whether each voxel was included (1) or excluded (0) in the region of interest (ROI). The surface of this three-dimensional hippocampal image was modeled as a mesh of square faces. Spherical harmonic (SPHARM) description was used to model the hippocampal surfaces (Brechtbuhler, Gerig, & Kubler, 1995). Briefly, this included parameterizing the hippocampal surfaces using spherical coordinates described by three spherical functions. Each surface was reconstructed using the SPHARM coefficients, which were normalized to preserve shape information while excluding translation, rotation, and scaling. The shape descriptor was then formed using a

set of surface landmarks that were uniformly sampled by normalized reconstruction and hence comparable across participants. Thus, for a given group of hippocampi, the mean shape was estimated by averaging those landmarks.

RESULTS

Intra- and Inter-rater Reliability Coefficients

Intra- and inter-rater reliability were assessed using the intraclass correlation coefficient (ICC) (Shrout & Fleiss, 1979). Intra-rater reliability ranged from 0.94 to 0.99 across raters and left and right hippocampal measurements (mean ICC = 0.96). Inter-rater reliability for right hippocampal volume was ICC = 0.96, with a mean volume difference between raters of 1.16% (± 1.98). Inter-rater reliability for the left hippocampal volume was 0.95 with a mean percent difference of -0.58 (± 1.40). All inter-rater differences for individual hippocampal volumes were below 5%.

Volumetric and Morphometric Data

Total ICV-adjusted volumes were 3.48 cc (± 0.43) for the left hippocampus and 3.68 (± 0.42) for the right hippocampus. There were no significant volume differences between males and females for either the left or the right ICV-adjusted hippocampal volumes ($p > .05$; Table 1). An expected sex difference in ICV was found, with males showing larger brain volumes ($p < .01$, Table 1). There were no significant correlations between ICV-adjusted hippocampal volumes and age or memory performance ($p > .05$). Results of SPHARM analysis of shape features are shown in Figure 2. The surface renderings represent the mean shape of the left and right hippocampi of the healthy older adult sample. The within-group variability for all surface locations is represented by the color scale.

DISCUSSION

This paper describes a standardized protocol for hippocampal volume and shape analysis developed in our laboratory, and presents normative data for an older adult sample. Key features of the hippocampal tracing methodology include the alignment of the images in the plane of the long axis of the hippocampus, and the use of the “telegraphing” function in the BRAINS software package to maximize visualization and demarcation of otherwise ambiguous anterior and posterior hippocampal boundaries. Together with advances in MR technology, these procedures permit manual segmentation of the entire hippocampus with high inter- and intra-rater reliability, as well as disambiguation of the hippocampal-amygdalar boundary and extraction of comprehensive hippocampal shape data.

Although manual segmentation of brain structures for volumetry and shape analyses has contributed extensively to progress in clinical neuroscience, there are significant limitations to these methods. Manual tracing strategies are time consuming and expert dependent. Robust automated approaches will circumvent these problems and facilitate analysis of data from larger scale studies. Software is currently being developed and validated for automated parcellation of numerous brain structures (e.g., Fischl et al., 2004; Tzourio-Mazoyer et al., 2002) including the hippocampus (Csernansky et al., 2000).

Another limitation has been the spatial resolution, signal to noise, and contrast of relatively small ROIs such as the hippocampus and related medial temporal structures located deep within the brain. New higher-field MR scanners operating at 3.0 Tesla and beyond are becoming increasingly available in clinical research settings. These high-field magnets generally yield more signal and better resolution, but may also introduce image artifacts particularly in the medial temporal region. New phased array and surface coils may help

address these issues. Overall, ongoing developments in MR-related hardware and software are likely to result in less labor-intensive, more detailed hippocampal measurements.

Improved segmentation methods and enhanced MR technology will also facilitate new directions in research on hippocampal function and dysfunction. For example, Csernansky and colleagues recently reported a protocol for structural analysis of hippocampal subfields based on segmented MR data (Csernansky et al., 2005). This appears useful for early detection of regionally specific pathology, such as seen in preclinical AD. Related methods could also enhance understanding of normal hippocampal function. The hippocampal unfolding method developed by Zeineh and colleagues to analyze hippocampal subfield specificity of fMRI activation facilitates conjoint structure–function analysis (Zeineh, Engel, & Bookheimer, 2000; Zeineh, Engel, Thompson, & Bookheimer, 2001). Hippocampal ROIs can also be useful for analyses of MR-based diffusion tensor and trace diffusivity data (West et al., 2005). These precise mapping approaches expand the potential for investigating structural integrity and neural activity associated with memory processing within the hippocampus and other memory-critical circuits. It has been a half century since the classic studies of bilateral temporal lobectomy patient H.M. (Scoville & Milner, 1957) and a century since Alzheimer (1907) identified the pathology associated with the disease that bears his name. Memory impairment is a pivotal concern in clinical neuro-psychological practice and neuroimaging now provides unprecedented opportunities for investigation of the neural substrates of human memory and its disorders.

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APPENDIX

Hippocampal Boundary Definitions

Anterior boundary

The anterior is the most difficult of the hippocampal boundaries to visualize. For the lateral aspect of the anterior boundary, the hippocampal formation is separated from the amygdala by the temporal horn (Jack, 1994). However, the amygdala and hippocampus are frequently juxtaposed to one another, particularly in the medial anterior aspect. The alveus, a thin band of white matter covering the hippocampus, is usually discernable on the sagittal view and serves as a useful demarcation (Figure 3A). A boundary line can be traced in the sagittal plane and rendered on the coronal view to guide the measurement (Jack, 1994; Watson et al., 1992). In the case where the alveus is not visible, following Jack (1994), a straight line was drawn from the lateral ventricle to the edge of ambient gyrus, creating telegraph marks

onto the coronal view to be used as guides. The anteriomedial edge can usually be telegraphed by tracing on the axial plane as well. The uncus can easily be seen as separate from the entorhinal cortex (EC) and coronal nucleus of the amygdala, in either the sagittal or axial plane (Figure 3B, arrow). This is more striking in the plane of the long axis of the hippocampus than in the AC–PC plane, where the amygdala is larger. The hippocampus generally has some digitations on the medial edge that point superiorly toward the amygdala, and we include these digitations in our tracings (Figures 3B, rightside, and 3C).

Posterior boundary

The tail of the hippocampus is visualized most readily in the sagittal plane, where it is surrounded by white matter on three sides (Duvernoy, 1988). According to our procedures, the boundaries are checked in the axial plane (where the hippocampal tail may appear to tilt down) (Figure 3E, arrows) and in coronal sections (where it is the only piece of gray matter, surrounded by white matter), and guide tracings can be made as needed (Figure 3F). Often the hippocampal tail extends medially to the third ventricle and should be traced to its full extent (Figure 3D, arrow). It is important to use all three orthogonal views to see the terminal segment of the hippocampal tail (Figure 3D–F). It should be noted that we generally trace the hippocampus posteriorly to anteriorly.

Lateral boundaries

The lateral border of the hippocampus is the CSF of the temporal horn of the lateral ventricle (Figure 4A, arrow, and Figure 4B). The dorsolateral aspect of the HF is demarcated by the temporal horn, the lateral aspect by the contrast between the gray matter of the HF and the white matter of the temporal stem (Jack, 1994).

Inferior boundaries

On the inferior bank, the subicular complex is included in the trace (Figure 4B, arrow). Separation from the entorhinal cortex is a concern and outlining of the subiculum is performed in the sagittal plane in multiple slices superiorly, adjacent to the lateral ventricle, as well as inferiorly, adjacent to the uncinate fasciculus. The border separating the subicular complex from the parahippocampal gyrus can be seen by using the angle formed by the most medial extent of the subiculum and parahippocampal cortex as recommended by both Jack (1994) and Watson and colleagues (1992).

Medial boundaries

The medial aspect is bounded by the CSF in the uncus and ambient cisterns, and the dorsomedial aspect is bounded by the choroidal fissure. Occasionally these boundaries are difficult to visualize, and the hippocampal head is sometimes better observed in the axial view, where the semilunar gyrus can be seen in the uncus (see Figure 3B). A composite of coronal hippocampal traces from posterior to anterior is shown in Figure 5. Hippocampal length varies from approximately 40 mm to 52 mm from anterior to posterior extent. Because of this variability, the number of slices traced differs between cases.

Figure 1. Orthogonal planes showing (A) axial, (B) coronal, and (C) sagittal views of the traced hippocampal boundaries. The crosshairs are in the anterior section of the hippocampus. Partial traces in the axial and sagittal views are represented by small crosses on the coronal view.

Figure 2.
Group mean shape of the segmented left and right hippocampi for a normal aging sample.
Each hippocampal image represents a surface rendering with within-group variance color mapped onto the surface.

Figure 3.

Anterior and posterior boundaries of the hippocampus. (A) The anterior boundaries between the hippocampus and amygdala are best visualized sagittally. The alveus (arrow) can be used as a boundary. (B) In the axial view, the uncus notch can discriminate the hippocampal medio-anterior boundary from the coronal nucleus of the amygdala (arrow). Outlining, as shown in the right side of the brain (shown on the left side of the image in radiological convention), will help segregate the head of the hippocampus from the amygdala boundaries. (C) Anterior boundary of the hippocampus in the coronal plane. (D) The most posterior area of the hippocampus is traced in the sagittal view. (E) The axial plane can help locate the end of the tail of the hippocampus where there are often variations in anatomy, e.g., it may turn medially or continue further anteriorly. Here, telemarks show the tail tipping downward in the radiologic right hippocampus, but not on the left (see arrows). (F) In the coronal view, the posterior (tail end) hippocampi are seen under the crus of the fornix.

Figure 4. Medial boundary of the hippocampus. (A) In the sagittal view, the medial aspect of the subiculum can be seen clearly and is outlined to show telemarks in the coronal plane. Also, telemarks from the axial plane can be seen outlining the head of the hippocampus. In the coronal view (B), the subiculum extends toward the CSF.

Figure 5. Series of coronal slices showing the hippocampus traced from the posterior, tail region, to the anterior, or head of the hippocampus.

Table 1

Hippocampal and intracranial volumes (cubic centimeters)

	Males	Females	<i>p</i>
Right hippocampus ^a	3.66 (0.44)	3.70 (0.42)	NS
Left hippocampus ^a	3.52 (0.56)	3.46 (0.38)	NS
Intracranial volume	1485.69 (115.16)	1364.51 (108.66)	.003

^aAdjusted for intracranial volume. Data are mean (*SD*). NS= not significant.