Hippocampal Volumetrics and Region of Interest Methodology in MRI: Identifying homogeneous observations in an inhomogeneous environment.

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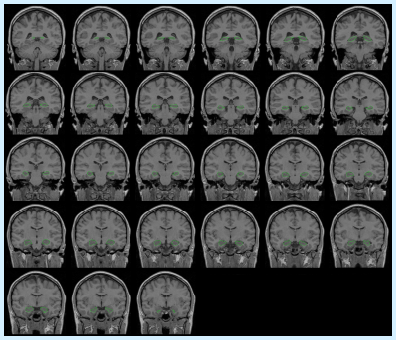
ABSTRACT

Hippocampal volumetrics are important for studying disease progression and diagnosis of temporal lobe epilepsy, Alzheimer's disease and schizophrenia. However, comparing volumetric variation across studies is difficult due to differing anatomical boundaries, subject characteristics, statistical analyses and image processing techniques. One approach to this problem is to create a database of the homogeneous aspects of studies to increase uniformity and get comparative results. The Internet Brain Volume Database (IBVD) was created to provide a comparison of the various aspects of volumetric studies. As an example of this approach, the current study evaluates normal ranges of volumes in the hippocampus across published studies with similar manual methods and anatomical boundaries. The purpose was to compare and evaluate region of interest (ROI) methods of volumetric analysis and generate a summary of trends and results. Twenty-one peer-reviewed studies involving ROI measurements of the hippocampus were surveyed for their methods and were selected if they included the hippocampal formation as the anatomical boundary and a figural image of the boundary in the research article. This approach was chosen to reduce confusion over anatomical boundaries of the hippocampus and to compare a more homogeneous sample. Other sources of variance were also compared including subject characteristics, image processing techniques and volumetric software. Our results suggest a wide variance of volumes across studies for normal ranges of hippocampal volumes. These results summarize and emphasize that anatomical boundaries, subject characteristics, slice thickness, image processing and image analysis all affect volumetric measurements and should be carefully reported in manuscripts and compared among studies.

INTRODUCTION

Comparing differences in volumetric variation across research laboratories is difficult due to differing segmentation methodology (ROI, VBM), anatomical boundaries, image processing (magnet strength, slice thickness, slice spacing, field of view, matrix), image analysis (volumetric software, statistical packages), and subject variables (age, gender, handedness). In essence, inhomogeneity results from variance. One approach to this problem is to create a database of the homogeneous aspects of studies in order to get uniformity and comparative results. The Internet Brain Volume Database (IBVD) was created to provide a comparison of the various aspects of volumetric studies and can be used to compare subsets of the dataset which include homogeneous methods. By comparing studies with homogeneous methods, it becomes possible to begin to provide some uniformity and framework for comparison of results. IBVD provides a web-based searchable database of brain neuroanatomic volumetric observations from published manuscripts and can be found on the web at http://www.cma.mgh.harvard.edu/ibvd/. IBVD enhances the ability to perform comparative and integrative studies, as well as meta-analysis and is designed to access both group volumetric results and volumetric observations in individual cases. As an example of this approach, the current study was designed to evaluate normal ranges of hippocampal volumetrics across published studies with similar manual methods and anatomical boundaries. The purpose of this study was to compare and evaluate ROI methods of volumetric analysis and generate a summary of trends and results. From this study, we attempted to obtain normative ranges of hippocampal volumes from twenty-one peer-reviewed published journal articles that utilized a similar basis for the definition of hippocampus and we documented the differences in methodologies among the papers that may account for the variances in volumetric measurements.



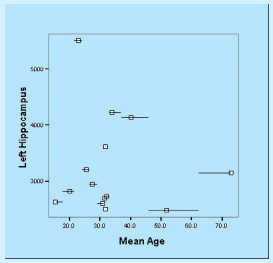
METHODS

We performed Medline searches that included the keywords, 'hippocampus', 'MRI' and 'structural' and found 696 matching records. From these records, we chose a subset of papers that:

1) included region of interest (ROI) manual segmentation methods,
2) defined the hippocampal formation as the anatomical boundary
3) provided a figural image of the anatomical boundaries in the manuscript.

Twenty-one research articles were chosen matching these three criteria and were included in the current study. In this study, we attempted to review papers with similar anatomical boundaries that measured the hippocampal formation; that is the hippocampus proper and other structures surrounding the hippocampus. Only articles that included a figural image of the written anatomical descriptions of the hippocampus were included in this review to insure the written descriptions were accurate. Other sources of reported volumetric variance were also considered including differences in statistical analyses, technological methods (include image analysis and image processing) and subject characteristics. Each of these variables were compared to illustrate how differences in volumetric variation can be approached.

Figure1. Normative Volumetric Ranges for Left hippocampus



RESULTS

21 peer-reviewed manuscripts reporting normative hippocampal volumes were compared. The four main sources of volumetric variability; anatomical definitions, statistical analyses, technological methods (image analysis and image processing) and subject characteristics were each compared. Figures 1 and 2 provide estimates of normative hippocampal volumes by hemisphere and age groupings (20 -70 yrs). Image processing and analysis methods including slice thickness, field of view, matrix and voxel size, scanner type, volumetric software, magnetic field strength and slice spacing were all compared across studies. In general, for the twelve studies employing a slice thickness < 2mm, a mean hippocampal volume of 5547mm3 was found and for the eight studies reporting a slice thickness >/= 2mm a mean hippocampal volume of 7195mm3 was found. In addition, the GE signa scanner was the most commonly employed among studies (n=8) followed by the Siemens scanner (n = 6) and the Phillips gyroscan (n = 2) and the Medspec S200 (n =1) while some studies failed to report their scanner type (n = 4). The majority of studies reported using a 1.5 Tesla magnetic field strength for the MRI machine (n =17). The volumetric software reported ranged widely from software created by the individual laboratories (n = 5) to software provided by MRI manufacturers (n = 5) to other commercially available software including Analyze, BRAINS, MIDAS and DISPLAY (n = 7), while some authors did not report the volumetric software at all (n = 4). Subject characteristics were reported in Table1 and showed that most of the studies reported age (n =20) and gender breakdown (n = 18) of study participants although very few reported volumetric measurements by gender (n = 6) or by handedness (n = 1). The total mean of the combined normative hippocampal volumes from these studies was 3180 mm3 for left hippocampi and 3145 mm3 for right hippocampi. Total mean hippocampal volume (right + left) for these studies was 6159 mm3. A comparison of hippocampal volumetrics by gender showed women (right = 3489 mm3, left volume = 3366 mm3) to have lower mean hippocampal volumes than men (right = 3741 mm3, left = 3589 mm3) Comparisons of studies with mean age ranges from 20 – 50 years showed mean hippocampal volumetrics including right hippocampus of 3326 mm3, left hippocampus of 3257 mm3, and total mean volume of 6891mm3.Studies with mean ranges > 50 years suggested hippocampal volumetric declines with age (right volume = 2429 mm3, left volume = 2377 mm3, total volume = 4210 mm3) . A comparison of hippocampal volumetrics and handedness was not possible due to the small number of studies reporting left-handed subjects volumetric measurements.

Figure 2. Normative Volumetric Ranges for Right Hemisphere

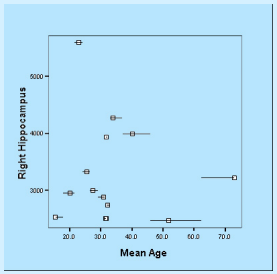


Table 1. Mean Hippocampal Volumes and subject demographics across studies

	Mean Hippocampal Volume				Adjusted Volume	Demographics		
Study	Left	Right	Total	R > L		n	Mean Age	M > F Volume
Abernethy 2002	2632	2530	5162	No	NO	8	15.5	NS
Achten 1995	5503	5595	11098	No	NO	14	23	NS
Agartz 1999	3571	3834	7405	Yes	NO	36	31.8	Yes
Bobinski 2000	NA	NA	4024	NA	NO	4	NA	NS
Csernansky 1998	2603	2874	5477	Yes	NO	15	30.9	NS
Dickerson 2001	1600	1500	3100	Yes	YES	34	70.3	NS
Eberling 2003	NA	NA	2420	NA	YES	84	69.4	Yes
Hackert 2002	3150	3220	6370	Yes	NO	511	73.0	NS
Lemieux 2000	2501	2497	4998	No	NO	20	31.7	NS
MacQueen 2003	2732	2738	5470	Yes	NO	37	32.3	NS
Piven 1998	2750	2855	5605	Yes	NO	36	20.2	Yes
Pruessner 2000	3209	3325	6533	Yes	NO	40	25.5	Yes
Seidman 2002	4140	3990	8130	No	NO	48	40.1	NS
Seidman 1999	NA	NA	9800	NA	NO	26	38.8	NS
Sheline 1999	2482	2468	4951	No	NO	24	51.8	NA
Sheline 1996	2544	2577	5121	Yes	NO	10	68.0	NA
Szabo 2001	2949	2999	5948	Yes	NO	34	27.5	NS
Tebartz 2003	3550	3890	7440	Yes	YES	8	30.5	NA
Watson 1997	4130	4214	8344	Yes	NO	61	34.0	Yes
Webb 1999	2700	2500	5200	No	NO	30	31.6	NS
Yucel 2002	3698	3804	7502	Yes	YES	42	31.1	Yes

CONCLUSIONS

Establishing normative volumetric values for anatomic structures is imperative to assess small but potentially pathological volumetric differences in brain structures in different neurological diseases. For example, hippocampal volumetric differences of a few cubic millimeters could suggest the insidious onset of Alzheimer's disease and provide the basis for pharmaceutical therapy early enough to delay clinical symptoms. Although a variety of methods could be valid if consistent internally, external consistency across research labs would permit integration of data across sites and studies. Establishing some basic homogeneous methods in hippocampal volumetry studies may provide the consistent results necessary for comparison of volumetric variance across research laboratories. This would include more complete reporting of study methodology of subject characteristics (age, gender, handedness), image processing (magnet strength, slice thickness, slice spacing, field of view, matrix), image analysis (volumetric software, statistical packages techniques), anatomical boundaries and segmentation methodology (ROI, VBM). The current study was designed to evaluate normal ranges of volumes in the hippocampus across published studies with similar manual methods and anatomical boundaries. It was used as an example to illustrate how to approach differences in volumetric variation and begin to increase uniformity and obtain more comparative results across studies.

Conflict of Interest: Drs. Worth and Sullivan are employees of Neuromorphometrics, Inc.