Quantitative analysis of the hippocampus using images obtained from 7.0 T MRI

Zang-Hee Cho a,⁎, Jae-Yong Han a, Seok-Il Hwang a, Dae-shik Kim d, Kyoungh-Nam Kim a, Nam-Beom Kim a, Seog Ju Kim b, Je-Geun Chi a,c, Chan-Woong Park a, Young-Bo Kim a

a Neuroscience Research Institute, Gachon University of Medicine and Science, Incheon 1198 Kuwol-dong, Namdong-gu, Incheon 405-760, Korea
b Department of Psychiatry, Gachon University of Medicine and Science, Incheon, Korea
c Department of Pathology, Seoul National University, Seoul, Korea
d Center for Biomedical Imaging, Boston University, Boston, MA, USA

A R T I C L E   I N F O

Article history:
Received 27 August 2009
Revised 2 November 2009
Accepted 3 November 2009
Available online 10 November 2009

Keywords:
Hippocampus
Volumetry
Neurological diseases
7.0 T MRI

A B S T R A C T

In-vivo volumetric measurements of hippocampus have proven to be highly informative for studying various neurological diseases such as Alzheimer’s disease. The usefulness of volumetric imaging, however, has been limited due to the poor image resolutions obtained by currently available MRI images. In this study, a new result of volumetric image measurement of the hippocampus using 7.0 T MRI images of high contrast and resolution is described. To verify the usefulness of the proposed method, its reliability and sensitivity were examined and compared with existing imaging techniques such as 1.5 T or 3.0 T MRI imaging. The results of our study with 7.0 T MRI clearly demonstrated superior boundary detection for the hippocampal head, body, and tail compared with low field MRIs. In conclusion, robust and reproducible volumetric measurements as well as 3D images of clear contrast obtained with 7.0 T suggest the usefulness of high field MRI imaging and its eventual use for the accurate diagnosis of hippocampal diseases and related research.

© 2009 Elsevier Inc. All rights reserved.

Introduction

Alterations in hippocampal shape and volume have been suggested to be closely associated with a number of neurological disorders. It is well known that the hippocampus plays many crucial roles in brain functions such as memory and mood regulation, among others. In the past, a large number of hippocampal morphological studies have been performed using magnetic resonance imaging (MRI). While several studies have reported global changes in brain volume and shape associated with neurological diseases (MacQueen et al., 2003; Schott et al., 2003; Maller et al., 2007), specific changes, such as localized volumetric deformations and atrophy proved to be especially challenging (Posener et al., 2007; Posner et al., 2009). Changes and changes that occur within the substructure because of localized boundary parcellation techniques for head and body. In order to investigate its potential for the elucidation of detailed hippocampal

cornu ammonis (CA 1–4) and dentate gyrus (DG) within its small volume. Therefore, it has been difficult to observe small volumetric changes and changes that occur within the substructure because of the limited resolution of the images obtained with previously available MRIs such as 1.5 T or 3.0 T MRIs. The present study hypothesizes that these limitations can be circumvented by utilizing the unique advantages of ultra high field MRI such as 7 T human MRI systems. The availability of 7.0 T MRI has now increased to nearly 30 units all over the world (26 units at the end of 2008). Along with the increased number of 7.0 T MRI scanners, the area of application for 7.0 T MRI studies have also expanded, including novel research subjects such as functional angiography (Cho et al., 2008), microvessel imaging (Kang et al., 2009), and cortical structural studies. 7.0 T MRI makes it possible to obtain ultra high-resolution images with resolutions as high as a few hundred microns in in-plane resolution with excellent image contrast (Li et al., 2006; Duyon et al., 2007; Cho et al., 2008a). In particular, previous studies demonstrated in vivo human imaging of the hippocampus with a high resolution as high as 250 μm in in-plane resolution with a 0.5–3 mm slice thickness using 7.0 T MRI (Cho et al., 2008b; Thomas et al., 2008; Theysohn et al., 2009).

In the present study, 3D high-resolution hippocampal imaging was performed and images of the hippocampal substructure down to as high as 0.35 × 0.35 × 0.35 mm³ were obtained. Based on these high-resolution and contrast images, we developed new delineating and boundary parcellation techniques for head and body. In order to investigate its potential for the elucidation of detailed hippocampal...
obtained were processed by manual tracings. First, the structure of the hippocampus was defined from 3-Dimensional images and traced manually using a part of two software packages, 3D slicer (http://www.slicer.org) and MRicro (http://www.sph.sc.edu/comd/orden/mricro.html). For the most part, the boundaries of the hippocampus were traced according to methods described in previous studies (Jack et al., 1995; Pantel et al., 2000), and the work of Duvernoy was used as a reference for anatomical details (Duvernoy 1998). The trace was begun at the anterior-most point of the sagittal slices of the 3D T2* images shown in Fig. 3a. As shown in Fig. 3b, after the anterior-most point was defined, the lateral portion of the hippocampus was delineated by manual tracings made in the sagittal plane along the lateral border, which was generally well distinguished from the temporal horn of the lateral ventricle. The medial portion of the hippocampus was delineated using coronal slices from the anterior to the posterior point, as shown in Fig. 3c. The 3D T2* image had superior contrast between tissue layers and, in most cases, was sufficient to trace the head and body of the hippocampus. Therefore, there was no need to define additional markers for manual tracing. However, the posterior hippocampal boundary was relatively difficult to define and needed special attention. The fascicular gyrus forms a transitional area that bridges the gap between the indusium griseum and hippocampal tail. Fig. 4a and b show the details of those connections on T2* weighted sagittal images (b shows an expanded view image). The two red lines intersecting Fig. 4b correspond to the two oblique axial images shown in Fig. 4ci (the superior red line) and 4cii (the inferior line). For the volumetric delineation, we defined the end of the hippocampal tail as the area of disconnect between the hippocampus and the fasciolar gyrus seen in Fig. 4ci indicated by the red arrows, the

**Methods**

**Subjects**

Sixteen healthy volunteers (7 females; 9 males; mean age of 42.5 years) were recruited for the study. Three cases were excluded because of motion and artifacts. Lifetime medical and psychiatric illnesses were assessed by conducting structured interviews. No subjects suffered from significant medical or neurological illness. In addition, no subjects had current or past Axis I psychiatric disorders as determined by the Structured Clinical Interview of the Diagnostic and Statistical Manual of Mental disorders IV (SCID-IV), which was conducted by a psychiatrist. The legal and ethical aspects of the study were reviewed and approved by the institutional review board (IRB) of the university as well as the Korean Food and Drug Administration (KFDA). The subjects were required to sign consent forms prior to the experiments.

**MR Imaging**

Brain images were obtained by 7.0 T (Magnetom, Siemens, Enlargen) and 1.5 T (Avanto, Siemens, Enlargen) MRI scanners. For the scan, a 3D fast low-angle shot (Spoiled FLASH) sequence was utilized; the imaging parameters used were repetition time (TR) = 50 ms, echo time (TE) = 25 ms, flip angle (FA) = 10°, pixel band width (BW) = 30 Hz/pixel, field of view (FOV) = 200 mm, matrix size = 512 × 576 × 60, 3/4 partial Fourier, and number of average (NEX) = 1. The total acquisition time (TA) was 14 min and 27 s. An isotropic image resolution of 0.35 × 0.35 × 0.35 mm³ voxels was obtained. To locate the exact slice position on the hippocampus, 2D low-resolution pre-scans were performed in the coronal and sagittal planes. Also, to reduce the scan time, the image plane was set parallel to the longest axis running through the hippocampus, and a 3/4 partial k-space acquisition was achieved along both the slice encoding and phase encoding directions. In this study, a homemade multichannel radiofrequency (RF) coil was utilized to perform the 7.0 T MRI experiments. The coil consisted of one dual Helmholtz Tx coil with a quadrature field and eight channels of single loop Rx coils. The loop Rx coils were evenly distributed in a single row and each loop dimension of the Rx coils was 130 mm in height (z direction) and 105 mm in width (xy plane), and the overall Rx coil diameter was 220 cm. The Tx coil was 300 mm in width and 150 mm in length. The design of the RF coil used incorporates multiple symmetric loop coils to encompass the entire brain area (Fig. 1).

Fig. 2 shows a reconstructed 3D image with three views, together with three sets of a few selected axial, coronal and sagittal images obtained by 7.0 T MRI. Fig. 2a shows a reconstructed 3D volume image, and (b), (c) and (d) show representative sagittal, coronal, and axial images of the hippocampus obtained by 7.0 T imaging. As shown, 7.0 T images distinctly show the clear boundary and surroundings of the hippocampus as well as defined internal structures. This high-resolution 3D image suggests the great potential of 7.0 T imaging, and the possibility of accurately parcelling the data to produce accurate and reliable volumetric images of the 3D structure of the hippocampus hitherto unseen for in vivo human brain imaging.

**Manual tracing**

Initially, the ultra high-resolution hippocampal images we obtained were processed by manual tracings. First, the structure
point immediately before the fasciolar gyrus bends toward the superior surface. The oblique axial section directly below in Fig. 4cii shows that the tail of the hippocampus and the fasciolar gyrus are in fact continuous.

High-resolution 7.0 T MRI images are also extremely helpful in delineating the inner structures of the hippocampus. The hippocampus was divided into head, body, and tail segments to perform subregional structural analysis (See Fig. 5). The hippocampal head is connected to the uncal apex. We defined the hippocampal head as the area from the anterior end of the hippocampus to the point at which the uncal apex no longer appears along the coronal plane (see the blue dotted circles in (iv) on the left of Fig. 5). Toward the end of hippocampus, two parts of the hippocampus lie in the coronal plane, i.e. the CA and the subiculum (see right side image of Fig. 5). When moving toward the posterior end of the hippocampus, the length of the CA increases gradually and becomes equal in length to the subiculum (coronal view (v) right side of the Fig. 5). We defined this point as the beginning of the tail of the hippocampus. The image acquisition plane was set parallel to the longest axis of the hippocampus, therefore, the borders delineating the “head and body” and the “body and tail” assumed in this study are perpendicular to the longest axis of the hippocampus. Middle image in Fig. 5 shows the volumetric image of the body of the hippocampus.

Finally Fig. 6 shows 3D volumetric images obtained by the parcellation technique discussed above and 3D T2* images of the hippocampus based on image data from 1.5 T and 7.0 T MRI, respectively. Our 7.0 T volumetric surface modeling is clearly superior in visualizing the detailed substructures showing the details of the head, body, tail, and subiculum of the hippocampus as seen from the inferior view (see Fig. 6a and b). In 7.0 T volumetric image, one can clearly see even the undulated structures of the hippocampal formation including subiculum, often mislabeled as dentate gyrus.

**Statistical analysis**

Two trained raters participated in the study to demonstrate the superior performance of 7.0 T T2* images in volumetric delineation and parcellation. We employed the Intraclass Correlation (ICC) to determine the inter-rater reliability of the manual tracings of the hippocampus. In addition to the ICC, we also evaluated the sensitivity of this technique (Pantel et al., 2000), which indicates the likelihood of agreement between two raters (see Table 1). Paired sample t-test was used to assess the significance of the differences in reliability (ICC) and sensitivity between 7.0 T and 1.5 T MRI. A P-value of less than 0.05 was considered significant.
Results

Table 1 presents data on the ICC, sensitivity, and raw volumes of the different parts of the hippocampus. The ICC and sensitivity for the tracings of the 7.0 T vs. 1.5 T MRI images are shown in Fig. 7. The values for 7.0 T were significantly better than 1.5 T (ICC, \( p < 0.05 \); sensitivity, \( p < 0.05 \)), although ICC and sensitivity were dependent on other factors. The mean volumes of the left and right hippocampal complexes were also calculated and listed in Table 1. It should be noted that the volume of the various parts of the hippocampus are influenced by other factors and appears to be larger with 7.0 T. This may be due to the accurate parcellation of the hippocampal boundaries in comparison to 1.5 T MRI.

Discussion and conclusion

The aim of this study was to measure the reliability and sensitivity of 7.0 T hippocampal image parcellation compared to 1.5 T. Therefore, the study was limited to normal healthy volunteers. The reliability (ICC) and sensitivity between two raters were very high for 7.0 T MRI and found to be substantially better than 1.5 T (see Table 1 and Fig. 7). The findings presented here demonstrate 7T's potential for the accurate quantification of volumetric changes in the hippocampus, which may be particularly valuable for the investigation of neurological diseases such as Alzheimer's disease.

Ultra high-field T2* contrast images display a number of advantages that may be of use for further research applications. Recently, many research groups have applied imaging parameters optimized for hippocampal analysis (Thomas et al., 2008; Theysohn et al., 2009) and demonstrated anatomical details with an excellent in-plane resolution of as low as few 100 microns. However, these studies were mostly focused on acquiring 2-D images with relatively thick slices, therefore, missing large portions of the hippocampal structure and details in the slice direction.

In addition to superior signal to noise ratio, ultra high field MRI such as 7.0 T has a number of advantages from the perspective of quantitative analysis. First, T2* weighted 3D volume images, due to better contrast and resolution, provide useful information for volumetry as well as for the identification of inner structures. Secondly, as shown in Fig. 2 (red arrows), many distinct boundaries can be observed within the hippocampal surroundings including the amygdala in 7.0 T images. The guidelines to distinguish between the hippocampus and the amygdaloid complex have been described in the previous reports (Pantel et al., 2000; Malykhin et al., 2007); however, their T1 contrast were relatively poor and did not allowed us to identify the border between the two structures. In 7.0 T images, however, it is possible to clearly differentiate between the hippocampus and the amygdaloid complex. Thirdly, the boundaries between the head and the body, and the body and the tail of the hippocampus can be clearly defined as we have demonstrated (See Fig. 4). As recent reports have indicated,
Fig. 4. Illustration of identification of the tail of the hippocampus. A sagittal image (a) shows the location of selected slices (red lines) that were used to determine the tail of the hippocampus. An expanded view of the a is shown in b. Panel c represents the two axial views corresponding to the red lines indicated in a and b. Red arrows indicate the area of disconnection and reconnection between the hippocampal tail and fasciolar gyrus seen in (c)i and (c)ii, respectively.

Fig. 5. Selected coronal slices of the hippocampus at the junctions of the head and body and the body and tail. The five coronal images on the left are slices at the boundary between the hippocampal head and body. The blue dotted areas represent the uncal apex. The uncal apex disappears gradually as the end of hippocampal head approaches the body. The image v on the left shows the initial portion of the hippocampal body. The coronal images on the right are slices at the boundary between the hippocampal body and tail. The red dotted area represents both CA and subiculum. The length of the CA gradually increases posteriorly and becomes equal to subiculum. We have defined this junction as the beginning of the tail.
quantitative regional analysis is becoming increasingly important due to the correlation between the morphology of the hippocampus and related diseases (Maller et al., 2007).

In conclusion, the hippocampus has received a considerable amount of attention, since it is believed to play many important roles in the brain. It has been implicated in the pathogenesis of a number of neurological diseases such as Alzheimer’s disease, depression, and schizophrenia. Although the association of hippocampal atrophy with depression and schizophrenia is still controversial, Alzheimer’s disease has proven to be strongly correlated with hippocampal atrophy (Schott et al., 2003). Some initial clinical cases have been obtained and exhibited close correlation to the hippocampal atrophy of actual Alzheimer’s patient. Work is in process and will be reported later. Therefore, the accurate volumetric measurement as well as the clear identification of hippocampal structures by high field MRI would be an extremely important adjunct for the accurate diagnosis of these diseases as well as for basic science research.

### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Area</th>
<th>7.0 T</th>
<th>1.5 T</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reliability (ICC)</td>
<td>Head</td>
<td>0.97</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>Body</td>
<td>0.93</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>Tail</td>
<td>0.97</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>0.93</td>
<td>0.90</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Head</td>
<td>0.89</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>Body</td>
<td>0.91</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>Tail</td>
<td>0.85</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>0.90</td>
<td>0.82</td>
</tr>
<tr>
<td>Volume (mm³)</td>
<td>Head</td>
<td>1626±220.9</td>
<td>1415.5±189.8</td>
</tr>
<tr>
<td></td>
<td>Body</td>
<td>1286±106.2</td>
<td>1037.7±114.5</td>
</tr>
<tr>
<td></td>
<td>Tail</td>
<td>317.6±140</td>
<td>426.8±154.9</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>3232.1±231.6</td>
<td>2883.5±297.4</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reliability (ICC)</td>
<td>Head</td>
<td>0.93</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>Body</td>
<td>0.94</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>Tail</td>
<td>0.96</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>0.94</td>
<td>0.88</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Head</td>
<td>0.90</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>Body</td>
<td>0.89</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>Tail</td>
<td>0.85</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>0.89</td>
<td>0.84</td>
</tr>
<tr>
<td>Volume (mm³)</td>
<td>Head</td>
<td>1800.2±251.3</td>
<td>1549.1±274.8</td>
</tr>
<tr>
<td></td>
<td>Body</td>
<td>1281.5±164.0</td>
<td>1097.3±145</td>
</tr>
<tr>
<td></td>
<td>Tail</td>
<td>255.3±99.5</td>
<td>468.7±177.3</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>3340.2±323.4</td>
<td>3112±332.4</td>
</tr>
</tbody>
</table>

P-value was calculated using both left and right hemisphere values together as raw data.

P-values of less than 0.05 between 7.0 T and 1.5 T were shown in both reliability (ICC) and sensitivity.

\[
\text{ICC} = \frac{1}{N^2} \sum_{i=1}^{N} (x_{i1} - \bar{x}) (x_{i2} - \bar{x}),
\]

where \(s^2 = \frac{1}{N} \sum_{i=1}^{N} (x_{i1} - \bar{x})^2 (x_{i2} - \bar{x})^2\) and \(N\) is the number of subjects.

\[
\text{Sensitivity} = \frac{A \cap B}{(A \cap B) + (A \cap \bar{B})}
\]

Fig. 6. 3D surface volume image modeling of the hippocampuses. The inferior view of 3D surface volume image models generated from 1.5 T (a) and 7.0 T (b) MRI of one typical healthy subject. Many details such as (1) the subiculum, (2) the ambient gyrus, (3) the uncal sulcus, and (4) the uncal apex can be visualized in the 7.0 T image.

Fig. 7. Bar plots for the reliability (ICC) and sensitivity of the hippocampal tracings. The reliability (a) and sensitivity (b) for the tracing of the left and right head, body, and tail of the hippocampus are shown. Significantly higher reliability as well as sensitivity are seen in 3D volume modeling using 7.0 T MRI compared with that of 1.5 T (both, \(P<0.05\)).
Acknowledgments

Grant support: This work is supported in part by the Ministry of Education, Science and Technology (MEST) of the Republic of Korea and the Korea Science and Engineering Foundation (KOSEF) (Grant no. 2009-0065597).

The authors declare no conflicting financial interests.

References


