HIPPOCAMPAL SUBFIELD SEGMENTATION SUMMIT
Conference Abstracts

Friday, June 21, 2013

Session 1

Notes

1:20 PM – 1:40 PM

Quantitative component summary; Altases and automation

Paul Yushkevich, University of Pennsylvania

The quantitative component of the HS3 meeting involves over 10 participants labeling hippocampal subfields (and, optionally, extrahippocampal medial temporal lobe structures) in a common dataset consisting of T1-weighted and T2-weighted 3 Tesla MRI, as well as T2 weighted 7 Tesla MRI, in the same subject. I will present the different submissions in a common anatomical space and provide summary quantitative measures of agreement between protocols. I will also briefly identify the online and computer resources that attendees can use themselves to review these submissions during and after the meeting. Additionally, I will review our group's progress on automating subfield segmentation with the ASHS software and development of a postmortem hippocampal atlas that may be helpful for future development of segmentation protocols.

1:40 PM – 2:00 PM

Manual subfield volumetry based on a high resolution T2 weighted high field (3T) hippocampus image

Susanne G. Mueller, University of California, San Francisco

The goal was to develop an efficient manual parcellation for hippocampal subfield volumetry that takes advantage of the internal hippocampal landmarks depicted in a high resolution T2 weighted image hippocampal image. The images are re-sampled to obtain a left and right image on which the coronal axis is exactly perpendicular to the long axis of the hippocampus. Subfields are marked on 5 consecutive slices in the rostral body. The most medial point of the temporal cortex is chosen as medial border of the ERC and the medial end of the collateral sulcus as its lateral border. The CA1/subiculum border is determined by drawing a line perpendicular to the edge of the subiculum touching the medial border of the hippocampus. The CA1/CA2 border is determined by dividing the line along the longest diameter of the hippocampus by two and drawing a line perpendicular to this line. A region supposed to represent mainly CA2 was marked in a square-like manner, i.e., its height at the CA1/CA2 boundary also determined its length. CA3 and dentate gyrus are marked as one region (CA3&DG) because there are no reliable landmarks to distinguish between these structures. The manual labeling takes about 30 min/ side and has reasonably high reliability (ICC: 0.7-0.9). It has been successfully used to investigate subfield specific abnormalities in a number of different disease states. Even though compromises regarding anatomical accuracy had to be made to allow for a reliable and efficient labeling, the scheme seems to reliable detect disease specific subfield volume loss that affects the whole hippocampus or the anterior body.

2:00 PM – 2:20 PM

Manual and automatic segmentation of hippocampal subfields on high-resolution 3T MR images

Julie Winterburn, Center for Addiction & Mental Health, Toronto

T1- and T2-weighted images were acquired from five healthy volunteers on a 3T GE MR 750 system. For each subject, three sets of two NEX were acquired at 0.45mm x 0.45mm x 0.6mm and then corrected for intensity inhomogeneities, rigidly aligned to a reference image, normalized to a fixed intensity range, and intensity-averaged to enhance signal

and contrast. The final average image of each subject is composed of 0.3mm isotropic voxels. T1-weighted images were used to manually segment the whole hippocampus of each subject; hippocampal subfields (CA1, CA2/CA3, CA4/dentate gyrus, strata radiatium/lacunosum/moleculare, subiculum) were identified on T2-weighted images. The protocol was devised using morphological and signal intensity features in the images, with the help of published histological and MR atlases. Bilateral segmentation of a single subject required approximately 40 hours of work. The intra-rater reliability of the protocol was evaluated by re-segmenting the right or left hippocampus of each subject and computing Dice's Kappa (whole hippocampus 0.91; CA1 0.78; CA2/CA3 0.64; CA4/DG 0.83; SR/SL/SM 0.71; subiculum 0.75). We have developed a new automatic segmentation method (MAGeT), which allows this protocol to be applied to a large novel subject set with no additional manual input. Briefly, atlas labels are propagated to an unlabeled subset of the subject population using non-linear registration. The labels from this population subset are then propagated to the rest of the subject set, and fused using voxel-wise majority voting. MAGeT has consistently performed very well in validation experiments and offers a time-efficient, reliable alternative to manual segmentation.

2:20 PM – 2:40 PM

Hippocampal subfield surface zone map on T1 scans

Lei Wang, Northwestern University

The hippocampus is one of the earliest brain structures affected by Alzheimer's disease, particularly its CA1 and subiculum subfields. It has been shown that individuals with very mild dementia of the Alzheimer type (DAT) exhibit abnormalities in hippocampal regions that approximate these subfields. In order to develop neuroimaging shape biomarkers for identifying DAT in its earliest course, we developed a hippocampal subfield surface zone map that approximated the underlying cellular subfields. A neuroanatomical atlas image, which was an MR scan of an elderly non-demented individual, was used to develop the protocol. The MR scan was collected on a 1.5T Siemens VISION scanner using a T1-weighted MPRAGE sequence at 1x1x1 mm3 resolution. The MRI volume was re-oriented to AC-PC and resampled to 0.125x0.125x0.125 mm3 resolution. The CA1, CA2, CA3, CA4, dentate gyrus (DG) and the subiculum (SUB) subfields were manually segmented following rules from the Duvernoy atlas textbook. Then, we projected the subfield segmentations onto the whole hippocampal surface previously generated in the same scan. This procedure created three zones on the whole hippocampal surface approximating the different subfields: a CA1 zone, a combined CA2-4+DG zone (they were combined because the surface representation for each was much smaller than either CA1 or SUB), and a SUB zone. We manually outlined the three hippocampal surface zones in ten additional scans, and compared with the surface zones as mapped from the above atlas. The intra-class correlation coefficients of the areas of the three surface zones were high (0.90–0.97).

2:40 PM – 3:00 PM

Hippocampal subfield segmentation for high-resolution functional MRI studies

Craig E. L. Stark, University of California, Irvine

In 2006, we (Kirwan et al., 2006-7) published a report on high-resolution (1.5 mm isotropic) fMRI imaging of the MTL as our first step at investigating hippocampal function at the level of subfields. Since then, much of our research has been focused on investigating the computational properties of different subfields and the effect of age on the hippocampal network. To this end, we developed a segmentation protocol (Kirwan & Stark, 2007) that would allow us to localize activity to the subiculum, CA1, or CA2,3,4/DG (typically referred to as DG/CA3). Of course, the protocol would allow us to calculate volumes or to localize morphological changes as well as a secondary goal. The protocol operates on oblique coronal images (perpendicular to the principle axis of the hippocampus) and is based on slice by slice template matching to segmentations provided in Duvernoy (1998). Typically, the hand segmentations are smoothed by a

3x3x3 voxel median filter. Individual participant segmentations can be used for localization either in their native space or to form a study-wide template (or probabilistic atlas) for the localization of fMRI activity. Note that unlike a number of other protocols, we currently make no attempt to dissociate regions such as DG and CA3 despite clear interest in separating these two. As BOLD fMRI is largely driven by synaptic activity (e.g., Logothetis, 2002), it is unclear how we would interpret activity localized to CA3 given the balance of strong Mossy fiber input from the DG and strong recurrent collateral connections. Given current uncertainty in the role of inhibitory activity on BOLD signals and the large role of inhibition in the DG, it is unclear what BOLD fMRI signals one would expect here. Thus, we join others in thinking of the DG/CA3 as a highly interconnected functional unit and combine their segmentations accordingly. Finally, we should note that although our segmentations have traditionally been done by hand, we have successfully automated the process using ASHS (Yushkevitch et al., 2010) to segment >100 participants.

Session 2

4:00 PM – 4:20 PM

Isotropic high res T2 (FIESTA) hippocampal scans at 7T and quantification of SRLM

Michael Zeineh, Stanford University

Hippocampal microstructure is best identified with T2-weighted contrast. However, achieving isotropic high-resolution T2-weighted images is quite difficult, so most hippocampal acquisitions are anisotropic. This complicates segmentation, and has resulted in a myriad of attempts to label the hippocampal head consistently and accurately. This stands in contradistinction to specimen MRI, in which full hippocampal head segmentation is possible at a resolution on the order of 0.2mm isotropic. Here, we report using balanced steady-state free precession (bSSFP) at 7.0T to achieve 0.4mm *in vivo* isotropic resolution with contrast that reveals hippocampal microstructure in clinically achievable scan times. Four subjects were scanned on a GE 7.0T Discovery MR950 scanner using a Nova coil (quadrature transmit, 32-channel receive). After acquiring localizers and performing high-order B0 shimming to approximately 20 Hz r.m.s. uniformity, we acquired 6-8 increments of phase-cycled bSSFP (FIESTA, coronal, BW 62, FOV 17, 420x420, FA 25, TR 8.2 ms, TE 4.1, 0.4mm slice thickness, 480 slices, 0.5NEX with 32 overscans, ARC 1.75x1.75, 5:11 per phase cycle). Individual phase cycle images were reconstructed and combined into an initial sum-of-squares (SOS-1). FSL's flirt was then used to coregister each phase cycle to the SOS-1, after which we recombined into a second SOS (SOS-2), and this procedure was repeated once to produce SOS-3. Images were visualized and the hippocampal cell layer stratum radiatum lacunosum moleculare (SRLM) was segmented using itk-SNAP. Resulting images demonstrated contrast comparable with T2-weighted FSE images with gray-white contrast enhanced by a significant component of iron contrast. In all subjects, fields CA3 and CA1 of the hippocampal head were readily discernible and separable in coronal section, and the entirety of SRLM could be segmented (Figure 1). Three to four hippocampal digitations were observable in coronal section with fluid in the adjacent hippocampal sulcus. Gray-white contrast in

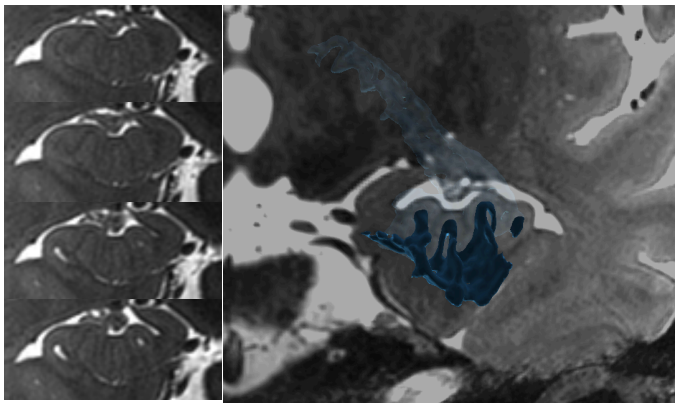

Figure 1: Left: serial coronal sections through the right hippocampus. Right: 3D rendering of SRLM.

the remainder of the brain was similar to 3-D T2 FSE acquisitions.

4:20 PM – 4:40 PM

Quantification of CA1 apical neuropil using high-resolution 7T scans

Geoffrey Kerchner, Stanford University

In Alzheimer's disease (AD), tau pathology first appears in the entorhinal cortex before spreading to the targets of perforant pathway. In postmortem studies, neurofibrillary tangle pathology is disproportionately concentrated in the CA1 apical neuropil, including inside the dendrites of CA1 pyramidal neurons in the stratum radiatum and stratum lacunosum-moleculare (CA1-SRLM). Synapse loss and thinning of the CA1-SRLM correlate with the degree of AD-related cognitive dysfunction. Conventional imaging fails to resolve the layered anatomy of the hippocampus at sufficient resolution to demonstrate such subtle disease-related change. Using 7.0-Tesla T2-weighted oblique coronal imaging (0.22 x 0.22 x 1.5 mm voxels) that reveals visually-identifiable subfield and stratal boundaries in the hippocampal body, I describe a semi-automated technique for measuring the width of the CA1-SRLM and the associated stratum pyramidale (CA1-SP). The user draws a line approximately through the middle of the CA1-SRLM or CA1-SP, and an edge-detection algorithm is applied using a Matlab script to integrate the thickness of each stratum. This technique correlates well with manual measurements. CA1-SRLM atrophy is evident in Alzheimer's disease, and the magnitude of the atrophy correlates strongly with delayed memory performance in AD and MCI. Other two-dimensional medial temporal lobe structural metrics used in my lab include DG/CA3 cross-sectional area, total hippocampal cross-sectional area, and entorhinal cortex thickness, which are determined manually in slices through the hippocampal body. I will discuss benefits and limitations of this high-resolution two-dimensional analysis of hippocampal stratal anatomy.

4:40 – 5:00 PM

Full-length hippocampal segmentation at 7T

Laura Wisse, University Medical Center, Utrecht

Animal and human autopsy studies suggest that subfields of the hippocampal formation are differentially affected by neuropsychiatric diseases. Therefore, subfield volumes may be more sensitive to effects of disease processes. We developed a protocol using 7 Tesla MRI with isotropic voxels to reliably delineate the entorhinal cortex (ERC), subiculum (SUB), CA1, CA2, CA3, dentate gyrus (DG)&CA4 along the full-length of the hippocampus. Fourteen subjects (aged 54-74 years, 2 men and 12 women) were scanned with a 3D turbo spin echo (TSE) sequence with isotropic voxels of 0.7x0.7x0.7 mm3 on a 7T MRI whole body scanner. Based on previous protocols and extensive anatomic atlases, a new protocol for segmentation of subfields of the hippocampal formation was formulated. ERC, SUB, CA1, CA2, CA3 and DG&CA4 were manually segmented twice by one rater from coronal MR images. Good-to-excellent consistency was found for all subfields (Intraclass Correlation Coefficient's (ICC) varying from 0.74 to 0.98). Accuracy as measured with the Dice Similarity Index (DSI) was above 0.82 for all subfields, with the exception of the smaller subfield CA3 (0.68-0.70). In conclusion, this study shows that it is possible to delineate the main subfields of the hippocampal formation along its full-length in vivo at 7T MRI. Our data give evidence that this can be done in a reliable manner. Segmentation of subfields in the full-length of the hippocampus may bolster the study of the etiology neuropsychiatric diseases.

5:00 – 5:20 PM

Histology-guided manual and automated segmentation of hippocampal subfields on MRI scans

John Pluta, University of Pennsylvania

We present a manual protocol for the segmentation of hippocampal subfields (CA1-3, CA4/DG, subiculum) throughout the entire hippocampal formation, along with extra-hippocampal medial-temporal lobe structures (ERC, PRC) from 3 Tesla T2-weighted MRI

with oblique coronal orientation, approximately 0.4mm x 0.4 mm in-plane resolution, and 2mm slice thickness. ERC and PRC are based on the definitions in (Ding et al., 2009, 2010) with training provided by an expert anatomist (S.D.). The subfield protocol was developed in three steps; first, subfields were segmented in Kluwer-Barrera stained histological slices obtained through the length of the hippocampus in postmortem tissue samples, with boundaries based on cell shape and density and subfields defined as in (Duvernoy, 2005). Secondly, high resolution MRI scans (0.2mm isotropic resolution) of ex-vivo samples scanned at 9.4T were segmented using histology as a guide. Ex-vivo data provides some macroscopic signs of subfield changes (e.g., thickness) and the high isotropic resolution allows for the modeling of the complex changes in the hippocampal structure, particularly in the head and tail regions. Finally, annotated post-mortem MRI was used to establish rule-based boundaries for delineating subfields in lower resolution in-vivo MRI. Both in-vivo and ex-vivo data were available for a single subject, and were used to directly compare the appearance of the same regions across the two modalities. The manual segmentations were used in conjunction with the multi-atlas segmentation algorithm (Yushkevich et al., 2010), allowing automated subfield delineation in in-vivo MRI.

5:20 PM – 5:40 PM

Building an atlas of the hippocampal formation using an *ex vivo* imaging-histology paradigm

Jean C. Augustinack, Juan Eugenio Iglesias, Koen Van Leemput, Bruce Fischl, Martinos Center, MGH

The human brain depends on the hippocampus and nearby parahippocampal gyrus to create declarative memories. Without a healthy hippocampus, memory circuits fail to generate episodic memories and we are unable to learn from experience. Identification and mapping of the substructures of the hippocampal formation in MRI offers several advantages including the ability to link structure with functional MRI, as well as track aging and disease longitudinally. However, the complexity of the human hippocampus presents various challenges including its general flexure, being intertwined with dentate gyrus, and most importantly, the inability to distinguish the CA (cornu ammonis) fields with standard MRI. To mitigate the lack of resolution in *in vivo* MRI, we are utilizing an ultra-high resolution *ex vivo*-histology paradigm to delineate substructures in the hippocampal formation. In addition, we are employing a standard surface model approach, so that the validated labels can be transferred from traditional histology to *in vivo* data. Low resolution images were acquired at 1.5 T with a multi-echo FLASH sequence (TR = 40 ms, TE = 1.85, 3.71, 5.62, 7.58, 9.59, 11.65, 13.76, 15.92) and yielded a 1 x 1 x 1mm resolution, which allows surface models to be reconstructed from *ex vivo* images. Next, high resolution images were acquired at 7.0 T with a FLASH sequence (TR= 40 ms, TE= 20 ms, flip angle = 20°, resolution = 120 µm isotropic), which allows comparison with classical histological staining to definitively assess anatomical accuracy. This three-pronged approach enables an *in vivo* atlas validated in cytoarchitecture. The labeled structures include: parasubiculum, presubiculum, subiculum, CA1, CA2, CA3, CA4, molecular layer of the hippocampus, dentate gyrus (granule layer), alveus, fimbria, hippocampal-amygdala-transition-area, and hippocampal fissure. Our laboratory has embarked on the task of manual labeling several hippocampal formations at ultra-high resolution *ex vivo* MRI (n=14) and validating with Nissl stained sections at 150 µm intervals in a subset of cases. Several structures were discernible based on the *ex vivo* MRI contrast, except for the CA fields and the hippocampal-amygdala-transition-area that frequently require cross referencing with the Nissl staining. The corresponding Nissl staining clarifies and validates the *ex vivo* MRI contrast. The atlas was encoded into a tetrahedral mesh with label probabilities at each vertex and will eventually be computed using a group-wise registration. The resulting atlas can be used to segment *in vivo* data and obtain quantitative measures in healthy, aging and disease populations.

6:20 PM – 7:00 PM – Keynote Address

Anatomical boundaries in the human hippocampal and parahippocampal region applied to Neuroimaging

Ricardo Insausti, Universidad de Castilla, La Mancha, Albacete, Spain.

The human hippocampus is a key player in memory processing and other neuropsychological functions. The hippocampus and surrounding cortices (parahippocampal region, PHR) are reciprocally interconnected, and both are necessary for processing and consolidation of memories. The hippocampus and the parahippocampal region are located in the ventromedial temporal lobe, stretching from the greater wings of the sphenoid (temporal pole cortex) as far as the tentorium of the cerebellum, and the beginning of the calcarine fissure (tail of the hippocampus and posterior parahippocampal cortex. PHC). Although the nomenclature applied to this brain region has somewhat changed over the time, a consensus of terminology can be achieved to provide a common nomination for different gross anatomical landmarks, which point to the relative extent of more elusive histological fields. The hippocampal formation is made up of several fields and types of cortices, in which the flow of information is characteristically unidirectional, and, ultimately, distributes in the cerebral cortex for storage and further use. Histologically, the hippocampal region can be classified as a “primitive” type of cortex named “archicortex” (largely made up of three layers, which corresponds to the Hippocampus proper (dentate gyrus and fields CA3, CA2 and CA1, as well as the subiculum). The presubiculum, parasubiculum (sometimes referred to as the subicular complex) and the entorhinal cortex are “periarchicortex”, and make up the rostral part of the parahippocampal gyrus. Experimental studies in nonhuman primates, as well as functional studies in humans, indicate that the entorhinal cortex receives cortical input from different polysensory association cortices, most notably the components of the PHR (temporopolar, TPC, perirhinal PRC, and posterior parahippocampal gyrus, PHC, which provide more than two-thirds of the cortical input to the entorhinal cortex. Layer II neurons of the entorhinal cortex project to the molecular layer of the dentate gyrus, which starts a cascade of unidirectional projections that progress from the dentate gyrus to CA1 and subiculum, but not the other way around. Ultimately, CA1 and the subiculum project to the deep layers of the entorhinal cortex. The projections from the entorhinal cortex to the dentate gyrus follow a phylogenetically preserved pattern of projection, and the rostral and medial entorhinal cortex projects to the uncal part of the hippocampus; increasingly more lateral parts of the entorhinal cortex project to the body (midportion) and tail (lateral part) of the hippocampus. The PHR in nonhuman primates and very likely in humans, provides highly processed polysensory input to the entorhinal cortex, the gateway of polysensory, highly processed information to the hippocampus, The PHR itself is one site where unimodal and polymodal association cortical areas converge. The hippocampal formation and the PHR, for the most part, lack consistent criteria for its delimitation and segmentation in structural and functional MRI studies in humans and nonhuman primates. Traditional cytoarchitectonic parcellations cannot be directly applied to MRI imaging because of resolution constraints. Therefore, and given the variability of the sulcal and gyral patterns among individuals, an indirect approach must be taken based on the correlation of gross anatomy points and their corresponding histological analysis to place more precise limits. The medial temporal lobe presents a structure that forms small prominences or bumps, which correspond to defined neuroanatomical structures that help in the delimitation of the cortical areas in the medial temporal lobe, in particular in the coronal plane of section. In a rostrocaudal sequence of steps, the following is likely to happen: The rostralmost part of the temporal lobe is TPC. Although some variability exists, the TPC in coronal sections extends for the first 6-8 mm, being more restricted to the dorsomedial part of the temporal pole as the neocortex of the superior and inferior temporal gyri appear laterally. The following landmark is the limen insulae at the frontotemporal junction, which points to the rostral limit of the insula, and is unmistakable on coronal sections. Approximately 2 mm behind the limen insulae, the entorhinal cortex starts. Around this

point, the rostralmost extent of the collateral sulcus is usually visible, which points out the commencement of the PRC. The start of the collateral sulcus is highly variable, and it leaves a dorsal portion of the perirhinal cortex, variable in extent, in front of the rostramost portion of the entorhinal cortex, separated by the rhinal sulcus. The amygdaloid complex begins about 5 mm behind the start of the entorhinal cortex. The anterior limit of the temporal horn of the lateral ventricle is variable, but usually it starts a few mm caudal to the amygdala. Shortly after the hippocampus appears as an ellipsoid structure that histologically corresponds to the subiculum, at the rostralmost point where the hippocampus forms the bend to the uncal portion of the hippocampus. The appearance of the white matter surrounding the cell layer of the subiculum would correspond to the molecular layer of the subiculum. From that point, the length of the hippocampus may vary between 3 and 5 cm, (and about 7-8 cm from the tip of the temporal pole). The hippocampus folds itself in a medial direction, forming the hippocampal head. The separation of fields in the hippocampal head acquires the highest complexity at any plane of section. From the beginning of the hippocampus, the complete set of hippocampal fields follows a rostrocaudal sequence: first, CA1 field joins the subiculum laterally; then, CA3 field arises dorsally, and separates a medial and lateral portions of CA1 (dorsal subiculum and CA1). The dentate gyrus becomes evident as a rounded, closed structure with its three sublayers (molecular, granular and polymorph). The molecular layer is separated from the underlying hippocampus by the fused hippocampal fissure, noted by the presence of small blood vessels. The hippocampal fissure opens up at a variable distance. Here, a number of digitations (between 3-5) indicate flexures that present a mixture of hippocampal fields, thereby several sections through the dentate gyrus may take place. The typical, C shape of the hippocampus becomes progressively evident, and the presubiculum appears medially. The subiculum is also continues medially into the amygdalo-hippocampal transitional area. On the other hand, a similar sequence takes place at the medial portion of the hippocampal head, thus forming the dorsal presubiculum, subiculum and hippocampal fields as far as the dentate gyrus at the band of Giacomini. However, it is worth noting that, in a caudal direction, the sequence of fields follows the opposite, thereby the presubiculum, subiculum, CA1 and CA3 progressively disappear in each of the digitations. The gyrus intralimbicus, a small, rounded structure at the caudalmost limit of the hippocampal head, containing only CA3 and some dentate gyrus. The hippocampal head span along a rostral-to-caudal direction is about 12 mm. The gyrus intralimbicus is a landmark easy to pick and heralds the caudal limit of the entorhinal cortex, as well as the caudal limit of the PRC, at the commencement of the lateral geniculate nucleus. At this point, the body of the hippocampus starts with all the hippocampal fields. The choroidal fissure points to the transition between the presubiculum and the parasubiculum, which continues with the entorhinal cortex, at the ventromedial aspect of the temporal lobe. The lateral geniculate nucleus extends for about seven mm, and it forms a distinct prominence in the basal diencephalon, easy to detect. The limit between body and tail of the hippocampus is indistinct. As an approximation, and consistent with nonhuman primate literature, the limit can be placed at the midpoint of the distance between the end of the gyrus intralimbicus and the end of the hippocampus. The basis for this distinction would be the separation provided by the entorhinal cortex projections to the molecular layer of the dentate gyrus thorough the angular bundle. In this way, the intermediate portion of the entorhinal cortex would be linked to the body of the hippocampus, while the lateral portion would be related to the tail of the hippocampus. The calcarine fissure, or parieto-occipital junction is present at the caudal part of the ventromedial surface. It is usually is coincident with the crura of the fornix, point at which the PHC ends and thorough the istmus of the parahippocampal gyrus, The caudal PHR is continuous around the splenium of the corpus callosum with the cortex at the cuneus, mostly formed by retrosplenial corex. While the criteria for the segmentation of the rostral PHR has been reported (Insausti et al., 1998), the PHC caudal limit on MRI images can be

placed approximately by the caudal part of the collateral sulcus (lateral limit), and the crura of the fornix at the approximate level of the end of pulvinar in the thalamus. In conclusion, the hippocampal formation the temporopolar, perirhinal and posterior parahippocampal cortices that constitute the parahippocampal region, benefit of the close relationship with gross anatomical landmarks, which can be used to place natural boundaries among those important regions of the human brain. Supported by Grants BFU 2006-12964, TSI-020110-2009-362 and BFU 2009-14705.

Saturday, June 22, 2013

Session 3

9:00 AM – 9:20 AM

Variability in collateral suclus anatomy: The challenge of segmenting entorhinal, perirhinal, and parahippocampal cortices

Valerie Carr, Karen LaRoque, Anthony Wagner, Stanford University

Our lab is interested in the psychological and neurobiological processes supporting human memory, with an emphasis on understanding the functional computations performed by the medial temporal lobe (MTL) circuit in healthy young adults, older adults, and memory impaired populations. To achieve the spatial resolution necessary to investigate MTL function at the subfield level, our studies employ 3T high-resolution functional MRI. Functional data are acquired using EPI parallel imaging (1.67 x 1.67 x 1.5mm), and T2-weighted anatomical images (0.43 x 0.43 x 2mm) are used to segment the MTL into its component subfields. Each participant's MTL is manually segmented into hippocampal (CA1, DG/CA23, subiculum, anterior hippocampal head, and posterior hippocampal tail) and cortical subfields (perirhinal, entorhinal, and parahippocampal cortices). Our segmentation protocol was originally developed by Dr. Susan Bookheimer and is based on MTL atlases and standards developed in structural MRI studies of the MTL. In addition to our current efforts to move towards a unified protocol for segmenting hippocampal subfields, it is equally important to come to a consensus on segmentation of the entorhinal, perirhinal, and parahippocampal cortices if we are to advance understanding of MTL contributions to memory. Such consensus is especially critical given that the collateral sulcus has a highly variable shape and length—both across and within subjects—creating challenges in the reliable application of segmentation guidelines to these regions. As such, I hope to use this time to generate a dialogue among attendees regarding extant cortical segmentation protocols, any newly-developed attendee protocols, and the application of these protocols to widely varying sulcal anatomy.

9:20 AM – 9:40 AM

Role of hippocampal subregions in disambiguating elements of temporal vs. spatial context in episodic memory

Dana Smuda, Colin Kyle, Abdul Hassan, Arne Ekstrom, University of California, Davis

Consistent with predictions of some theoretical models (Katz et al. 2007), we propose that CA3 and CA1 are involved in processing both spatial and temporal context but differ in their underlying representations of the two. To test this idea, fifteen participants learned the delivery order and spatial layout of stores in a virtual taxi-driver game, then judged relative serial position (temporal context) and relative distance (spatial context) while undergoing high-resolution echo-planar imaging. We manually demarcated subregions in in FSL (Ekstrom et al., 2009,) including: CA2/CA3/Dentate Gyrus, CA1, Parahippocampal Cortex, Subiculum, Perirhinal Cortex, and Entorhinal Cortex. To address differences in underlying neural representations, we employed representational similarity (RS) analysis, which tracks change in the pattern of active voxels between conditions (Kriegeskorte et al., 2007). ROI-based RS analyses demonstrated a

significant main effect of subregion, a significant interaction effect of condition (spat/temp) x proximity (near/far), and a significant interaction effect of subregion x condition x proximity (p<.01). Post-hoc analyses demonstrated greater RS for near vs. far temporal discriminations in CA23DG, an effect present to a significantly lesser extent in CA1. These findings suggest that CA23DG plays a greater role than CA1 in discriminating differences in temporal context. Searchlight analyses also revealed significantly greater RS for near vs far spatial judgments in CA23DG, suggesting CA23DG's additional role in spatial discriminations. Together, our results argue that both subregions play roles in representing contextual information, with a specific role for CA23DG in differentiating elements of spatiotemporal context.

9:40 AM – 10:00 AM

Hippocampal subregion volume in post-injury Traumatic Brain Injury patients

Abdul Hassan, Dana Smuda, Kia Shahlaie, Gene Gurkoff, Arne Ekstrom, University of California, Davis

Traumatic brain injury (TBI) results in deficits and impairments in memory and cognition, leaving an estimated 5.3 million Americans needing long-term or lifelong assistance due to their injuries. Given the importance of the hippocampal circuit to memory processing, we investigated whether TBI resulted in volume loss in specific hippocampal subfields, as suggested in other neurological conditions such as medial temporal lobe epilepsy (MTLE). Patients 12 – 18 months post-injury and with a GOS-E score ranging from lower moderate to lower good recovery were selected for this study. Patients (N=8) and controls (N=13) underwent high-resolution hippocampal imaging and whole-brain MPRAGE scans ($1mm^3$). The hippocampal sequence was applied perpendicular to the long-axis of the hippocampus. We segmented hippocampal subfields using FSLview as described in Ekstrom et al. 2009 Neuroimage. Medial and posterior slices included the CA3 (combined DG/CA2), CA1, SUB, and PHC; anterior slices included CAant (combined CA3/CA2/CA1/DG), SUB, EC and PC. We extracted volumes from subfield masks using fslstats and normalized them for head size using SIENAX. Results identified a decrease in total TBI hippocampal volume versus controls, with the regions of CA3, CA1, PHC, SUB, and PC showing relative reductions in size. These findings suggest that there are volumetric reductions in multiple hippocampal subfields and surrounding cortical areas accompanying TBI, although with our small sample size we are limited in determining the degree of specificity in these reductions. While TBI is generally a heterogeneous injury, these results suggest that there is a high probability that TBI patients with chronic deficits in memory and cognition have damage to hippocampal subfields and surrounding cortical structures.

10:00 AM – 10:20 AM

High-resolution cortical unfolding at 7T

Nanthia Suthana, University of California, Los Angeles

Visualizing the function of individual human hippocampal subfields remains challenging due to their small sizes and convoluted structures. In this study we investigated healthy participants using a memory paradigm during high-resolution fMRI scanning at 7 tesla. Utilizing computational cortical unfolding and separate region of interest (ROI) based approaches we were able to localize BOLD activity separately to the anterior hippocampal cornu ammonis (CA) field 2 and CA3 during learning, and to the posterior CA2 field and the posterior subiculum during recall. These advances in fMRI data acquisition and analysis provide a unique opportunity for future investigations of hippocampal subregion function in healthy individuals as well as those suffering from neurodegenerative diseases.

10:20 AM – 10:40 AM (via remote connection)

Methodological steps in the EADC-ADNI harmonization of protocols for hippocampal segmentation

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The available segmentation protocols for hippocampal volumetry, a biomarker for AD, lead to different volume estimates. A harmonization effort has been carried out to define a consensual protocol for standard segmentation of the hippocampus on MRI. The first methodological step consisted in extracting the variability across segmentation protocols and operationalizing it, i.e. reducing the wide and fuzzy landmark variability to a limited number of elements that can be handled. The operationalized landmark variability was rendered as positive units, i.e. as "pieces" of hippocampus that can be independently segmented and measured (Segmentation Units, SUs). As the second step, the quantitative information collected on SUs was fed to a panel of experts in hippocampal segmentation that could take decisions based on both their experience and on evidence. The quantitative information regarded the percentage of hippocampal tissue represented in each SU, segmentation reliability, and the informative value as to AD-related atrophy. A questionnaire was launched through a web-platform allowing anonymous answers, and a Delphi procedure (Murphy et al, 1998) was followed: in subsequent rounds, statistics regarding the answers of all panelists and the reasons for such answers were provided, and the level of agreement with majority choices was investigated using Lickert scales. This procedure was followed recursively until a statistically significant majority of panelists voted for the most popular choices. Five rounds allowed to achieve a consensual definition of all landmarks, segmentation modalities and image orientation. All info about the EADC-ANI Harmonized Protocol project can be found at www.hippocampal-protocol.net