In vivo quantification of human hippocampal subfields in health and in organic amnesia using 7.0-Tesla 0.4mm2 3-D fast spin echo imaging

Clive R Rosenthal[1], Thomas D Miller[1], Tammy W C Ng[2], Stuart Golodetz[3], Christopher Kennard[1], and Penny A Gowland[4]

[1]Clinical Neurosciences, University of Oxford, Oxford, Oxfordshire, United Kingdom, [2]Department of Anaesthesia, Univerisity College London Hospital, London, London, United Kingdom, [3]Computer Science, University of Oxford, Oxford, Oxfordshire, United Kingdom, [4]Sir Peter Mansfield Magnetic Resonance Centre, University of Nottingham, Nottingham, Nottinghamshire, United Kingdom

Background

Computational neuroanatomical models and rodent studies suggest that hippocampal (Hc) subfields support discrete functions, but are less well studied in humans because reliable in vivo identification of human Hc subfields remains a significant challenge. Partial volume effects are particularly significant in the anterior and posterior Hc regions, because the main axis curves with respect to the imaging plane. Here, we sought to delineate and quantify human Hc subfields along two interlocking convoluted layers of neurons - the dentate gyrus (DG/CA4) and the cornu Ammonis (CA1-3) - and the subiculum (SUB), in healthy adults and in adults with bilateral hippocampal-mediated amnesia, using a single-acquisition MRI sequence that would be amenable to participant comfort and minimise time in the scanner.

Method

A 32-element volume-transmit receive coil array with three-dimensional fast-spin echo imaging at 7.0-Tesla was used to acquired images in 12 healthy adults and in three adults with bilateral hippocampal-mediated amnesia. Visualization of DG/CA4, CA3, CA2, CA1 and SUB Hc subfields along the full transverse axis was conducted *in vivo* at an unprecedented resolution by using a slice thickness of 0.1 mm and an in-plane resolution of 0.4 x 0.4 mm^2. Two raters performed manual delineation to segment bilateral DG/CA4, CA3, CA2, CA1 and SUB Hc subfields, using the manual segmentation tool in ITK-SNAP 3.0. Hc subfield delineation was guided by the Duvernoy et al. (2013) hippocampus atlas, the 7.0-Tesla protocol of Wisse et al. (2013), and the 4.7- and 3.0-Tesla protocols of Malykhain et al. (2010) and Bonnici et al. (2012), respectively. Both hippocampi were identified in all participants as lobulated structures, between the ambient cistern and temporal horn on the 3D-FSE images. As in the Wisse et al., we did not include the alveus and fimbria as part of the segmentation protocol. Intra-rater segmentation repeatability and inter-rater segmentation was assessed for full 3-D whole hippocampus segmentations of each subfield in the healthy adults and in the amnesic adults using Dice overlap indices (Dice, 1945).

Results

Unlike previous studies, we were able to visualize a hypointense border between CA1 and SUB fields along the transverse axis of the hippocampus, so the border was followed as it moved medially into the head and eventually body of the hippocampus. The DG typically appeared within 2.0-3.0 mm of the anterior-most hippocampal slice, within the folds of the CA1 regions of the *digitationes hippocampi,* with clear delineation of the DG usually ending approximately 1.5-3.0 mm from the posterior-most extent of the hippocampus. The border between CA1 and CA2 became visible within 2.0-3.0 mm of the anterior-most appearance of the hippocampus, and usually disappeared < 1 mm from the posterior-most extent of the hippocampus. The polymorphic layer of the DG was present immediately above the DG cell layer, but was not readily differentiated from CA4 because the borders were ambiguous. Subfield volumes in the healthy adults yielded distributions along the transverse axis that were consistent with histological data. Average Dice index based reliability between two raters was generally high for both groups, indicating that the scanning protocol was suited to reliable delineation of the Hc subfields in health and in disease. The results also revealed that our protocol tolerated flow driven artifacts (associated with over 20% bilateral whole hippocampal volume loss relative to the healthy age-matched control participants), because it was possible to segment and identify pathology (volume loss) that was isolated to particular subfields.

Conclusion

In vivo three-dimensional Fast-Spin Echo 7.0-Tesla imaging conducted at 0.4 x 0.4 x 0.1 mm resolution can be used to visualize human hippocampal subfields in health and in disease. The results from our novel neuroimaging and segmentation protocol have the potential to test whether hippocampal pathology associated with focal organic hippocampal amnesia is manifest in specific subfields that are otherwise inaccessible at 1.5-Tesla or even 3.0-Tesla MR neuroimaging, and thereby enable discovery of important information about functional differentiation along the axis of the hippocampus that can be incorporated into models of human computational neuroanatomy.

References

Bonnici HM, Chadwick MJ, Kumaran D, Hassabis D, Weiskopf N, et al. (2012) Multi-voxel pattern analysis in human hippocampal subfields. Front Hum Neurosci 6: 290.

Dice, L. R. (1945) Measures of the Amount of Ecologic Association Between Species. Ecology 26: 297–302

Duvernoy HM, Cattin F, Risold P-Y (2013) The human hippocampus: functional anatomy, vascularization and serial sections with MRI. 4th Edition.

Malykhin NV, Carter R, Seres P, Coupland NJ (2010) Structural changes in the hippocampus in major depressive disorder: contributions of disease and treatment. J Psychiatry Neurosci 35: 337-343.

Wisse LE, Gerritsen L, Zwanenburg JJ, Kuijf HJ, Luijten PR, et al. (2012) Subfields of the hippocampal formation at 7 T MRI: in vivo volumetric assessment. Neuroimage 61: 1043-1049.

Acknowledgements

The work was supported by the UK Medical Research Council (P.A.G), National Institute for Health Research (NIHR) Oxford Biomedical Research Centre based at Oxford University Hospitals NHS Trust and University of Oxford (C.R.R., CK.), John Fell OUP Fund (C.R.R, C.K.), the Guarantors of Brain, the Patrick Berthoud Charitable Trust and the Encephalitis Society (T.D.M).