Seizure (2008) **17**, 234—246

ELSEVIER

SEIZURE

www.elsevier.com/locate/yseiz

Rhinal cortex asymmetries in patients with mesial temporal sclerosis

Catherine E. Meade*, **Stephen C. Bowden, Greg Whelan, Mark J. Cook**

St. Vincent's Hospital Melbourne, Clinical Neurosciences, Victoria Pde, Fitzroy, Melbourne, Victoria 3065, Australia

Received 13 April 2007; received in revised form 2 July 2007; accepted 10 July 2007

KEYWORDS
Rhinal cortex;
Handedness;
Hippocampus;
Memory;
Volumetric imaging

Summary

Purpose: The rhinal cortex, comprising the entorhinal (ErC) and perirhinal (PrC) cortices, is one component of the limbic system that may be affected in patients with epilepsy and other temporal lobe pathologies. This study extended quantitative examination of the limbic system through development and validation of volumetric protocols to measure the ErC and PrC.
Methods: Volumes were calculated from MRI studies using ANALYZE 7.5 and based on detailed anatomical definitions developed for the study. Subjects were 61 temporal lobe epilepsy patients with mesial temporal sclerosis (MTS: 33 left, 28 right) and 20 neurologically normal controls. Inter-rater reliabilities for the ErC and PrC volume protocols were found to be high (range 0.86—0.92).
Results: Ipsilateral hippocampal volume was reduced in patients with MTS, while contralateral volume did not differ significantly from controls. In the patients, rhinal cortex volumes were reduced as a function of laterality of disease. The pattern of correlations between ErC and PrC differed between disease groups. Hippocampal and rhinal cortex volumes were not significantly correlated. A significant four-way interaction was found between side of MTS, hemisphere, structure and handedness.
Conclusions: This quantitative study demonstrates reliable *in vivo* evidence of morphometric changes in ErC and PrC in a substantial number of patients with unilateral MTS. The relationship observed between handedness, structure and disease status may suggest a role for cerebral dominance in modulating the expression of MTS.

Introduction

The entorhinal (ErC) and perirhinal (PrC) cortices are crucial components in the pathway through which highly processed information from the neocortex

* Corresponding author. Tel.: +61 39288 3073; fax: +61 39288 3551.
E-mail address: catherine.meade@svhm.org.au (C.E. Meade).

1059-1311/$ — see front matter © 2007 Published by Elsevier Ltd on behalf of British Epilepsy Association.
doi:10.1016/j.seizure.2007.07.010

reaches the hippocampal formation and the amygdala.[1] ErC, PrC as well as the parahippocampal gyrus (PHG) are heavily interconnected.[2] The PrC receives input from the temporal, parietal, occipital, cingulate and insular cortices and is one of the major inputs to the ErC, which then conveys this highly processed information to the hippocampus via the perforant pathway.[3,4] So, while the ErC connects directly to the hippocampus, connections from the PrC and PHG to the hippocampus are indirect, via relays in the ErC.[5,6] The hippocampus is thus the final stage of convergence within the medial temporal lobe.[7]

Progress in the modelling of medial temporal lobe (limbic system) function has been limited by the technological problems associated with characterising deep brain structures *in vivo*.[8] The advent of volumetric magnetic resonance imaging (MRI) analysis provides an opportunity to clarify issues of human temporal lobe structure, by permitting a direct investigation of *in vivo* morphology. MRI volumetry is based on the principle that the response of neurons to disease is gliosis and cell loss.[9] It follows that neural disease may be reflected in the measurement of discrete structures *in vivo*. Indeed, several studies have documented a close correlation between histopathologically determined cell loss and atrophy as measured through hippocampal volume measurements.[10–12] Several research groups now regard volumetric MRI as a surrogate for histological examination of the hippocampus[9,13] and incorporate this technique routinely in their pre-surgical analysis of temporal lobe epilepsy (TLE) patients with mesial temporal (hippocampal) sclerosis (MTS).

The exact limbic structures involved in MTS remain uncertain.[14] Histopathologically, MTS has been defined as cell loss and reactive gliosis in the hippocampus, predominantly in field CA4, but often involving areas CA1 and CA3 and the subiculum.[15] The amygdala and dentate fascia are also often affected.[16] Attempts to define the extent of damage in adjacent structures, namely the ErC and PrC, have been sparse.[17] Recently, one group documented ErC volume reductions ipsilateral to the epileptic focus in MTS patients with hippocampal volume reductions,[18] as well as those with normal hippocampal volume.[19] In the latter study, nine of 22 patients had histopathologically confirmed MTS, but ErC volumes were examined in the group as a whole, making it difficult to draw conclusions about the significance of ErC changes. Salmenpera and colleagues documented ErC changes in a subpopulation of patients with cryptogenic TLE, with mixed pathology, but did not examine MTS patients separately.[20] The involvement of ErC in the generation and propagation of temporal lobe seizures has been documented in animal and human research.[21,22] The PrC, with its close anatomical and functional connections with the ErC, may also show morphometric changes in patients with MTS. Bernasconi and colleagues found PrC abnormalities in two of six TLE patients examined. However, the distributional properties of the volume changes were not discussed.[23]

The present study extends quantitative examination of the limbic system through the development and validation of detailed volumetric protocols to measure the ErC and PrC. The volumetric protocols will then be used to examine relationships in the rhinal cortex in a substantial homogeneous group of TLE patients, all with MTS. The fact that this disorder can result in pathological changes in different mesial temporal structures also provides a unique opportunity to explore relationships between structures of interest, without the confounds of invasive techniques. The proposed research has the potential to improve our understanding of the patterns of limbic pathology in patients with MTS.

Materials and methods

Participants

Subjects were 61 consecutive patients with TLE admitted to the Comprehensive Epilepsy Program at St. Vincent's Hospital, Melbourne. The Commission on Classification and Terminology of the International League Against Epilepsy[24] classifies TLE as a symptomatic form of location-related (focal or partial) epilepsies and syndromes. Patients were identified on the basis of clinical features, interictal scalp/sphenoidal EEG, prolonged EEG-video monitoring and neuropsychological studies. Fifty-nine of the 61 patients have so far proceeded to anterior temporal lobectomy, with histopathological confirmation of MTS in all cases. Till date, two patients have chosen not to proceed with surgery, but results of the above investigations are suggestive of typical MTS. Thirty-three patients had left MTS, 28 had right MTS. Of the patients with left MTS, 14 were male and 19 were female, with a mean age of 37 years (S.D. = 9.4). Nine of the left MTS group were left-handed, 24 were right-handed. Handedness was defined as laterality preference, as assessed by a handedness questionnaire routinely administered by the treating neurologist during initial consultation. The questionnaire is available on request from the first author. For brevity, laterality of preference will be referred to subsequently as handedness. Of the right MTS group, 15 were male and 13 were female, with a mean age of 36 years (S.D. = 11.9). Six of this group were left-handed, 22 were right-