Neurobiology of Aging 65 (2018) 86–97

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Age-related functional changes in domain-specific medial temporal lobe pathways

David Berron [a,b,*], Katja Neumann [a,b], Anne Maass [b,c], Hartmut Schütze [a], Klaus Fliessbach [d,e], Verena Kiven [e], Frank Jessen [f,g], Magdalena Sauvage [h,i], Dharshan Kumaran [j], Emrah Düzel [a,b,j]

[a] Institute of Cognitive Neurology and Dementia Research, Otto-von-Guericke University, Magdeburg, Germany
[b] German Center for Neurodegenerative Diseases, Magdeburg, Germany
[c] Helen Wills Neuroscience Institute, University of California, Berkeley, CA, USA
[d] University Hospital Bonn, Bonn, Germany
[e] German Center for Neurodegenerative Diseases, Bonn, Germany
[f] German Center for Neurodegenerative Diseases, Bonn-Cologne, Germany
[g] Department of Psychiatry, University of Cologne, Cologne, Germany
[h] Leibniz-Institute for Neurobiology, Functional Architecture of Memory Department, Magdeburg, Germany
[i] Medical Faculty, Otto-von-Guericke University, Magdeburg, Germany
[j] University College London, Institute of Cognitive Neuroscience, London, UK

ARTICLE INFO

Article history:
Received 24 July 2017
Received in revised form 19 December 2017
Accepted 19 December 2017
Available online 31 January 2018

Keywords:
fMRI
Mnemonic discrimination
Aging
Entorhinal cortex
Perirhinal cortex
Hippocampus
Objects and scenes

ABSTRACT

There is now converging evidence from studies in animals and humans that the medial temporal lobes (MTLs) harbor anatomically distinct processing pathways for object and scene information. Recent functional magnetic resonance imaging studies in humans suggest that this domain-specific organization may be associated with a functional preference of the anterior-lateral part of the entorhinal cortex (alErC) for objects and the posterior-medial entorhinal cortex (pmErC) for scenes. As MTL subregions are differentially affected by aging and neurodegenerative diseases, the question was raised whether aging may affect the 2 pathways differentially. To address this possibility, we developed a paradigm that allows the investigation of object memory and scene memory in a mnemonic discrimination task. A group of young (n = 43) and healthy older subjects (n = 44) underwent functional magnetic resonance imaging recordings during this novel task, while they were asked to discriminate exact repetitions of object and scene stimuli from novel stimuli that were similar but modified versions of the original stimuli ("lures"). We used structural magnetic resonance images to manually segment anatomical components of the MTL including alErC and pmErC and used these segmented regions to analyze domain specificity of functional activity. Across the entire sample, object processing was associated with activation of the perirhinal cortex (PrC) and alErC, whereas for scene processing, activation was more predominant in the parahippocampal cortex and pmErC. Functional activity related to mnemonic discrimination of object and scene lures from exact repetitions was found to overlap between processing pathways and suggests that while the PrC-alErC pathway was more involved in object discrimination, both pathways were involved in the discrimination of similar scenes. Older adults were behaviorally less accurate than young adults in discriminating similar lures from exact repetitions, but this reduction was equivalent in both domains. However, this was accompanied by significantly reduced domain-specific activity in PrC in older adults compared to what was observed in the young. Furthermore, this reduced domain-specific activity was associated to worse performance in object mnemonic discrimination in older adults. Taken together, we show the fine-grained functional organization of the MTL into domain-specific pathways for objects and scenes and their mnemonic discrimination and further provide evidence that aging might affect these pathways in a differential fashion. Future experiments will elucidate whether the 2 pathways are differentially affected in early stages of Alzheimer's disease in relation to amyloid or tau pathology.

* Corresponding author at: Institute of Cognitive Neurology and Dementia Research, Otto-von-Guericke University Magdeburg, House 64, Leipziger Str. 44, 39120 Magdeburg, Germany.
E-mail address: david.berron@med.ovgu.de (D. Berron).

https://doi.org/10.1016/j.neurobiolaging.2017.12.030

1. Introduction

In the medial temporal lobe (MTL), there are domain-specific pathways that support different types of information processing and memory (Ranganath and Ritchey, 2012; Ritchey et al., 2015). The 2 pathways receive information from 2 different visual streams, which connect regions that are involved in object and spatial vision with the perirhinal cortex (PrC) and parahippocampal cortex (PhC), respectively (Kravitz et al., 2011; Mishkin et al., 1983). While the PrC is more involved in the processing of (Diana et al., 2012; Litman et al., 2009) and memory for objects and content (Davachi et al., 2003; Ekstrom and Bookheimer, 2007; Libby et al., 2014; Schultz et al., 2012; Sheldon and Levine, 2015; Staresina et al., 2011, 2013), the PhC is associated with the processing of (Diana et al., 2012; Epstein and Kanwisher, 1998; Litman et al., 2009) and memory for spatial layouts, context, and scenes (Ekstrom and Bookheimer, 2007; Libby et al., 2014; Schultz et al., 2012; Staresina et al., 2011, 2013). Studies in rodents suggest that the 2 pathways extend toward the entorhinal cortex (ErC). In rodents, the lateral ErC (LEC) is more involved in object memory and processing of local landmarks, whereas the medial ErC (MEC) is critical for spatial memory and processing of global landmarks (Knierim et al., 2014). Recent functional magnetic resonance imaging (fMRI) studies used functional connectivity analyses to investigate the human homologs of LEC and MEC in rats and found strong evidence that these subdivisions correspond to the anterior-lateral part of the entorhinal cortex (alErC) and posterior-medial entorhinal cortex (pmErC) in humans, respectively (Maass, Berron et al., 2015; Schröder, Haak et al., 2015).

The hippocampus (HC), especially the dentate gyrus (DG), plays an important role in pattern separation—a mechanism which is hypothesized to be critical for the discrimination of very similar memories (Leutgeb, 2007; Neunuebel and Knierim, 2014). Hippocampal pattern separation thereby relates to the decorrelation of similar input patterns to create distinct and independent representations that reduce the interference between these similar memories (McClelland et al., 1995; Treves and Rolls, 1992). Strong evidence for the role of the human DG in pattern separation has been shown in fMRI studies using mnemonic discrimination tasks that are likely to pose high demands on pattern separation (Bakker et al., 2008; Berron et al., 2016; Lacy et al., 2011). However, it is less clear how subregions in extrahippocampal pathways such as the PrC, PhC, and ErC are involved in mnemonic discrimination. A recent study from Reagh and Yassa showed that not only PrC and PhC but also the ErC are involved in mnemonic discrimination of similar objects and changes in object location (Reagh and Yassa, 2014). On the other hand, studies on perceptual discrimination of objects and scenes with patients who either have lesions including the PrC or the HC also suggest the involvement of extrahippocampal regions. While PrC has been shown to have a special role in the discrimination of objects with high feature overlap, the HC seems to be critically involved in scene discrimination (Barense et al., 2005; Lee et al., 2005a,b).

Mnemonic discrimination has been shown to decline with age (Stark et al., 2013; 2015). Studies using mnemonic discrimination tasks showed that older adults tend to call similar items more likely old compared to young individuals, with no difference in judging repeated items as old. This is often interpreted as a deficit in pattern separation functions and a concomitant bias toward pattern completion (Stark et al., 2015; Vieweg et al., 2015; Yassa et al., 2011a). These behavioral deficits may be related to an impairment of MTL subregions in aging as well as neurodegenerative diseases affecting the integrity of brain systems and subregions in the MTL. For example, age-related degradation in perforant pathway integrity and blood-oxygen-level dependent hyperactivity in CA3 have been associated with impairments in mnemonic discrimination (Bakker et al., 2012; Yassa et al., 2011b). However, one of the earliest cortical sites where Alzheimer's disease (AD)–related pathology can be detected even before being evident in the HC is the transentorhinal region, which is part of the PrC and the ErC (Braak and Braak, 1991). This has received support by recent neuroimaging studies demonstrating a decrease in cerebral blood volume and reduced gray matter thickness in the anterior temporal lobe including the PrC and ErC in preclinical and early AD (Khan et al., 2014; Krumm et al., 2016; Yushkevich et al., 2015). Given that ErC, PrC, and PhC are critically involved in memory for objects and scenes, the impairment in PrC-alErC and PhC-pmErC can also yield degraded inputs to the HC and thus contribute to the impaired discrimination of similar lures.

To investigate age-related behavioral and functional changes related to the 2 memory domains, we developed a novel object-scene mnemonic discrimination task, which poses high demands on pattern separation. This task was designed to allow the investigation of behavioral discrimination performance as well as the neural organization of mnemonic discrimination of objects and scenes. In addition, the paradigm provides 2 potential imaging measures of functional integrity. First, we will analyze domain specificity within both MTL pathways to investigate their functional architecture as well as age-related effects. Second, we will investigate the involvement of MTL pathways in mnemonic discrimination by analyzing lure-related novelty responses based on a repetition suppression approach. In this study, we used these measures to investigate the organization and integrity of MTL pathways in a group of young as well as healthy older individuals using fMRI.

2. Materials and methods

2.1. Participants

Forty-six healthy young and 47 healthy older subjects participated in this experiment. Subjects were recruited in Bonn and Magdeburg. We excluded subjects with extensive head motion within the scanner (>2 mm [translation], n = 3) before any functional analysis. Furthermore, we did not analyze data from subjects whose task performance was more than 2 standard deviations (SDs) below the group mean performance (n = 3). The final sample consisted of 43 young (mean age = 24; SD = 3.5; 21 female) and 44 older subjects (mean age = 68.8; SD = 5.7; 21 female). Subjects were screened for known metabolic disorders (known history of hypertension or diabetes) and neurologic or psychiatric history and excluded from further examination in case of incidents reported during history taking. In addition, normal and corrected vision was assessed using standard procedures and printed stimulus materials comparable to the materials used during the experiments. Mini–Mental State Examination scores were available for the older group from only one site (mean score 29 [SD = 1.6]). To make sure that both older groups were comparable in cognitive performance, we statistically compared task performance of subjects with and without a Mini–Mental State Examination test score. This analysis showed no difference between the groups in object or scene discrimination performance. The study was conducted and designed in accordance with the Declaration of Helsinki (Williams, 2008) and all subjects gave informed and written consent for their participation in accordance with ethic and data security guidelines of the Otto-von-Guericke University Magdeburg and the German Center for Neurodegenerative Diseases (DZNE). The study was approved by the local ethics committees in Magdeburg and Bonn.

2.2. Stimuli and setting

Stimuli consisted of computer-generated (3ds Max, Autodesk Inc., San Rafael, USA) and isoluminant images. The images