Neurobiology of Learning and Memory 129 (2016) 113–119

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

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

Spatial pattern separation differences in older adult carriers and non-carriers for the apolipoprotein E epsilon 4 allele

David P. Sheppard [a,b], Lisa V. Graves [c], Heather M. Holden [c], Lisa Delano-Wood [d,e], Mark W. Bondi [d,e], Paul E. Gilbert [a,c,*]

[a] Department of Psychology, San Diego State University, San Diego, CA, USA
[b] Department of Psychology, University of Houston, Houston, TX, USA
[c] San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA
[d] VA San Diego Healthcare System, La Jolla, CA, USA
[e] Department of Psychiatry, University of California San Diego, School of Medicine, La Jolla, CA, USA

ARTICLE INFO

Article history:
Received 9 January 2015
Revised 13 April 2015
Accepted 23 April 2015
Available online 5 May 2015

Keywords:
Aging
Pattern separation
Spatial memory
Interference
Apolipoprotein E

ABSTRACT

We examined the performance of healthy young ($n = 57$) and older adults ($n = 43$) genotyped as apolipoprotein E-ε4 (APOE-ε4) carriers or APOE-ε4 non-carriers on a delayed match-to-sample task involving varying degrees of spatial interference hypothesized to assess spatial pattern separation. Older adult ε4 carriers were further divided into "impaired" and "unimpaired" groups based on their performance on a standardized test of verbal memory. We found that performance on the spatial pattern separation test increased as a function of decreased spatial interference across all groups. The older ε4 carriers in the impaired group performed significantly worse ($p < .05$) than unimpaired ε4 carriers, ε4 non-carriers, and young adults. The data suggest that spatial pattern separation may be less efficient in a subset of healthy older adults with subtle memory decline who are carriers of the ε4 allele. However, pattern separation performance may be comparable to that of young adults in a subset of older adult ε4 carriers and more broadly among non-carriers. Our findings offer additional evidence that pattern separation may vary in older adults, and they provide novel insight into pattern separation efficiency in ε4-positive older adults.

1. Introduction

Age-related differences on tasks thought to tax pattern separation have been well documented in recent studies (Doxey & Kirwan, 2014; Holden, Hoebel, Loftis, & Gilbert, 2012; Leal & Yassa, 2014; Ly, Murray, & Yassa, 2013; Pidgeon & Morcom, 2014; Reagh et al., 2014; Roberts, Ly, Murray, & Yassa, 2014; Stark, Yassa, Lacy, & Stark, 2013; Stark, Yassa, & Stark, 2010; Tolentino, Pirogovsky, Luu, Toner, & Gilbert, 2012; Toner, Pirogovsky, Kirwan, & Gilbert, 2009; Yassa, Lacy, et al., 2011; Yassa, Mattfeld, Stark, & Stark, 2011). Pattern separation is a mechanism that separates partially overlapping patterns of neural activation so that one pattern may be retrieved as separate from other similar patterns. Pattern separation may reduce potential interference or similarity among memory representations, thereby increasing the likelihood of accurate encoding and subsequent retrieval (Holden & Gilbert, 2012). There is considerable evidence that the dentate gyrus (DG) and CA3 hippocampal subregions play a critical role in pattern separation (for reviews see Gilbert & Brushfield, 2009; Kesner & Rolls, 2014; Schmidt, Marrone, & Markus 2012; Yassa & Stark, 2011).

The human hippocampus has been shown to undergo structural and functional changes as a result of aging (Allen, Bruss, Brown, & Damasio, 2005; Driscoll & Sutherland, 2005; Good et al., 2001; Raz et al., 2005; Small, Tsai, DeLaPaz, Mayeux, & Stern, 2002; Walhovd et al., 2010). However, the DG subregion may be particularly susceptible to these age-related changes (Small et al., 2002). A recent study by Doxey and Kirwan (2014) used functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) to measure functional and structural correlates of behavioral pattern separation in the hippocampus and medial temporal lobe. They found that the size of left hemisphere DG/CA3 regions was the strongest predictor of performance, other than age, on a task

* Corresponding author at: SDSU/UCSD Joint Doctoral Program in Clinical Psychology, 6363 Alvarado Court, Suite 103, San Diego, CA 92120, USA. Fax: +1 (619) 594 3773.
E-mail addresses: dpsheppard@uh.edu (D.P. Sheppard), lvgraves@gmail.com (L.V. Graves), hholden365@gmail.com (H.M. Holden), ldelano@ucsd.edu (L. Delano-Wood), mbondi@ucsd.edu (M.W. Bondi), pgilbert@mail.sdsu.edu (P.E. Gilbert).

http://dx.doi.org/10.1016/j.nlm.2015.04.011
1074-7427/

hypothesized to tax pattern separation. Diffusion in white matter tracts and resting function connection strengths did not significantly predict task performance (Doxey & Kirwan, 2014). However, age-related changes are evident in the perforant pathway input to the DG (Yassa, Mattfeld, et al., 2011), and a study that used high-resolution fMRI and ultrahigh-resolution DTI showed that decreased pattern separation activity in the DG/CA3 regions of older adults was associated with structural changes in the perforant pathway. It was hypothesized that these changes weaken the processing of new information and strengthen the processing of stored information (Yassa, Mattfeld, et al., 2011), which may result in less efficient pattern separation.

There is a growing body of evidence that older adults are impaired relative to young adults on behavioral tasks hypothesized to tax pattern separation for visual objects, spatial locations, temporal order, verbal stimuli, and emotional information (Doxey & Kirwan, 2014; Holden et al., 2012; Leal & Yassa, 2014; Ly et al., 2013; Pidgeon & Morcom, 2014; Reagh et al., 2014; Roberts et al., 2014; Stark et al., 2010, 2013; Tolentino et al., 2012; Toner et al., 2009; Yassa, Lacy, et al., 2011; Yassa, Mattfeld, et al., 2011). However, numerous studies have demonstrated that pattern separation efficiency varies among older adults. These studies borrowed an approach commonly used in animal studies of aging (e.g., Gallagher et al., 2006), whereby aged subjects are dichotomized into "impaired" and "unimpaired" groups based on performance on a well-characterized test (such as the water maze test in animals) and then the subjects are tested on a different test to examine group differences in performance. Numerous recent studies have modeled this approach to dichotomize older humans into "older-impaired" and "older-unimpaired" groups based on performance on standardized serial list learning tests and then investigate differences between the two groups on pattern separation tasks (Holden, Toner, Pirogovsky, Kirwan, & Gilbert, 2013; Holden et al., 2012; Reagh et al., 2014; Roberts et al., 2014; Stark et al., 2010, 2013).

Stark et al. (2010) were the first to assess potential age-related variability on a task designed to measure spatial pattern separation. In the initial comparison of young and older adults, no group differences were found. However, when the older adult group was divided into aged-impaired and aged-unimpaired groups based on performance on a standardized verbal list learning task, the young adults and aged-unimpaired older adults performed significantly better than the aged-impaired older adults on the trials that taxed pattern separation. Holden et al. (2012) replicated these findings using a different task to assess spatial pattern separation and found that the pattern of deficits was remarkably similar to those of Stark et al. (2010). The older-impaired group showed pattern separation deficits relative to the young adults and older-unimpaired adults (Holden et al., 2012). A more recent study reported similar results using an incidental encoding task involving objects presented in various locations (Reagh et al., 2014). In addition to spatial tasks, studies have produced similar results on tests hypothesized to assess pattern separation for temporal order memory (Roberts et al., 2014) and visual object information (Holden et al., 2013; Stark et al., 2013). Therefore, this approach has provided unique insight into the variability among older adults when performing behavioral tasks designed to measure pattern separation.

One factor that might contribute to differences on cognitive tasks among older adults is the presence of the apolipoprotein E-ε4 (APOE-ε4) allele on chromosome 19. The APOE gene codes for a protein called apolipoprotein E, which plays a role in the transfer of cholesterol and other lipids between cells and organs. The ε4 allele of the APOE gene also has been linked to Alzheimer's disease (AD). Although a number of risk factors for AD have been discussed—such as increased age, a diagnosis of mild cognitive impairment (MCI), and a positive family history—one of the most significant risk factors is possession of the ε4 variant of the APOE gene (Combarros, Alvarez-Arcaya, Sánchez-Guerra, Infante, & Berciano, 2002; Holmes, 2002; Roses & Saunders, 1997; Saunders et al., 2000; Selkoe, 2001). Cognitive differences have been well documented between healthy older adults who carry the ε4 allele versus those who do not (Bondi et al., 1995; Caselli et al., 2001; Lehmann et al., 2006; Lind et al., 2006; Mayeux, Small, Tang, Tycko, & Stern, 2001; Rosen et al., 2005; Seeman et al., 2005; Swan, Lessov-Schlaggar, Carmelli, Schellenberg, & La Rue, 2005; Tupler et al., 2007; Wilson et al., 2002). In addition, the allele has been implicated in functional and structural brain changes observed across the aging spectrum (Bondi, Houston, Eyler, & Brown, 2005; Bookheimer et al., 2000; Filbey, Chen, Sunderland, & Cohen, 2010; Han et al., 2007; Johnson et al., 2007; Lind et al., 2006; Mondadori et al., 2007; Wierenga et al., 2012; Yang et al., 2014). Hippocampal atrophy is greater in nondemented older adults who are ε4 carriers compared to ε4 non-carriers (Cohen, Small, Lalonde, Friz, & Sunderland, 2001; Den Heijer et al., 2002; Lind et al., 2006; Plassman et al., 1997; Soininen et al., 1995) and longitudinal comparisons reveal that the APOE ε4 allele is linked to a greater reduction in hippocampal volume (Crivello et al., 2010; Jak, Houston, Nagel, Corey-Bloom, & Bondi, 2007; Stewart et al., 2011) and a decline in white matter integrity in the posterior corpus callosum and medial temporal lobes (Nierenberg et al., 2005; Persson et al., 2006). Critically, neuroimaging studies examining subregions of the hippocampus have implicated the DG/CA3 subregions as being particularly susceptible to volumetric (Mueller, Schuff, Raptentsetsang, Elman, & Weiner, 2008; Mueller & Weiner, 2009; cf. Lyall et al., 2013) and functional (Bookheimer et al., 2000; Han et al., 2007; Suthana et al., 2010) changes in older adults who are carriers of the ε4 allele. Given the association between APOE-ε4 genotype and changes in the DG subregion, and the importance of this subregion in pattern separation, we hypothesized that pattern separation would be impaired in older adult carriers of the APOE-ε4 allele.

To the authors' knowledge, only one published study has examined the association between pattern separation and possession of the APOE-ε4 allele. Wesnes, Annas, Basun, Edgar, and Blennow (2014) examined pattern separation abilities of older adults diagnosed with mild to moderate AD with and without the ε4 allele. Their results indicated that, compared to ε4 non-carriers, ε4 carriers were impaired in their ability to discriminate between pictures with features that were similar to those presented previously—a condition hypothesized to tax pattern separation. However, no study to our knowledge has examined whether pattern separation performance is affected in older adult ε4 carriers without a neurocognitive disorder. The present study sought to test young adults and healthy older adults with and without the APOE-ε4 allele on a previously published behavioral task hypothesized to measure spatial pattern separation.

2. Materials and methods

2.1. Participants

The participant sample for the current study consisted of 57 young adults, ranging in age from 18 to 25 years old, and 43 healthy older adults over 65 years of age. The young adults were recruited from a pool of college students at San Diego State University and the older adults were community dwelling individuals recruited from the San Diego community. All procedures were approved by the Institutional Review Boards at San Diego State University and the University of California at San Diego, and all participants provided written informed consent. The older adult participants were genotyped for APOE using a polymerase chain