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Aged rats with intact memory show distinctive recruitment in cortical regions relative to young adults in a cue mismatch task

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Abstract

Similar to elderly humans, aged Long Evans rats exhibit individual differences in performance on tasks that critically depend on the medial temporal lobe memory system. Although reduced memory performance is common, close to half of aged rats in this outbred rodent population perform within the range of young subjects, exhibiting a stable behavioral phenotype that may signal a resilience to memory decline. Increasing evidence from research on aging in the Long Evans study population supports the existence of adaptive neural change rather than avoidance of detrimental effects of aging on the brain, indicating a malleability of brain function over the lifespan that may preserve optimal function. Augmenting prior work that centered on hippocampal function, the current study extends investigation to cortical regions functionally interconnected with the hippocampal formation, including medial temporal lobe cortices and posterior components of the default mode network. In response to an environmental manipulation that creates a mismatch in the expected cue orientation, aged rats with preserved memory show greater activation across an extended network of cortical regions as measured by immediate early gene expression. In contrast, young subjects, behaviorally similar to the aged rats in this study, show a more limited cortical response. This distinctive cortical recruitment in aged unimpaired rats, set against a background of comparable activation across hippocampal subregions, may represent adaptive cortical recruitment consistent with evidence in human studies of neurocognitive aging.

Keywords

Double rotation; Medial temporal lobe; Aging; Memory; Default mode network

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Declarations of interest:

M.G. is the founder of AgeneBio Incorporated, a biotechnology company that is dedicated to discovery and development of therapies to treat cognitive impairment. She has a financial interest in the company. The authors (M.G. and R.A.H.) are inventors on Johns Hopkins University intellectual property that is licensed to AgeneBio. Otherwise, M.G. has had no consulting relationships with other public or private entities in the past three years and has no other financial holdings that could be perceived as constituting a potential conflict of interest. All conflicts of interest are managed by Johns Hopkins University. A.B. and A.M. have no conflicts of interests to declare.

Introduction

Individual differences in cognitive outcomes in old age is a topic of great interest in laboratory animal studies and clinical research. A substantial body of work in a well-characterized outbred Long Evans study population has focused on the hippocampus as a source of biological changes associated with differential memory outcomes. Aged rats in the study population with memory impairment have overactive neural circuits localized within the hippocampal formation (Wilson, Gallagher, Eichenbaum, & Tanila, 2006), a finding that has translated to human subjects with age-related memory impairment using in vivo functional magnetic resonance imaging (fMRI) (Yassa, Mattfeld, Stark, & Stark, 2011). In that context, it is notable that aged rats with preserved memory performance exhibit an augmentation of inhibitory mechanisms in the hippocampal formation that differs from young adults and may be adaptively recruited to normalize excitatory/inhibitory homeostasis necessary to preserve neural plasticity (Haberman, Colantuoni, Koh, & Gallagher, 2013; Tran, Gallagher, & Kirkwood, 2018). Consistent with that concept, therapeutic restoration of excitatory/inhibitory function in the hippocampal formation in memory impaired rats and humans has been shown to improve memory performance (Bakker et al., 2012; Koh, Haberman, Foti, McCown, & Gallagher, 2010).

Other clinical research has highlighted dynamic modulation of the medial temporal lobe memory system via its anatomical and functional connectivity with a more extensive cortical network (Eyler, Sherzai, Kaup, & Jeste, 2011; Spreng, Wojtowicz, & Grady, 2010). In comparison to studies in humans, such investigations for detection of individual differences in neurocognitive aging in rodents have been limited (Ash et al., 2016; Haberman, Koh, & Gallagher, 2017).

Across species, the hippocampal formation interfaces with neocortical processing systems engaged in memory function via cortical regions in the medial temporal lobe (MTL). Inputs to entorhinal cortex from surrounding perirhinal and postrhinal/parahippocampal cortices provide the primary gateway to the hippocampal formation for multimodal cortical processing, alongside a more modest direct projection. (Agster & Burwell, 2013; Burwell & Amaral, 1998; Suzuki & Amaral, 1994). Posterior neocortical regions of the default mode network (DMN), a resting state network comprised of specific medial prefrontal, posteromedial and temporal cortices, are strongly associated with the MTL (Buckner, Andrews-Hanna & Schacter, 2008), particularly with respect to the retrosplenial cortex (RSC). Evidence suggests the RSC mediates DMN effects on episodic memory (Vincent et al., 2006). Altered DMN function has been tied to the regulation of memory performance in both younger and elderly adults. (Amlien, Sneve, Vidal-Pineiro, Walhovd, & Fjell, 2018; Huijbers et al., 2013).

Recent investigations of resting state functional connectivity in rodents has identified a DMN in rats that substantially overlaps with the human DMN (Gozzi & Schwarz, 2016). Furthermore, DMN connectivity obtained in the aged Long Evans study population (Ash et al., 2016) has shown distinct RSC functional connectivity associated with the differential outcomes of preserved versus impaired memory in aging, favoring greater functional connectivity according to more preserved age-related memory function in the rodent model.

Those data suggest that the connections between the hippocampal formation and DMN posterior cortices may form an extended memory network that is modulated with aging and sensitive to individual differences.

Anchored in this perspective, the current study examines cortical activation patterns in posterior regions of the DMN and medial temporal cortex of aged and young rats during a behavioral task known to recruit hippocampal function. As a measure of neural activity, immediate early gene (IEG) expression was quantified after a test session in which a manipulation of the cue configuration of the explored environment contrasted with the remembered, familiar cue configuration experienced during previous days of testing (Knierim, 2002).

The findings in the current study are an extension of a previous study which examined hippocampal activation in the same cue mismatch task (Branch et al., 2019). Only aged rats with memory performance on par with young subjects were included in these studies so as to equate behavioral performance across young and aged groups and establish network patterns associated with preserved memory function. Our earlier published report showed similar neural activity dependent IEG expression between young and aged unimpaired rats in subfields of the hippocampal formation, consistent with clinical findings of high performing older adults (Eyler et al., 2011; Pudas et al., 2013). Here we examine behaviorally induced IEG expression in the RSC and posterior parietal cortex (PPC), as DMN-associated structures, as well as perirhinal (PER), postrhinal (POR) and entorhinal cortex components of the medial temporal system. Entorhinal cortex was also assessed as medial (MEC) and lateral (LEC) subdivisions based on anatomic parameters with correspondence to distinctions in connectivity and function (Connor & Knierim, 2017). Our data reveal that outside the hippocampal formation, cortical activation patterns differ between young and high-performing aged rats. These differences may be indicative of adaptive network reorganization in aging that could contribute to resilience against age-related cognitive decline. Importantly, this work establishes a paradigm in which to examine differential cortical activation patterns in an aged animal model that allows manipulation of network components to test their contribution to cognition in aging.

Materials and Methods

Subjects

Aged, male Long-Evans rats were obtained at 8–9 months of age from Charles River Laboratories (Raleigh, NC) and housed in a vivarium at Johns Hopkins University until 24–26 months of age. Young rats obtained from the same source were tested around 4–6 months of age. All rats were individually housed at 25°C and maintained on a 12 hr light/dark cycle. Food and water were provided ad libitum until indicated otherwise. The rats were examined for health and pathogen-free status throughout the study, as well as necropsies at the time of sacrifice. As standard practice in this research program, rats that showed impaired health or disabilities that could impact behavioral performance (e.g. poor eyesight, clinical evidence of renal impairment, pituitary or other tumors) were excluded from the study. All procedures were approved by the Johns Hopkins University Institutional Animal Care and Use Committee in accordance with the National Institutes of Health directive.

Behavior

Behavioral methods are briefly summarized below and illustrated in Fig 1A. The complete behavioral procedures for all rats used in this study can be found in Branch et al. (2019).

Water Maze Characterization—All rats were first characterized in a standardized watermaze protocol to assess the integrity of spatial memory. Relative to young adult rats, the aged Long Evans rat study population shows a larger range of individual differences in memory performance such that some older rats perform on par with the normative range of younger adult performance while others perform outside that range (Gallagher, Burwell, & Burchinal, 1993; Haberman et al., 2011). Briefly, rats were trained for eight days (three trials per day) to locate a camouflaged escape platform. Every sixth trial consisted of a probe trial (no escape platform for the first 30s of the trial) which served as the basis for a learning index (LI) generated from the proximity of the rat to the escape platform location. A learning index cutoff was used to segregate aged rats into unimpaired (AU, LI < 240) and impaired (AI, LI > 240) such that AU rats fell within the range of young (Y) normative data collected over many years (Gallagher, Burwell, & Burchinal, 1993; Haberman et al., 2011; Spiegel, Koh, Vogt, Rapp, & Gallagher, 2013). Young (N=14) and AU (N=16) rats were selected to equate learning indices across age groups [Fig 1B; 1W-ANOVA; ($F(1,28) = 0.104$, $p = 0.75$)] AI rats were excluded from further behavioral work because prior experiments showed that AI rats exhibit diminished behavioral responses to the double rotation task described below, unlike young and AU rats (unpublished data). From this cohort, Y and AU animals were then pseudo-randomly assigned to one of two conditions [double rotation (DR) or no change (NC), see below] such that learning index scores were similar across the two conditions. Final group sizes were as follows: Y: NC = 7, DR = 7; AU: NC = 7, DR = 9.

Double Cue Rotation task—The double cue rotation protocol was adapted from that used originally by (Knierim, 2002). Following watermaze characterization, all rats were placed on a food restricted diet and weighed every day to maintain body weight at 85% of free-feeding weight. All Y and AU rats were then acclimated to run clockwise (CW) on a circular track to collect bacon crumble rewards placed at arbitrary locations on the track. The track was composed of four textured surfaces that served as local cues placed in a circular, curtained environment (2.7-m diameter) in which six distinct peripheral objects were present either on the floor or on the curtain, serving as global cues. Each session lasted 20 minutes for days 1–5, after which each session was 20 min or 20 laps whichever occurred first. On the test day (day 11), rats were placed on the track with either the same cue orientation as during the acclimation period (no change, NC), or with cues rotated (double rotation, DR) such that local cues were rotated 90 degrees counter-clockwise and global cues were rotated 90 degrees clockwise for a total of 180-degree mismatch. This results in a novel cue configuration where local cues are placed in maximum conflict with the global cues, a manipulation that has been previously shown to impact computational processing and hippocampal encoding (Knierim & Neunuebel, 2016; H. Lee, Wang, Deshmukh, & Knierim, 2015; I. Lee, Yoganarasimha, Rao, & Knierim, 2004; Neunuebel & Knierim, 2014). The number of laps completed in each training session was recorded to ensure rats were adequately traversing the track and did not differ between Y and AU (Branch et al., 2019).

As a measure of environmental investigation, head scans (Monaco, Rao, Roth, & Knierim, 2014) were manually counted from digital recordings from a camera mounted directly above the track. A head scan was counted when a rat paused in its locomotion around the track and rotated his head side to side and required that the rat proceed at least two steps forward before a second head scan could be recorded.

In situ hybridization

Rats were perfused 2 hours from the beginning of each rat's test day session with 4% paraformaldehyde. At this time point, expression levels of select lEGs (such as Zif268 and cFos) and downstream effector genes reflect neural activation and synaptic plasticity mechanisms as was observed previously (Branch et al., 2019; Haberman et al., 2017; Haberman, Lee, Colantuoni, Koh, & Gallagher, 2008). Quantitative *in situ* hybridization was performed on 40 pm coronal sections cut in 1 in 24 series with radiolabeled Zif268 (Egr1) or Tubg1 mRNA probes as in (Branch et al., 2019). Brain regions of interest were outlined by hand from phosphorimager scans (Typhoon 9410, GE Healthcare), matched for level along the anterior-posterior axis and quantified, blind to experimental conditions, using ImageQuant (GE Healthcare, PA). All intensity values were normalized to radioactive standards exposed at the same time as the brain sections. The CA3, CA1, and dentate gyrus (DG) hippocampal subfields (reported previously) as well as the RSC, PPC (extending approximately −2.8 mm to −4.16 mm relative to bregma) and PER (−3.84 to −6.84 relative to bregma) were quantified from the same set of sections. The MEC and LEC (approximately −6.0 to −7.8 mm relative to bregma) along with POR (approximately −7.6 to −8.3 mm relative to bregma) were quantified from an independent set of sections from the same subjects. Region boundaries were determined based on the atlas of Paxinos and Watson (2014) for parietal cortex and retrosplenial cortex and all other ROIs were guided by *The hippocampus atlas* online (Kjonigsen, Leergaard, Witter, & Bjaalie, 2011). All layers were included for all cortical analyses.

Statistical analysis

Zif268 is an immediate early gene responsive to neural activity and used here as an indicator of such activity. The NC condition was included to control for gene induction due to the physical performance of the task and exposure to the environment. Therefore, all gene measures were normalized to the average of NC condition within each age group. A mixed design ANOVA was performed on the DR data to compare induction levels with regions as the repeated measures and age as a between subjects factor. Follow-on analyses were performed as in Branch et al (2017) in which gene expression levels were analyzed independently for each region of interest and each age group using one-way ANOVA. For between group comparisons of scanning behavior, a two-way ANOVA was run with age (Y and AU) and test condition (NC or DR) as between subject factors. Pearson correlations were used to assess the relationship between variables and the Jennrich test for differences between matrices. Statistical comparisons with p values of < 0.05 are considered significant. All statistical analysis was conducted using SPSS PASW Statistics (version 24.0, IBM, Chicago, IL, USA).

Results

As previously reported in detail elsewhere (Branch et al., 2019), memory unimpaired aged rats (AU) and young adults (Y) behaved very similarly in the cue mismatch task, both on acclimation days and on the critical test day. On test day, both Y and AU rats in the DR condition showed an increase in number of laps and head scans (Fig. 1C) relative to the baseline measure (performance during last 2 acclimation days). Rats in both age groups in the NC condition showed similar numbers of laps and head scans during baseline and test (Branch et al., 2019).

Expression of the immediate early gene, Zif268, was measured in regions of interest by quantitative *in situ* hybridization two hours after the test day track exposure. We first asked if there was an overall difference between gene induction in the DR condition between Y and AU rats. Using a mixed design ANOVA, we compared DR values, normalized to average NC (see methods), across regions with age as a between subjects factor. We observed a main effect of region ($F(5,70) = 4.120$, $p = 0.002$), a main effect of age ($F(1, 14) = 17.928$, $p = 0.001$) and a region by age interaction ($F(5, 70) = 2.755$, $p = 0.025$), indicating age-dependent differences in induction across cortical regions. Consistent with the previous study in these subjects (Branch et al., 2019), we determined which cortical regions responded to the cue mismatch environment by comparing DR to NC values for each age group. In Y rats (Fig. 1D, F), Zif268 expression in the PPC was elevated in the DR condition relative to the NC condition (1W ANOVA, $F(1,12) = 8.594$, $p = 0.013$). All other regions examined in Y rats showed highly consistent expression between control and mismatch environments [RSC ($F(1,13) = 0.059$, $p = 0.812$), PER ($F(1,13) = 0.111$, $p = 0.745$), POR ($F(1,12) =0.149$, $p = 0.707$), MEC ($F(1,13) = 0.212$, $p = 0.653$, and LEC ($F(1,13) = 0.003$, $p = 0.958$)]. Similar to Y, AU rats (Fig 1E, F) in the DR condition increased Zif268 expression in the PPC relative to the NC condition (1W ANOVA, $F(1,15) = 6.37$, $p = 0.024$). In contrast to Y, significantly increased Zif268 expression was observed in AU rats in the DR condition in the RSC ($F(1,15) = 7.56$, $p = 0.015$), PER ($F(1,15) = 6.477$, $p = 0.023$), POR ($F(1,14) =7.461$, $p = 0.016$), and LEC ($F(1,15) = 7.503$, $p = 0.016$). Only the MEC showed similar expression between DR and NC conditions in the AU rats (1W ANOVA, $F(1, 15) = 0.022$, $p = 0.884$). As a control gene, we analyzed Tubg1 by in situ hybridization in the RSC, PPC and PER. No significant differences were observed for any region [Y: RSC: $F(1,13) = 0.465$, $p = 0.51$; PPC: $F(1,12) =0.315$, $p = 0.59$ PER: $F(1,12) =0.047$, $p = 0.83$; AU: RSC: $F(1,15) = 3.72$, $p = 0.08$; PPC: $F(1,14) =1.572$, $p = 0.23$; PER: $F(1,14) =2.994$, $p = 0.11$)]. Together, these data indicate that Y rats show a more limited mismatch-dependent increase in Zif268 cortical induction compared to AU rats.

Studies of network functional connectivity obtained in human neuroimaging studies have widely reported differences in aging (Andrews-Hanna et al., 2007; Sperling et al., 2009). Correlational analysis of activity dependent gene expression has been used previously as a proxy for functional connectivity (Babayan et al., 2017). Here, we calculated Pearson correlations of Zif268 expression across all subjects in each age group and plotted the r-value intensities in a matrix of pairwise comparisons (Fig. 2A). Zif268 expression data from individual hippocampal subfields [as reported in (Branch et al., 2019)] were included in these analyses alongside behavioral metrics and cortical regions reported in Fig 1.

Comparison of the matrices (Fig 2A) reveals different patterns of correlated gene expression for each age group. More positive correlations (indicated by greater number and size of white dots) occur in the AU rats compared to young with a significant difference between Y and AU matrices (Jennrich test; χ^2=102.4, p<0.00001). In the context of the prior analyses within anatomical regions, AU rats exhibited a strong association between LEC expression and that of PER, POR, and RSC (Fig 2B) which is not as robust in Y subjects. In contrast, MEC, despite stable Zif268 expression across behavioral conditions and age, shows strong negative correlations with hippocampal subfields in Y rats but not AU. To further highlight the data trends associated with DMN regions (RSC and PPC), Fig. 2C shows those subcomponents in relation to hippocampal formation subfields. The within-hippocampal associations are equally strong for each age group while AU rats exhibit relatively greater strength in associations with posterior DMN in a profile that is similar to young. Considering the correlational analysis of activity dependent gene expression as a proxy for functional connectivity, the AU rats may have strengthened neural activation across cortical regions against a background of similar hippocampal activity and connectivity.

Discussion

Leveraging material collected in a previous study that was directed at an analysis of the hippocampal formation (Branch et al., 2019), here we examined neural activity induced in cortical regions interconnected with the hippocampus. Neurobiological assessment occurred after subjects experienced an environmental manipulation known to recruit hippocampal functions essential for memory (Knierim & Neunuebel, 2016; Knierim, Neunuebel, & Deshmukh, 2014; I. Lee et al., 2004). Our new analysis augments previous data on adaptive hippocampal activation patterns in aged unimpaired rats and suggests that interactions among medial temporal lobe structures and posterior-medial cortices (RSC and PPC) potentially distinguish aged rats with preserved memory performance from young adults.

In contrast to young adults, AU rats exhibited a distinctive Zif268 elevation in DR relative to NC in the LEC together with PER, POR and RSC. This profile involves a network of strongly interconnected circuits where prominent age-related alterations have been observed in studies of rodents and humans. Effects of aging on impaired memory performance show consistently diminished functional engagement during mnemonic tasks together with reduced structural integrity in LEC, relative to MEC, that extends to connected circuit components including PER, parahippocampal/POR and parietal cortex (Berron et al., 2018; Burke, Hartzell, Lister, Hoang, & Barnes, 2012; Khan et al., 2014; Maurer, Burke, Diba, & Barnes, 2017; Stranahan, Haberman, & Gallagher, 2011). Poorer cognitive performance in older subjects associated with this MTL network suggest that the recruitment of these regions in the current task may reflect a greater reliance on LEC-associated circuit function in AU subjects.

As an extension into posterior DMN, human neuroimaging studies report that retrieval of episodic memories normally induces increased activation in a subset of posterior DMN regions (Hutchinson, Uncapher, & Wagner, 2009; Sestieri, Corbetta, Romani, & Shulman, 2011). In fMRI studies at older ages, such activation during retrieval is generally reduced (Amlien et al., 2018; Huijbers et al., 2012; Vannini et al., 2013). While those studies have

not considered individual differences in age-related cognitive decline, evidence for relatively preserved DMN network modulation exists for high performing older adults (Miller et al., 2008). Additionally, greater activation during retrieval appears to provide support for memory performance in older individuals (Fjell et al., 2015; Wang et al., 2010). Because the task in the current study was based on memory for a familiarized environment, augmentation in activation would be consistent with a retrieval function engaged during test day performance, as observed for both Y and AU rats in PPC.

The distinctive Zif268 upregulation in RSC in AU rats has relevance to a recent study in 180 elderly subjects who were well-characterized for episodic memory capacity (Kaboodvand, Backman, Nyberg, & Salami, 2018). Individual episodic memory capacity was most strongly associated with MTL-RSC functional connectivity within the study population. In addition, RSC served as a hub of connectivity between the MTL and DMN in a mediational analysis, similar to the current findings (Fig. 2C). Elsewhere, an analysis of resting state functional connectivity, generated with RSC as a seed region, resulted in a net positive increase in AU subjects relative to AI and young rats in the same study population used in the current research (Ash et al., 2016). Thus, as a consequence of behavioral performance the increased Zif268 expression in AU but not Y rats reported here is consistent with prior observations suggesting a somewhat distinctive role for RSC in episodic memory processes in high performing older individuals.

The current Zif268 expression data are consistent with studies demonstrating that pharmacological and behavioral induction of lEGs, as measures of neural activity, are responsive to MTL functional impairment. Pharmacological induction of neural activity, measured by cFos, identified elevated neural activity within aged PPC and RSC that was tightly correlated to memory impairment (Bucci, Rosen & Gallagher, 1998; Haberman, et al., 2017). Furthermore, both aged PER and LEC show altered activity patterns via the IEG, Arc, associated with poorer memory in aged rats in behavioral paradigms testing object recognition (Burke, et al., 2012; Maurer et al., 2017). Alongside the current work, these data connect activation of the extended MTL cortical circuit to individual differences in cognitive outcomes in aging models.

The cortical regions under study in the current work not only provide critical contributions to memory processing, but many of these network components are also sites of early pathology in late-onset Alzheimer’s disease for which aging is the primary risk factor. The RSC and PPC are sites of the early accumulation of amyloid plaques in older humans (Jones et al., 2016). Amyloid levels, measured by PET imaging, correlate with impaired DMN function and may contribute to changes in episodic memory function beyond the condition of normal aging (Andrews-Hanna et al., 2007; Sperling et al., 2009). The entorhinal cortex is also vulnerable to pathological neurofibrillary tangle accumulation that is more tightly associated with progression of neurodegeneration and worsening cognitive and clinical status in AD (Braak & Braak, 1995). In humans, tangle accumulation begins in the trans-entorhinal regions which is approximated in the rat to the perirhinal/lateral entorhinal junction. Specific vulnerability of the lateral EC relative to the medial EC has also been confirmed in aged rodents as noted earlier (Stranahan et al., 2011) as well as in Alzheimer’s disease models (Chin et al., 2007).

In summary, the current study contributes to a growing body of work across species that suggests that increased cortical recruitment in older individuals with relatively preserved cognition may reflect a functional adaptation across networks needed/used to preserve memory function. However, the mechanistic consequences of this activity remain unclear. Manipulation of cortical activation in aged rats within the current paradigm could begin to test the contribution of augmented cortical activation such that manipulation of network components could further elucidate the functional relevance of this activity.

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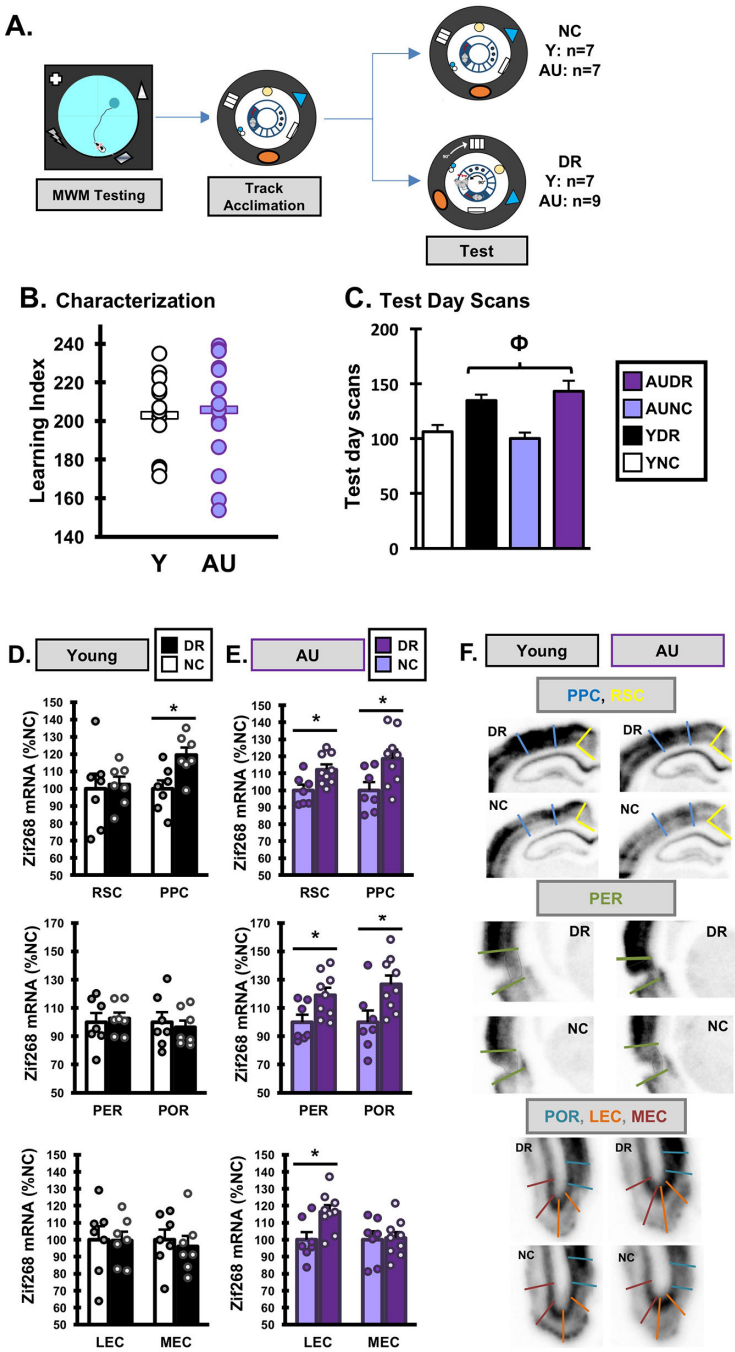

Figure 1:

A. Schematic of behavioral paradigms as detailed in text. Rats are characterized for spatial memory on a standardized water maze task. AU and Y rats are acclimated for 10 days on a circular track followed by test day with the cues rotated (DR) or in a familiar position (NC). **B.** Learning index distributions are similar for AU and Y rats. **C.** Head scanning behavior (represented as % baseline) is increased in DR condition in Y and AU rats. (ANOVA, condition: $F(1,26) = 16.761$, $p = 0.0001$) **D- E.** Zif268 expression levels are normalized to the NC condition average for each region by age group (RSC, PPC, POR, PER, LEC and

MEC as described in the text). Bar graphs represent average data while circles represent those of individual subjects. **D**) Y rats and **E**) AU rats. **F.** Representative images of Zif268 in situ hybridization. Colored lines delineate regions of interest as follows: PPC -blue; RSC - yellow; PER - green; POR - teal; LEC - orange; MEC - red. Panels A-C have been reprinted with permission from Branch et al., 2019.

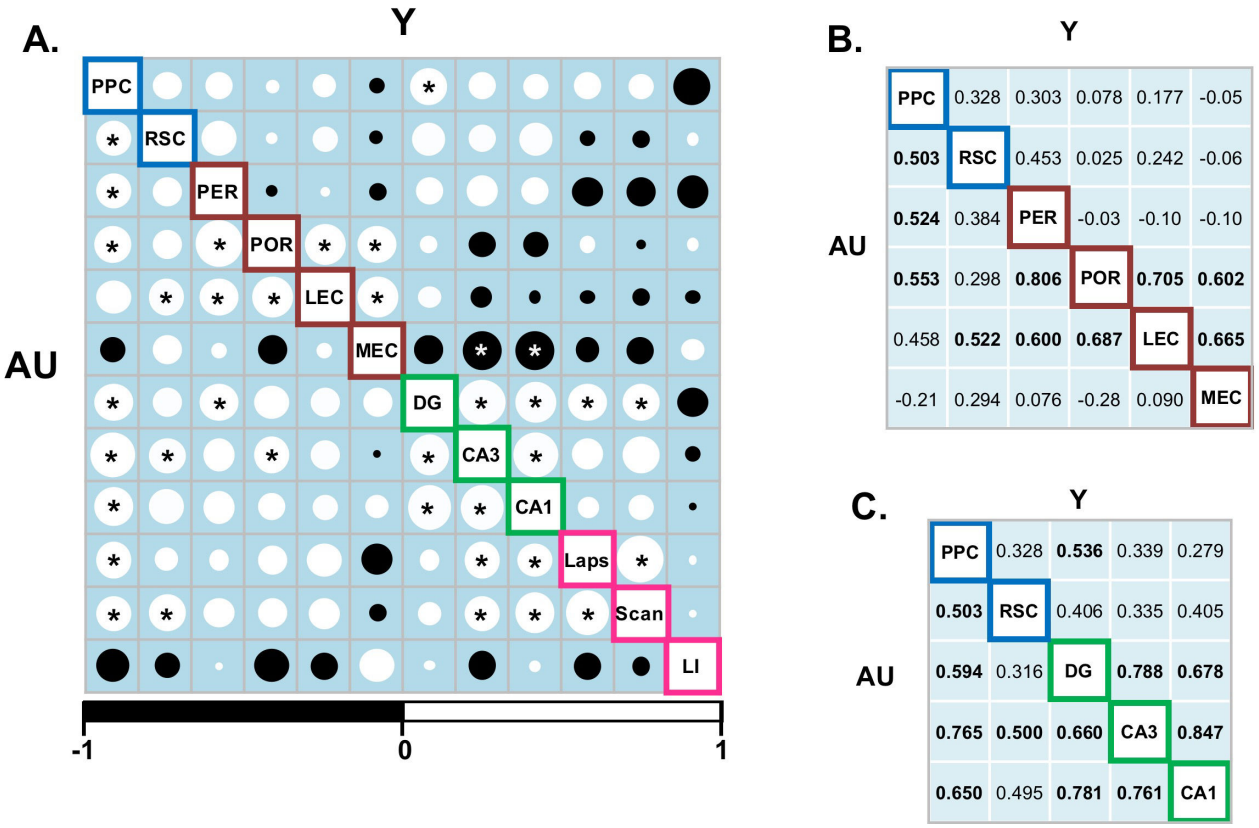

Figure 2:

A. Correlation matrix of hippocampal and cortical co-activation. Zif268 expression intensities for each region were correlated across subjects within each age group. Y Pearson r-values were plotted on the top right while AU values on the lower left, with circle size illustrating the correlation coefficient. White circles represent positive correlations while negative correlations are in black. Stars denote significant r-values at $p<0.05$. Note the greater prominence and size of white circles in the AU correlations. **B.** A subset of the correlation matrix from A. with r-values includes DMN and medial temporal cortex highlighting the greater regional correlations in AU. **C.** A subset of the correlation matrix shown in A with r-values illustrates the posterior memory network including the RSC, PPC and hippocampal subfields. Numbers in each square denote Pearson r-values. Significance at $p<0.05$ are in bold.