Journal Club

Editor's Note: These short reviews of recent *JNeurosci* articles, written exclusively by students or postdoctoral fellows, summarize the important findings of the paper and provide additional insight and commentary. If the authors of the highlighted article have written a response to the Journal Club, the response can be found by viewing the Journal Club at www.jneurosci.org. For more information on the format, review process, and purpose of Journal Club articles, please see http://jneurosci.org/content/preparing-manuscript#journalclub.

Amyloid and Tau Pathology in Normal Cognitive Aging

Emilie T. Reas
Department of Radiology, University of California, San Diego, La Jolla, California 92093
Review of Marks et al.

Detecting deviations from healthy brain aging is critical for identifying individuals at greatest risk for developing dementia. Yet because there is substantial overlap in patterns of cognitive decline and neural changes between those with dementia and nondemented older adults, dissociating normal from pathological aging remains a significant challenge (Fjell et al., 2014). The hippocampus, a critical hub in a distributed cortical memory network, undergoes atrophy and functional alterations in both aging and Alzheimer's disease (AD) (Fjell et al., 2014). Even accumulation of amyloid-β plaques and neurofibrillary tangles comprising hyperphosphorylated tau, considered hallmarks of AD, does not clearly distinguish normal from pathological aging. Despite the well-accepted involvement of amyloid-β and tau pathology in AD, questions remain regarding their causal role in the onset and progression of AD, partly because some older individuals who remain cognitively intact have high levels of amyloid-β plaques and neurofibrillary tangles (Bennett et al., 2006). Because effects of amyloid-β and tau pathology on cognitive and neural alterations during normal aging in the absence of dementia are poorly characterized, our understanding of the preclinical brain state remains obscured, precluding a clear definition of "normal" brain aging.

Studies have reported that the hippocampus can become hyperactive with advanced age, and that hyperactivity correlates with memory deficits (Miller et al., 2008; Yassa et al., 2011). In addition, older adults demonstrate a specific memory deficit in the ability to determine whether a new encounter is different from a previous encounter. This ability relies on the hippocampus to create distinct neural representations of similar experiences, a process referred to as pattern separation. Rather, older adults demonstrate a bias to merge distinct representations, termed pattern completion (Stark et al., 2010; Yassa et al., 2011). Similar changes to the hippocampus appear relatively early in AD, but they occur downstream of morphological and functional neural changes that appear first in the entorhinal cortex, subsequently spreading to limbic circuits and eventually throughout the cortex (Braak et al., 1993).

In a recent study published in *The Journal of Neuroscience*, Marks et al. (2017) examined the role of AD-related pathology in normal brain aging in the absence of overt cognitive impairment. Specifically, they evaluated the relationship between aging-related memory deficits and structural and functional alterations in the medial temporal lobe, and they assessed whether the observed neural changes are mediated by levels of amyloid-β and pathological tau. Groups of older and younger adults underwent structural MRI and then completed a pattern-separation task while undergoing fMRI. During the task, participants viewed a sequence of images of objects that were never presented before (new), similar to a previously presented object (lure), or identical to a previously presented object (old), and were asked to determine whether each object was new, similar, or old. Pattern-separation ability was assessed with a lure discrimination index, which measured the likelihood that a lure was correctly identified as "similar." Although both young and older participants accurately classified new and old objects, the older participants were impaired at identifying lures, consistent with prior findings (Stark et al., 2010; Yassa et al., 2011). Whereas young adults identified most lures as "similar," older adults were more likely to report that lures were old, demonstrating the expected age-related pattern-separation deficit and pattern-completion bias.

The older adults also underwent two types of PET that measure brain amyloid-β fibrils and plaques, and neurofibrillary tau. Greater numbers of individuals with high amyloid-β levels were intentionally recruited to enrich the sample for AD-related pathology, with 45% of participants exhibiting above-threshold amyloid levels. The majority (66%) also met criteria for Braak Stage I/II levels of tau neurofibrillary tangles, which reflect early-stage tau pathology localized to the entorhinal cortex and hippocampus (Braak and Braak, 1991).

Because the pattern-separation task relies on the medial temporal lobe, and because this region is susceptible to aging-

Received May 20, 2017; revised July 1, 2017; accepted July 3, 2017.
Address correspondence to Dr. Emilie T. Reas, Center for Multimodal Imaging and Genetics, 9500 Gilman Drive, Mail Code 0841, La Jolla, CA 92093-0841. E-mail: ereas@ucsd.edu.
DOI:10.1523/JNEUROSCI.1388-17.2017
 0270-6474/17/377561-03$15.00/0

related changes, analysis of fMRI activations during memory encoding focused on medial temporal structures, including the hippocampus, entorhinal cortex, perirhinal cortex, and parahippocampal cortex. Both activation and deactivation were observed throughout the medial temporal lobe during encoding of objects that were later correctly (hits) or incorrectly (false alarms) identified as old. Other medial temporal lobe activation patterns occurred when encoding objects for which the subsequent lure was correctly identified as similar. Generally, older participants showed greater activation in the hippocampus, entorhinal cortex and parahippocampal cortex than younger participants, across various task conditions, consistent with prior reports of medial temporal lobe hyperactivation with aging (Miller et al., 2008; Yassa et al., 2011).

Notably, age-related differences in task activation were correlated with AD-associated neuropathology. Reduced deactivation in older adults during encoding of subsequent hits was correlated with elevated amyloid-β, whereas increased activation during viewing of subsequent false alarms correlated with increased tau deposition (Braak Stage I/II). In other words, aberrant activity during both successful and unsuccessful memory encoding was associated with higher burden of neuropathological biomarkers associated with AD. Furthermore, abnormal activation patterns that were associated with neuropathology were also correlated with memory impairment and reduced entorhinal cortex thickness. Differences in tau, but not amyloid-β, accumulation explained the association between pathological activation and entorhinal cortex thinning.

This study by Marks et al. (2017) supports previous research demonstrating selective deficits in hippocampus-dependent pattern-separation abilities in normally aging older adults (Stark et al., 2010; Yassa et al., 2011). It further confirms that such memory impairments are associated with hippocampal and entorhinal cortex atrophy as well as with widespread aberrant activation patterns across the medial temporal lobe, including both hyperactivation and reduced deactivation. Importantly, this work directly links AD-associated pathology with memory-related neural changes in normal aging, and provides support for its role in the functional and structural brain changes that may contribute to cognitive decline.

Although hippocampal hyperactivation has previously been observed in both aging and mild cognitive impairment (Miller et al., 2008; Yassa et al., 2011; Bakker et al., 2012), the mechanisms contributing to this dysfunctional activity are not fully characterized. Amyloid-β peptides can induce hyperactivity in neighboring neurons (Busche et al., 2008), and neural activity may also exacerbate amyloid-β aggregation (Bero et al., 2011). Thus, increased regional activation in memory circuits, occurring with aging-related neural reorganization or incipient disease, could theoretically promote cortical amyloid spread, triggering a feedback loop of expanding pathological hyperactivity. Further, aging-related compromise of hippocampal inhibitory signaling (Patrylo and Williamson, 2007) could lead to hyperactivation. This in turn may disrupt sparse coding, representing information with a small fraction of active neurons, used by the hippocampus to support memory (Rolls et al., 1993; Wixted et al., 2014). Finally, hyperactivation could also reflect compensatory processes supporting memory (Buckner, 2004), accounting for the increased activation and reduced deactivation throughout distributed cortical memory networks observed in older adults with poor memory performance (Miller et al., 2008).

While both amyloid-β and tau neurofibrillary tangles were associated with pathological medial temporal lobe activity that occurred with aging-related memory impairment, only tau pathology explained the link between this aberrant activation and anatomical brain changes. Previous work reported that tau pathology in transentorhinal regions precedes amyloid deposition (Braak and Braak, 1991) and tau pathology more closely corresponds with AD severity and clinical outcomes (Arriagada et al., 1992; van Rossum et al., 2012). The current findings lend further support for the crucial involvement of tau in degeneration of a central memory network hub.

Because this study focused a priori on the medial temporal lobe, further research is needed to clarify how AD-related pathology affects structural or functional changes in aging beyond this region. A possible explanation for the link of amyloid-β and tau pathology with aberrant memory-related medial temporal lobe activation is that these hallmarks of AD play a causal role in neural changes that promote cognitive decline in normal aging. Alternatively, functional and structural neural changes mediated by amyloid-β or tau neurofibrillary tangles may reflect subclinical AD, rather than inherent features of typical brain aging. To examine effects of amyloid-β and tau pathology, Marks et al. (2017) selected a sample of healthy older adults enriched in AD-associated pathology. It is therefore possible that this cohort was at elevated risk for AD and possibly included individuals with preclinical AD. Indeed, not all studies have reported hippocampal hyperactivation during aging (Duverne et al., 2009), supporting the possibility that memory-related hyperactivation resulted in part from preclinical neuropathological changes. The findings by Marks et al. (2017) further highlight the overlapping neural and behavioral manifestations of normal and pathological aging and raise the critical question of what determines the switch from typical aging to a trajectory toward dementia.

This investigation by Marks et al. (2017) reveals a multimodal association between aging-related functional, anatomical, and molecular changes in the medial temporal memory network. It expands upon previous work to demonstrate distinct associations of amyloid-β and tau pathology with memory impairments in late life, highlighting a specific association of tau pathology with brain structure–function relationships. As these findings further implicate AD-related pathology in the mechanisms of normal cognitive aging, further research is warranted to better characterize the spectrum of aging- and disease-related neurobiological changes contributing to memory decline.

References

Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT (1992) Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology 42: 631–639. CrossRef Medline

Bakker A, Krauss GL, Albert MS, Speck CL, Jones LR, Stark CE, Yassa MA, Bassett SS, Shelton AL, Gallagher M (2012) Reduction of hippocampal hyperactivity improves cognition in amnestic mild cognitive impairment. Neuron 74:467–474. CrossRef Medline

Bennett DA, Schneider JA, Arvanitakis Z, Kelly JF, Aggarwal NT, Shah RC, Wilson RS (2006) Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology 66:1837–1844. CrossRef Medline

Bero AW, Yan P, Roh JH, Cirrito JR, Stewart FR, Raichle ME, Lee JM, Holtzman DM (2011) Neuronal activity regulates the regional vulnerability to amyloid-beta deposition. Nat Neurosci 14:750–756. CrossRef Medline

Braak H, Braak E (1991) Neuropathological staging of Alzheimer-related changes. Acta Neuropathol 82:239–259. CrossRef Medline

Braak H, Braak E, Bohl J (1993) Staging of Alzheimer-related cortical destruction. Eur Neurol 33:403–408. Medline

Buckner RL (2004) Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. Neuron 44:195–208. CrossRef Medline

Busche MA, Eichhoff G, Adelsberger H, Abramowski D, Wiederhold KH, Haass C, Staufenbiel M, Konnerth A, Garaschuk O (2008) Clusters of hyperactive neurons near amyloid plaques in a mouse model of Alzheimer's disease. Science 321:1686–1689. CrossRef Medline

Duverne S, Motamedinia S, Rugg MD (2009) The relationship between aging, performance, and the neural correlates of successful memory encoding. Cereb Cortex 19:733–744. CrossRef Medline

Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB (2014) What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. Prog Neurobiol 117:20–40. CrossRef Medline

Marks SM, Lockhart SN, Baker SL, Jagust WJ (2017) Tau and beta-amyloid are associated with medial temporal lobe structure, function, and memory encoding in normal aging. J Neurosci 37:3192–3201. CrossRef Medline

Miller SL, Celone K, DePeau K, Diamond E, Dickerson BC, Rentz D, Pihlajamäki M, Sperling RA (2008) Age-related memory impairment associated with loss of parietal deactivation but preserved hippocampal activation. Proc Natl Acad Sci U S A 105:2181–2186. CrossRef Medline

Patrylo PR, Williamson A (2007) The effects of aging on dentate circuitry and function. Prog Brain Res 163:679–696. CrossRef Medline

Rolls ET, Cahusac PM, Feigenbaum JD, Miyashita Y (1993) Responses of single neurons in the hippocampus of the macaque related to recognition memory. Exp Brain Res 93:299–306. Medline

Stark SM, Yassa MA, Stark CE (2010) Individual differences in spatial pattern separation performance associated with healthy aging in humans. Learn Mem 17:284–288. CrossRef Medline

van Rossum IA, Visser PJ, Knol DL, van der Flier WM, Teunissen CE, Barkhof F, Blankenstein MA, Scheltens P (2012) Injury markers but not amyloid markers are associated with rapid progression from mild cognitive impairment to dementia in Alzheimer's disease. J Alzheimers Dis 29:319–327. CrossRef Medline

Wixted JT, Squire LR, Jang Y, Papesh MH, Goldinger SD, Kuhn JR, Smith KA, Treiman DM, Steinmetz PN (2014) Sparse and distributed coding of episodic memory in neurons of the human hippocampus. Proc Natl Acad Sci U S A 111:9621–9626. CrossRef Medline

Yassa MA, Lacy JW, Stark SM, Albert MS, Gallagher M, Stark CE (2011) Pattern separation deficits associated with increased hippocampal CA3 and dentate gyrus activity in nondemented older adults. Hippocampus 21:968–979. CrossRef Medline