Neurobiology of Aging 105 (2021) 318–326

Contents lists available at ScienceDirect

Neurobiology of Aging

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

The relationship of functional hippocampal activity, amyloid deposition, and longitudinal memory decline to memory complaints in cognitively healthy older adults

Xi Chen[a,b,c], Michelle E. Farrell[a,d], Melissa M. Rundle[a], Micaela Y. Chan[a], William Moore[e], Gagan S. Wig[a,f], Denise C. Park[a,f,*]

[a] School of Behavioral and Brain Sciences, University of Texas at Dallas, Richardson, TX, USA
[b] Present affiliation: Molecular Biophysics and Integrated Bioimaging, Lawrence Berkeley National Laboratory, Berkeley, CA, USA
[c] Present affiliation: Helen Wills Neuroscience Institute, University of California Berkeley, Berkeley, CA, USA
[d] Present affiliation: Athinoula A. Martinos Center for Biomedical Imaging, Department of Neurology, Massachusetts General Hospital, Boston, MA, USA
[e] Department of Radiology, University of Texas Southwestern Medical Center, Dallas, TX, USA
[f] Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA

ARTICLE INFO

Article history:
Received 3 October 2020
Revised 16 March 2021
Accepted 21 April 2021
Available online 14 May 2021

Keywords:
Beta-amyloid
Subjective cognitive decline
Metamemory
Hippocampus
fMRI
Longitudinal cognitive decline

ABSTRACT

We evaluated whether self-reports of worse cognition in older adults with normal cognitive function reflected actual memory decline, amyloid pathology, and subtle vulnerabilities in hippocampal function. We measured subjective cognitive decline (SCD) in 156 older participants from the Dallas Lifespan Brain Study. Functional hippocampal activation during encoding, measured with fMRI, and longitudinal memory change that was measured in the four years preceding the SCD measures were used to predict the magnitude of SCD. A subsample (N=105) also underwent ^{18}F-Florbetapir PET imaging that measured amyloid burden. Results showed that increased SCD were associated with greater prior memory decline and amyloid deposition. Importantly, decreased hippocampal activation during encoding was a significant predictor of SCD, particularly in young-old adults below 69 years old, above and beyond prior memory change and amyloid deposition. These results indicate that multiple measures of neural and cognitive dysfunction are simultaneously associated with SCD. Moreover, SCD in younger seniors appears to reflect deficient hippocampal activity that increases their reports of poorer memory, independent of amyloid. This manuscript is part of the Special Issue entitled "Cognitive Neuroscience of Healthy and Pathological Aging" edited by Drs. M. N. Rajah, S. Belleville, and R. Cabeza. This article is part of the Virtual Special Issue titled COGNITIVE NEU-ROSCIENCE OF HEALTHY AND PATHOLOGICAL AGING. The full issue can be found on ScienceDirect at https://www.sciencedirect.com/journal/neurobiology-of-aging/special-issue/105379XPWJP.

1. Introduction

Many older adults report that they are experiencing memory dysfunction and are concerned that their perception of decline is symptomatic of Alzheimer's Disease (Bolla et al., 1991; Slavin et al., 2010). This so-called "subjective cognitive decline (SCD)" in cognitively normal older adults may be one of the earliest symptoms of the preclinical stage of AD (Sperling et al., 2011). In fact, the recent NIA-AA framework (Jack et al., 2018) suggested SCD as one of the potential behavioral markers that may signal preclinical AD, given its association with AD pathology, particularly amyloid deposition (Rabin et al., 2017). Recent evidence of the legitimacy of SCD shows that actual memory performance and longitudinal memory change are also predictors of SCD in cognitively normal adults (Snitz et al., 2015). Our previous findings further implicated actual longitudinal memory decline as a primary mediator of the amyloid/SCD relationship (Chen et al., 2019).

* Corresponding author at: School of Behavioral and Brain Sciences, University of Texas at Dallas, 1600 Viceroy Dr., Suite 800, Dallas, TX 75235, Tel.: 972-883-3255.
E-mail addresses: xi.chen@lbl.gov (X. Chen), mfarrell13@mgh.harvard.edu (M.E. Farrell), mmr150930@utdallas.edu (M.M. Rundle), mchan@utdallas.edu (M.Y. Chan), william.moore@utsouthwestern.edu (W. Moore), gwig@utdallas.edu (G.S. Wig), denise@utdallas.edu (D.C. Park).

0197-4580/$ – see front matter
https://doi.org/10.1016/j.neurobiolaging.2021.04.020

Despite the accumulating research on the clinical importance of SCD, little is known about how multiple measures related to memory dysfunction, simultaneously contribute to SCD. The present study incorporated measures of brain function (hippocampal activation during memory encoding), brain pathology (amyloid deposition), and actual memory decline (episodic memory change over approximately four years), and examined their contributions to SCD.

Despite the importance of the hippocampus to memory, there is limited data on brain activity differences measured by functional magnetic resonance imaging (fMRI) in individuals with and without memory concerns (Erk et al., 2011; Hu et al., 2017; Rodda et al., 2011), particularly during memory encoding (Rodda et al., 2009). One recent study showed decreased activation in occipital and parietal regions during successful encoding in individuals with SCD relative to controls and suggested it might reflect visual and attentional processing deficits (Hayes et al., 2017). However, the data on individual difference of functional activity and its relationship to SCD are much more limited, particularly in the hippocampus, which plays a key role in memory processing (Squire, 1992) and age-related memory decline (O'Brien et al., 2010).

The hippocampus is not only a fundamental component of the memory system for encoding (Eichenbaum, 2004; Kim, 2011), but also plays a critical role in AD-related pathology (Braak and Braak, 1995). The hippocampus evidences decreased volume in early AD in combination with amyloid deposition (Petersen et al., 2016), and also undergoes substantial neuronal loss as disease progresses (West et al., 1994). Recent evidence also suggests that altered hippocampal activation during encoding in cognitively normal older adults is associated with amyloid (Song et al., 2016) and tau pathology (Huijbers et al., 2019), as well as greater AD risk (McDonough et al., 2020). Given the essential function of hippocampus in memory as well as its vulnerability to aging and early stages of AD when SCD becomes prevalent, we focused on the relationship of hippocampal activity to SCD in the present study.

There is also evidence that increased amyloid burden is related to increased SCD in normal individuals (Amariglio et al., 2012; Perrotin et al., 2012). A unique aspect of the present study was our ability to assess the simultaneous contributions of hippocampal activity and amyloid deposition to SCD, allowing us to determine whether the relationship of hippocampal activity to SCD is independent of or interactive with amyloid. Several fMRI studies have reported irregular hippocampal activity linked to amyloid deposition (Edelman et al., 2017; Leal et al., 2017; Mormino et al., 2012). For example, our lab reported that high amyloid burden is associated with significantly decreased hippocampal activity in the younger group of senior participants (aged 60 to 74 years old), and that the sensitivity of hippocampal activity to amyloid pathology appeared to be generally weak in oldest age (Song et al., 2016), suggesting a possible interactive effect of hippocampal activity and amyloid on SCD, particularly in young-old adults.

To summarize, the individual effects of amyloid and longitudinal memory change have been separately established to contribute to SCD, but there is very limited information regarding their joint contributions of these variables to SCD, and the role of functional activity in the hippocampus to SCD is largely unexplored. Given the complexity of mechanisms underlying SCD (Ossenkoppele and Jagust, 2017), we investigated the roles of these factors simultaneously in the present study. We recently reported that prior longitudinal memory decline over past four years mediated the relationship between amyloid burden and SCD in cognitively normal individuals (Chen et al., 2019). We built on this research and investigated hippocampal activity during encoding in a larger sample of cognitively normal older adults (n=156). We hypothesized that older adults with decreased hippocampal function would report increased SCD concerns, and that this neural effect may be above and beyond the behavioral effect of actual longitudinal memory change. In addition, in a subset of participants who had undergone ^{18}F-Florbetapir PET imaging to measure amyloid burden (n=105), we examined the contribution of amyloid to SCD, as well as the effect of hippocampal activity to SCD after accounting for amyloid pathology. We hypothesized that increased SCD may reflect both deficient hippocampal function during encoding and greater amyloid deposition and that hippocampal activity might show a greater effect on SCD in individuals with elevated amyloid.

2. Methods

2.1. Participants

This study included 159 cognitively normal older adults (aged 55-93) from the Dallas Lifespan Brain Study (DLBS). All participants had completed two waves of data collection roughly spaced four years apart, that included cognitive testing, structural and functional MRI, as well as a detailed questionnaire about subjective memory and memory concerns to measure SCD (Dixon et al., 1988) that was introduced at Wave 2. In addition, 105 of the 159 subjects underwent ^{18}F-Florbetapir PET imaging to measure neocortical amyloid deposition. We used Wave 1 and 2 data to estimate actual prior memory change over a mean interval of 3.85 years (SD=0.38 yrs, min=2.48 yrs; max=5.62 yrs) with 92.3 percent completing between 3.5 to 4.5 years. Wave 2 data (when SCD measures were collected) were used for all other measures. All participants had an MMSE score greater than or equal to 26, were recruited locally from the community, and were right-handed with normal or corrected to normal vision. Participants were screened for neurological and psychiatric disorders, loss of consciousness for more than ten minutes, a history of drug or alcohol abuse, and a history of major heart surgery or chemotherapy within five years. This study was approved by the University of Texas Southwestern and the University of Texas at Dallas institutional review boards. All participants provided written informed consent and were debriefed according to human investigations committee guidelines.

2.2. Behavioral methods

SCD was measured using the perceived capacity subscale from the Metamemory in Adulthood questionnaire (Dixon et al., 1988) in our primary analyses. It is a psychometrically-validated questionnaire that assesses participants' beliefs about their memory function and processes. The domain of perceived memory capacity consists of participants' self-appraisal of memory performance regarding memory successes and failures in everyday situations (e.g., "I have no trouble keeping track of my appointments"), and is the most studied SCD domain in the literature (Molinuevo et al., 2017; Wang et al., 2020). The subscale contains 17 items, and subjects judge how applicable the statement is to self on a five-point Likert scale, with the possible total score ranging from 17 to 85. Additionally, we explored whether potential findings may be replicated in another SCD measure, perceived memory stability, that has also been previously studied (Perrotin et al., 2012) and found to be sensitive to amyloid deposition in cognitively normal adults (Chen et al., 2019). This domain is measured by the perceived stability subscale that asks participants to rate their perception of memory changes (e.g., "I'm less efficient at remembering things now than I used to be"). It contains 18 items with the possible score ranging from 18 to 90. For both measures, a lower score indicates worse perceived memory capacity/stability, or more SCD concerns.

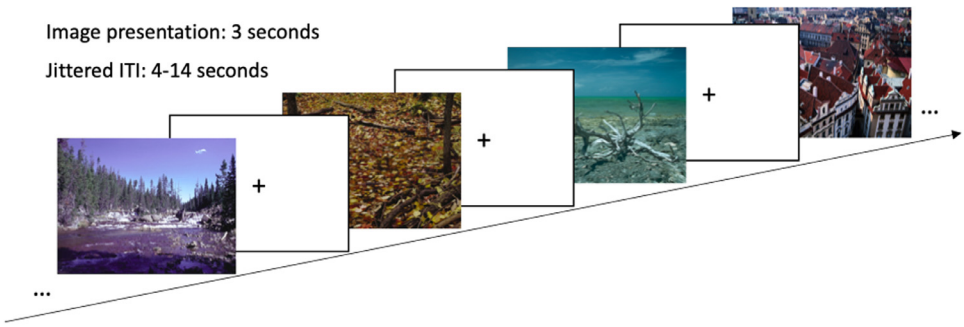

Fig. 1. Scene pictures were encoded in the subsequent memory fMRI task.

To measure prior memory change, we used four episodic memory measures collected in both Wave 1 and Wave 2 of the DLBS. These included immediate free-recall, delayed free-recall and delayed recognition scores from the Hopkins Verbal Learning Test (Brandt, 1991) and immediate free-recall from the CANTAB Verbal Recognition Memory (Robbins et al., 1994). The scores were standardized and then averaged to form a single composite that represents participants' memory performance in each wave. The Wave 2 score was standardized based on the mean and standard deviation of Wave 1 score. Prior longitudinal memory change was measured as the difference score between two waves (Wave 2 – Wave 1). A lower score indicates worse longitudinal memory change.

In addition, participants also completed the Center for Epidemiological Studies-Depression scale (CES-D (Radloff, 1977)) as the measure of the subclinical depressive symptoms, which was included as a covariate in the analyses.

2.3. Functional imaging methods

2.3.1. MRI acquisition

Participants were scanned using a 3T Philips Achieva scanner with an 8-channel head coil. High-resolution anatomical images were collected with a T1-weighted magnetization-prepared rapid gradient-echo sequence with 160 sagittal slices, field of view (FOV) = 204 × 256 × 160 mm; voxel size: 1 × 1 × 1 mm^3; time to repetition: 8.1 ms; echo time: 3.7 ms; flip-angle: 12°. Blood Oxygen Level Dependent (BOLD) fMRI data were acquired using a T2* weighted echo-planar imaging sequence with TR/TE/flip-angle=2000ms/25ms/80° and FOV = 220 × 220 mm^2. In each volume, 43 interleaved axial slices were acquired parallel to the AC-PC line covering the whole brain, voxel size 3.4 × 3.4 × 3.5 mm^3. Five additional volumes collected at the beginning of each run for T1 stabilization were discarded.

2.3.2. fMRI task

Participants viewed 96 pictures of outdoor scenes in the scanner and responded if there was any water in the scene by pressing yes/no button (Fig. 1) (Gutchess et al., 2005). Half of the pictures contained water. Stimuli were presented using E-prime software (Psychology Software Tools, Pittsburgh, PA, USA). Each picture was presented for 3s in an event-related design with jittering range from 4 to 14 seconds.

Approximately 20 minutes after the end of the presentation, a recognition test was administered outside of the scanner. Participants were presented with a total of 192 pictures, with 96 previously presented target pictures and 96 lures that were closely matched to the target pictures for similar content and composition (e.g., both consisted of an alpine scene with mountains and lake). Participants were instructed to indicate whether they remembered seeing the picture by making one of three judgments: 1. "high-confidence remember" indicating that the participant was confident the exact picture was presented; 2. "low-confidence remember" indicating that the participant remembered seeing the picture with low confidence; 3. "new item" indicating that the participant judged that it was not previously presented. This recognition task was self-paced with a maximum of 4s for each trial.

2.3.3. fMRI data processing

Statistical Parametric Mapping (SPM12, University College London, UK) was used for imaging preprocessing and data analysis. For preprocessing, functional images were first corrected for motion, and realigned to the mean image across all the runs for each participant, and then co-registered to the anatomical scan using a linear rigid-body transformation. The anatomical scan was segmented to allow the estimation of deformation parameters for different tissues using the Segment function in SPM12. Next, all functional images were co-registered to the MNI template via the anatomical image by using one transformation matrix that realigned and normalized to MNI template. Finally, spatial smoothing was implemented with a full-width-half-maximum (FWHM) of 8 mm. All structural and functional images were carefully inspected, and three participants were removed due to excessive motion and/or poor registration, resulting the final sample of 156 participants.

2.3.4. fMRI data analysis

At the individual level, we modeled a hemodynamic response function by convolving the signal time course with the stimulus event. Seven nuisance regressors were included to model movement variance and the difference in the mean signal across runs. An autoregressive model, AR(1), was used to estimate and correct for the temporal autocorrelation.

To measure hippocampal functional activity during encoding, we specifically focused on encoded items that were successfully remembered with high confidence. We created hippocampal regions of interest (ROIs) using the anatomical masks of left and right hippocampus from Automated Anatomical Labeling (Tzourio-Mazoyer et al., 2002). Then, we extracted the mean activation based on the contrast between high-confidence remembered trials and the baseline (fixation) using the MarsBar toolbox in SPM12 (Brett et al., 2002).

2.4. PET imaging methods

2.4.1. PET protocol

Participants were injected with a 370 MBq (10 mCi) bolus of 18F-Florbetapir. A 2-frame by 5-minute each dynamic emission acquisition was started 50 minutes post-injection on an ECAT HR PET scanner (Siemens Healthineers), as previously described (Kennedy et al., 2012; Rodrigue et al., 2012).

2.4.2. PET data processing

The PET scan was co-registered to the participant's anatomical image using FLIRT (https://fsl.fmrib.ox.ac.uk/fsl) with a mutual-information cost function. To process the PET data, the individual's T1 image was processed using FreeSurfer (FreeSurfer 5.3, http://surfer.nmr.mgh.harvard.edu/) with thorough manual editing to validate the automated segmentation (Savalia et al., 2017) that was used to obtain cortical parcellations based on the Desikan-Killiany atlas (Desikan et al., 2006). As in past studies (Farrell et al., 2017), the mean cortical amyloid burden was measured using the global standard uptake value ratios (SUVR), computed from seven FreeSurfer-derived regions of interest (ROIs) across the cortex using the whole cerebellum as the reference region, following the existing processing pipeline in DLBS (Caballero et al., 2020; Chen et al., 2019; Farrell et al., 2017). The seven ROIs were bilateral dorsolateral prefrontal (including caudal middle frontal, rostral middle frontal, pars opercularis, pars triangularis, pars orbitalis, and superior frontal cortices), orbitofrontal (including lateral orbitofrontal and medial orbitofrontal cortices), lateral parietal (including inferior parietal, supramarginal, and superior parietal cortices), lateral temporal (including middle temporal and superior temporal cortices), precuneus, isthmus cingulate, and rostral anterior cingulate cortices.

2.5. Statistical analysis

As presented in the introduction, we were interested in the role of hippocampal activity in predicting SCD, hypothesized that it had independent contribution to SCD beyond the effects of actual memory change and amyloid pathology, and used hierarchical regression to test it. Correlations among these predictors were at a modest level, ranging from r=-.04 to r=-.148 (Supplemental Table 1, Supplemental Table 2), suggesting little evidence of collinearity among the variables. The first hierarchical regression model, Model 1, examined the effects of actual memory change and hippocampal activity in the full sample on perceived memory capacity, the primary measure of SCD. The first step of the model controlled for sex, depression, education, and baseline memory performance in Wave 1. These covariates were included because of previous reports of their influence on perceived memory capacity (Balash et al., 2013; Chen et al., 2019; Crumley et al., 2014; Drouin et al., 2020). In the second step, we included actual prior memory change while controlling for age, and then in the third step included hippocampal activation and the age x hippocampal activation interaction. Hippocampal activity was included last because little is known about its relationship to SCD relative to the other variables, and entering it last was a stringent test of its unique contribution. We included the age x hippocampal activation term *a priori* because our previous study found the sensitivity of hippocampal activity signal to AD-related changes varied across age, even within older adults (Song et al., 2016).

The second model, Model 2, was the same as Model 1, except that global amyloid SUVR was inserted as a separate and third step, followed by the hippocampal measures as a fourth step.

Finally, in addition to the primary outcome, perceived memory capacity, we explored the same relationships with an additional measure of SCD – perceived memory stability. We repeated the analyses to examine the consistency and generalization of our findings.

For all analyses, we examined the variance inflation factor (VIF) for all variables. We found all VIFs were smaller than 2.1, further suggesting little evidence of multicollinearity (Kutner et al., 2005; Sheather, 2009). We used 95% confidence interval (CI) from a bias-corrected and accelerated (BCa) bootstrap procedure with 2000 iterations to determine significance. A bootstrapping procedure resamples the data and provides inferences based on the resampled data, so it appropriately examines the stability and reliability of the result and is not susceptible to the influence of outliers (Hesterberg, 2011). BCa CI further corrects for bias and skewness during resampling and has become increasingly recommended as an alternative approach of the hypothesis testing based on p values (Gardner and Altman, 1986; Ho et al., 2019). Analyses were conducted using R 3.6.3 (R Core Team, 2020) with *lmtest* package (Zeileis and Hothorn, 2002), *boot* package (Canty and Ripley, 2021; Davison and Hinkley, 1997), and *interactions* package (Long, 2019), as well as SPSS v25.

3. Results

3.1. Demographics

Participants' characteristics are shown in Table 1. Of the 156 individuals, 105 had amyloid measure available. For descriptive purpose, we report sample characteristics in Table 1 using a SUVR threshold of 1.09 to define amyloid positivity, set two SDs above the mean SUVR calculated relative to a young reference group in the Dallas Lifespan Brain Study (Farrell et al., 2017). We used continuous mean SUVR for amyloid burden and continuous age in all analyses.

3.2. Hippocampal activation related to perceived memory capacity

The fMRI analysis of the hippocampal activation was based on the contrast of high-confidence remembered items versus baseline, using the anatomical hippocampal ROIs. The mean number of high-confidence remembered responses was 51.8 (SD=14.1) with a range of 15 to 78 trials across all participants. As expected, the contrast yielded significant activation in left and right hippocampus, with family-wise error (FWE) corrected $p<0.05$ (Fig. 2A). A reverse contrast (baseline > high-confidence remembered) did not show any significant activation in the hippocampus. We then examined the correlation between the mean activation in the hippocampus and participants' high-confidence hit rate (mean=.54, SD=.14, min=.15, max=.81; chance level=.33), which was calculated based on the number of trials remembered with high confidence divided by the total number of old trials. We report the usual relationship that higher hippocampal activation was related to better subsequent memory performance (r=.212, p=0.008, BCa 95% CI=[0.054, 0.352], Fig 2B). When we partialed out age, the relationship remained significant (r_p=.213, p=0.008, BCa 95% CI=[0.045, 0.354]).

Using hierarchical regression, we first examined the effect of actual prior memory change on reports of perceived memory capacity, and then added hippocampal related effects to examine if hippocampal activation affected reports of perceived memory capacity above and beyond the behavioral effect of prior memory change. First, we found a significant effect of prior memory change on perceived memory capacity (b=2.381, p=0.032, BCa 95% CI=[0.253, 4.549]), where people with greater memory decline, indexed by a lower change score, reported lower perceived memory capacity (Fig. 3A). The likelihood ratio test revealed that adding hippocampal-related effects in the second step improved the model ($\chi^2(2)$=5.9, p=0.05). There was a significant age x hippocampal activation interaction (b=-0.322, p=0.024, BCa 95% CI=[-0.592, -0.068]) that occurred because lower hippocampal activation was predictive of lower perceived memory capacity particularly at younger ages (Fig. 3B). To investigate the significance of the hippocampal effect at different ages, we used the Johnson-Neyman procedure and found that the effect of hippocampal activation was significant until age 64. To explore the reliability of the effect, we

Table 1
Demographic information and participants' characteristics.

	Total (N=156)	Amyloid Subsample		
		Total (N=105)	Negative (N=69)	Positive (N=36)
Mean Age (SD)	70.98 (9.26)	72.05 (9.24)	70.04 (8.80)	75.92 (8.93)*
Sex	100F 56M	67F 38M	41F 28M	26F 10M
Education, yrs (SD)	15.63 (2.24)	15.39 (2.09)	15.29 (1.92)	15.56 (2.40)
Depression: CES-D (SD)	3.81 (4.13)	4.16 (4.50)	3.90 (4.57)	4.67 (4.40)
MMSE (SD)	28.95 (1.24)	28.83 (1.31)	29.06 (1.24)	28.39 (1.36)*
ADAS-Cognition (SD)	5.64 (3.50)	5.97 (3.65)	5.70 (3.87)	6.49 (3.18)
Testing Interval, yrs (SD)	3.85 (0.38)	3.75 (0.34)	3.70 (0.37)	3.83 (0.24)
Perceived Memory Capacity (SD)	55.95 (8.66)	55.02 (8.62)	55.78 (8.63)	53.56 (8.52)
Perceived Memory Stability (SD)	50.70 (10.77)	50.67 (10.77)	51.77 (10.72)	48.56 (10.71)
Prior Memory Change (SD)	-0.01 (0.74)	-0.08 (0.74)	-0.13 (0.76)	0.02 (0.72)
Hippocampal Activation (SD)	0.70 (0.61)	0.71 (0.61)	0.69 (0.66)	0.74 (0.51)
Mean SUVR (SD)	-	1.11 (0.18)	1.02 (0.04)	1.29 (0.22)*
High-confidence Hit Rate (SD)[1]	0.54 (0.14)	0.54 (0.15)	0.56 (0.14)	0.51 (0.16)
Hippocampal Volume, mm^3 (SD)	7.46 (1.06)	7.43 (1.00)	7.61 (0.92)	7.09 (1.07)*

Note: We used the continuous variable of mean SUVR in all analyses. We report sample characteristics based on amyloid positivity for descriptive purpose. Abbreviations: CES-D: Center for Epidemiological Studies – Depression scale. MMSE: Mini-mental State Examination. ADAS-Cognition: Alzheimer's Disease Assessment Scale – Cognitive Subscale. SUVR: Standardized Uptake Value Ratio.

* Amyloid negative and positive individuals had a significant group difference, $p<0.05$. [1] Chance level = 0.33.

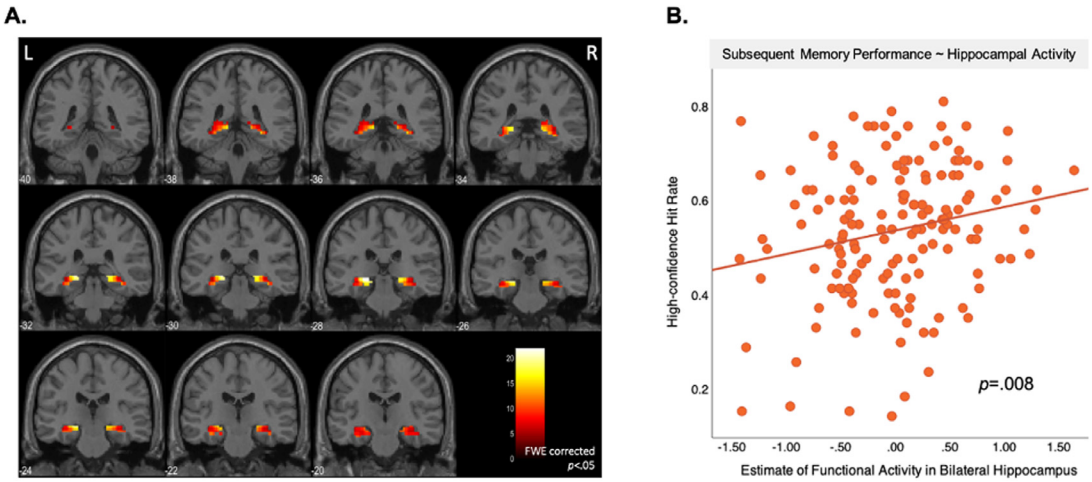

Fig. 2. (A). Significant bilateral hippocampal activation during encoding (high-confidence remembered > baseline). Family-wise error (FWE) corrected, $p<0.05$. There is no significant activation in the hippocampus using baseline > high-confidence remembered contrast. (B). Individuals with higher hippocampal activity during encoding also showed better subsequent memory performance, indexed by higher high-confidence hit rate, $r=.212$, $p=0.008$.

separately examined the activation in the left and right hippocampus in *post hoc* analyses and found that the results were consistent for the left and right hippocampus (left: b=-0.285, p=0.017, BCa 95% CI=[-0.516, -0.066]; right: b=-0.336, p=0.011, BCa 95% CI=[-0.612, -0.053]).

To further confirm this finding, we conducted a series of supplementary analyses. First, we only focused on the voxels in the hippocampus that showed significant activation during high-confidence successful encoding (FWE corrected $p<0.05$), and repeated our analyses with the mean activation in those voxels. By excluding the non-activated voxels, we could focus on the core task-related subregions within the hippocampus. We found that the regions largely overlapped with the anatomical hippocampal ROI – 77.1% of the hippocampus showing significant activation (left: 82.6%, right: 71.7%, Supplemental Figure 1) – and that all reported effects remained significant. Then, we considered potential influence of hippocampal structural differences and controlled for hippocampal volume estimated by FreeSurfer. We found that hippocampal volume was not significant (p=.891) and that all results remained significant. Finally, given that hippocampal activation was positively related to task performance, we also explored whether the significant effects were confounded by differences in the in-scanner task performance. We controlled for participants' task performance (high-confidence hit rate) and found that the reported effects remained significant. We also examined if removing extremely low performers of the fMRI task would change any results. We defined extremely low performers as those with a high-confidence hit rate below chance level (0.33, N=12). The reported effects largely remained similar, with only the prior memory change effect approaching significance (p=0.063).

3.3. Effect of hippocampal activation on perceived memory capacity independent of amyloid

In Model 2, we inserted global amyloid SUVR into Model 1 as the third step with hippocampal activity entered as the fourth step. We found that amyloid SUVR had a significant effect (b=-8.482, p=0.046, BCa 95% CI=[-20.358, -0.020]): participants with higher amyloid burden reported lower perceived memory capacity (Fig. 3C). Importantly, when we further added hippocampal-related effects in the model, the model was significantly improved ($\chi^2(5)$=16.40, p=0.006) and the age x hippocampal activation ob-

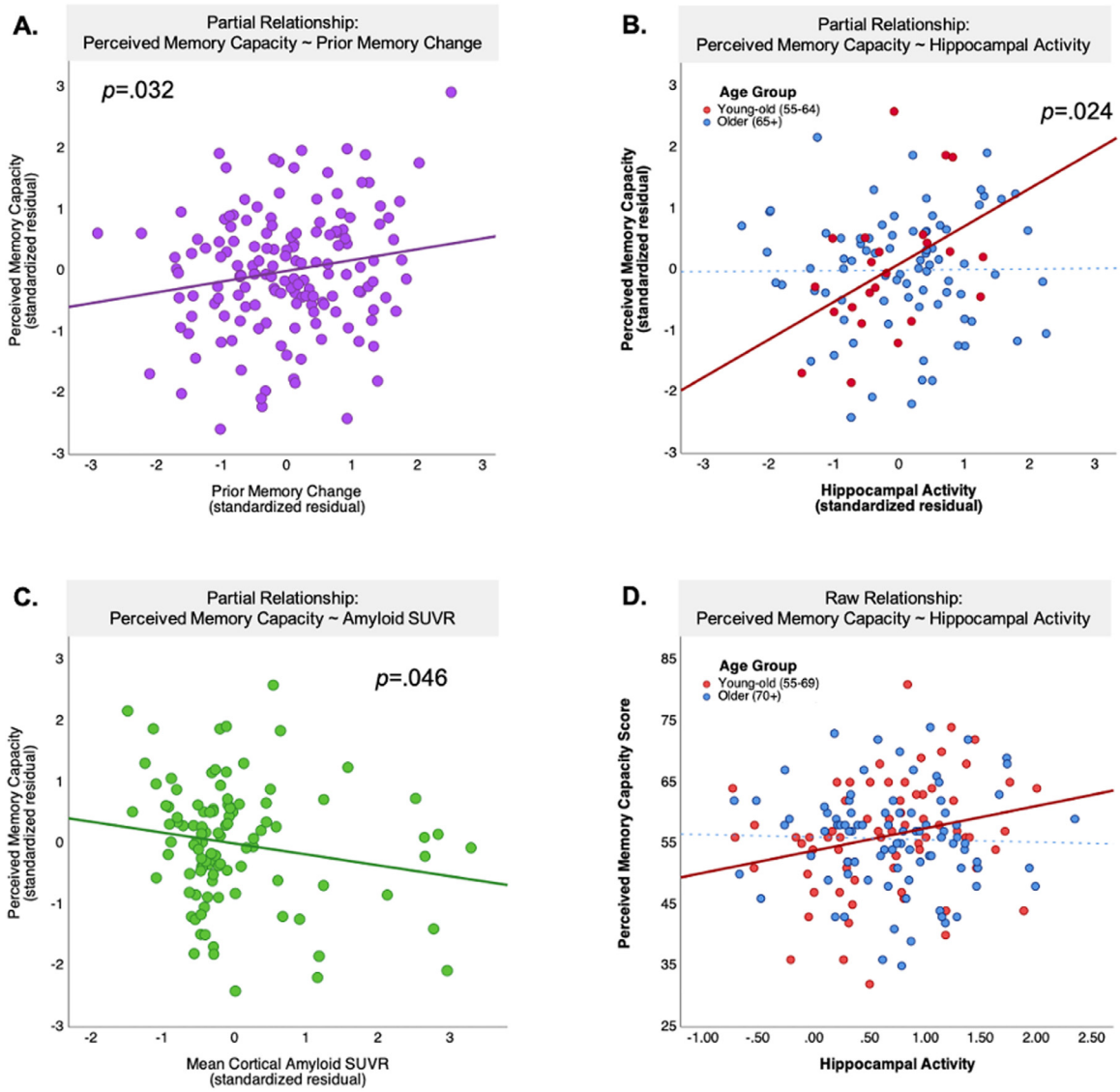

Fig. 3. (A). Greater prior memory decline (indexed by a lower value on prior memory change score) was related to lower perceived memory capacity. (B). Effect of age x hippocampal activity on perceived memory capacity. Lines represent slopes of hippocampal effects in younger-old individuals (55–64 yrs) and older individuals (65+ yrs). Moderating age (64) was defined using the Johnson-Neyman procedure in Model 1. The solid red line represents significant relationship in younger-old adults where lower hippocampal activation was related to worse perceived memory capacity and stability. The dashed blue line represents the non-significance in the older individuals. (C). Higher amyloid burden was related to lower perceived memory capacity. (D). Raw data depicting the relationships between hippocampal activation and perceived memory capacity, separated by younger-old individuals (55–69 yrs) in red and older individuals (70+ yrs) in blue. Moderating age (69) was defined using the Johnson-Neyman procedure in Model 2 when amyloid effect was taken into account. (Color version of figure is available online)

served earlier remained significant (b=-0.744, p=0.001, BCa 95% CI=[-1.239, -0.243]). Using the Johnson-Neyman procedure, we determined that age 69 was the break point for the moderation effect of hippocampal activity after amyloid effect being accounted for (Fig. 3D). Follow-up analyses indicated that the findings were consistent in left (b=-0.604, p=0.002, BCa 95% CI=[-0.814, -0.172]) and right hippocampi (b=-0.752, p<0.001, BCa 95% CI=[-0.982, -0.272]). We note that adding a final step to assess the amyloid-related interactions (age x amyloid, amyloid x hippocampal activation, age x amyloid x hippocampal activation) showed no trends towards significance (p's>.450), suggestive of an independence between amyloid and hippocampal influences on perceived memory capacity.

When we focused only on the voxels in the hippocampus that showed significant activation, all reported effects remained significant. Controlling for hippocampal volume or fMRI task performance also did not change any significance. All reported effects also remained significant after removing extremely low performers (N=9).

3.4. Replicate hippocampal effects for additional measure of SCD – perceived memory stability

Finally, we attempted to replicate the findings using another measure of SCD, perceived memory stability, that has been studied as an additional measure of SCD in previous literature (Chen et al., 2019; Perrotin et al., 2012). As would be expected, it was moderately correlated with perceived memory capacity (r=.547, Supplemental Table 1), with sufficient variance remaining to develop separate regression models. The model for the full sample yielded a similar result pattern. Prior memory change was related to lower perceived memory stability (b=2.714, p=0.043, BCa 95% CI=[0.011, 5.465]). Adding hippocampal related effects further improved the

model for the right hippocampus ($\chi^2(2)$=6.00, p=0.049) and the age x right hippocampal activation interaction was significant (b=-0.400, p=0.019, BCa 95% CI=[-0.732, -0.094]). In the second model with amyloid, age x hippocampal interaction remained (b=-0.411, p=0.062, BCa 95% CI=[-0.893, -0.009]), primarily driven by the right hippocampus (b=-0.504, p=0.019, BCa 95% CI=[-0.950, -0.102]). Overall, the findings suggest that decreased hippocampal activity had a similar effect on both SCD measures.

4. Discussion

The goal of the present study was to determine how functional, pathological and behavioral contributors predict SCD in cognitively normal older adults, and specifically whether hippocampal activity and amyloid separately or jointly contributed to SCD. We found that all three were significantly related to SCD, and that the effect of hippocampal activity on SCD was above and beyond actual memory change and amyloid pathology, in relatively younger old adults, with none of the amyloid-related interactions approaching significance. The findings suggest that multiple factors appear to contribute to SCD and that hippocampal activity likely plays an important and independent role in SCD. This is particularly true for individuals beginning to enter late adulthood, even after amyloid pathology and actual prior memory decline are considered.

Historically, SCD literature suggested that memory complaints in cognitively normal individuals just reflected unnecessary concerns in the "worried well" (Balash et al., 2013). Our findings, along with other accumulating evidence (Buckley et al., 2017; Chen et al., 2019; Erk et al., 2011; Hayes et al., 2017; Rabin et al., 2017; Rodda et al., 2009), suggest that participants' reports about their memory ability have validity and may reflect actual memory decline, amyloid pathology, and even low functional activity. Although recent studies have demonstrated individual associations between subjective and objective cognitive measures (Mitchell et al., 2014), few have had available actual retrospective longitudinal change measures to establish the validity of subjective concerns (Brailean et al., 2019; Zimprich and Kurtz, 2015). The present study, along with Chen et al (2019), shows that self-reports of worsening memory have some legitimacy, as subjective memory ratings indeed reflected objectively measured memory change. We note that an examination of the memory change score (Supplemental Figure 2) yielded evidence of memory decline for a subset of participants over the previous four-years, with others showing stability or even some improvement in performance which was likely due to practice effects (Machulda et al., 2013) or differences in state (emotions) or context (world events) that cannot be controlled. In sum, the findings provide evidence that participants' self-appraisal of their memory ability and whether it declined reflected, to some extent, actual changes in memory performance.

Moreover, the findings indicate that reports of worsening memory may also reflect lower activation in the hippocampus, primarily in earlier stages of old age. Previous studies have shown that lower hippocampal activity is associated with poorer memory (O'Brien et al., 2010), but the present finding is unique in demonstrating that low hippocampal activity in a single session predicts participants' accurate assessment of memory decline over past four years. We suggest that the findings reflect encoding difficulties associated with lower hippocampal activity that participants experience, which accurately translate into self-report of greater memory problems. Interestingly, the sense of memory difficulty based on insufficient hippocampal activity occurred even after actual memory decline and fMRI task performance were included in the model, likely suggesting the sensitivity of the brain marker in revealing subtle deficits in cognitively normal individuals.

The effect of hippocampal activity on SCD appeared to primarily occur in the young-old adults (aged below 69 years old, as identified by the Johnson-Neyman procedure with all predictors included; raw data depicted in Fig. 3D), suggesting that there is an early sensitivity to neural deficits. The lack of hippocampal effect in oldest adults may reflect their advanced brain degradations, such that their SCD responses are no longer sensitive to losses in brain function that is common in advanced age (Kennedy et al., 2015; Song et al., 2016). Moreover, task-related activations are increasingly less specific and dedifferentiated with increasing age (Carp et al., 2011; Park et al., 2004). This may be due to various factors including greater comorbidities and accumulated lifetime experience in old age (Bischof and Park, 2015; Koen and Rugg, 2019), likely resulting a lack of specificity in its relation to behavior in old age.

Another important feature of the study is that the utilization of multi-modal datarevealed that functional activity measure predicted SCD beyond PET measure of amyloid. Alterations in hippocampal function in older adults may be a downstream event of normal and pathological aging (Jack et al., 2018; Leal and Yassa, 2015). Hippocampal function is considered more proximate to cognitive decline (Sperling et al., 2014) and thus may have a more immediate relationship with subtle behavioral changes than AD biomarkers.

Finally, we found little evidence of interactive effects between hippocampal activation and amyloid on SCD. This may suggest that SCD in older adults are likely associated with multiple factors that affect hippocampal memory system besides amyloid, for example, tau deposition (Harrison et al., 2019), alcoholism (Anderson et al., 2012), head injuries (Bigler et al., 2002), tobacco use (Kenney and Gould, 2008), and neurological disorders besides AD. It is also plausible that SCD also results from deteriorations that lead to deficient hippocampal encoding as part of normal aging (Dennis et al., 2007; Jagust, 2013) independent of amyloid.

One limitation of the present study is that we did not have manual traced or sophisticated subregional hippocampal volumetric measures. Hippocampal volume reflects neurodegeneration in these individuals and subregional measures may help explore the structural aspect of mechanisms underlying SCD. We nevertheless included estimates of total hippocampal volume obtained from FreeSurfer after carefully validating the brain masks (Savalia et al., 2017) and visually checking the segmentation, and showed that it did not change any significance we observed. Studies have also reported increased tau pathology in cognitively normal older adults, particularly in the hippocampus (Crary et al., 2014). Future study may investigate whether this age-related tau deposition may explain the effect of hippocampal activation on SCD. We also acknowledge that the two measures of SCD were both focused on beliefs about memory where correlation between the two measures is likely to be present. It would be useful to investigate the relationship of complaints about other cognitive processes such as reasoning, speed of responding, word finding. Finally, the current study consists of a typical longitudinal sample of relatively highly educated individuals who may have experienced only moderate change in memory. This sample may be more likely to subjectively sense changes in their memory function and sustain pathological changes (Burmester et al., 2016). It is possible that the impact of amyloid may be larger and even overtakes the effect of hippocampal activation on SCD in a vulnerable population.

5. Conclusion

In conclusion, the present study indicates that lower hippocampal functional activity during encoding is related to greater SCD about worse perceived memory capacity and lower perceived

memory stability, particularly in younger old adults. This relationship appears to be independent of amyloid burden, likely suggesting multiple concurring but independent mechanisms underlying memory complaints in older adults, including hippocampal function, amyloid pathology, and actual memory decline. The results are in agreement with a classic finding by social psychologists Nisbett and Wilson (Nisbett and Wilson, 1977). They noted that people can "tell more than they can know" about many situations. This insight appears to even apply to human brain activity, where participants accurately reported poor memory, which reflected low hippocampal function that would be inaccessible to them.

Disclosures

The authors report no conflicts of interest.

CRediT authorship contribution statement

Xi Chen: Conceptualization, Investigation, Data curation, Methodology, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Michelle E. Farrell:** Methodology, Investigation, Writing – review & editing. **Melissa M. Rundle:** Data curation, Project administration, Writing – review & editing. **Micaela Y. Chan:** Methodology, Investigation, Writing – review & editing. **William Moore:** Validation, Writing – review & editing. **Gagan S. Wig:** Methodology, Validation, Writing – review & editing. **Denise C. Park:** Funding acquisition, Project administration, Validation, Writing – review & editing.

Acknowledgement

This study was supported by funding from the National Institute on Aging 5R37AG-006265 (DP) and RC1AG036199 (DP). The tracer was provided for the study by Avid Radiopharmaceuticals, a wholly-owned subsidiary of Eli Lilly, Inc. Avid also provided financial support for PET imaging costs.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2021.04.020.

References

Amariglio, R.E., Becker, J.A., Carmasin, J., Wadsworth, L.P., Lorius, N., Sullivan, C., Maye, J.E., Gidicsin, C., Pepin, L.C., Sperling, R.A., Johnson, K.A., Rentz, D.M., 2012. Subjective cognitive complaints and amyloid burden in cognitively normal older individuals. Neuropsychologia 50 (12), 2880–2886.

Anderson, M.L., Nokia, M.S., Govindaraju, K.P., Shors, T.J., 2012. Moderate drinking? Alcohol consumption significantly decreases neurogenesis in the adult hippocampus. Neuroscience 224, 202–209.

Balash, Y., Mordechovich, M., Shabtai, H., Giladi, N., Gurevich, T., Korczyn, A.D., 2013. Subjective memory complaints in elders: depression, anxiety, or cognitive decline? Acta Neurol Scand 127 (5), 344–350.

Bigler, E.D., Andersob, C.V., Blatter, D.D., 2002. Temporal lobe morphology in normal aging and traumatic brain injury. Am J Neuroradiol 23 (2), 255–266.

Bischof, G.N., Park, D.C., 2015. Obesity and aging: consequences for cognition, brain structure and brain function. Psychosom med 77 (6), 697.

Bolla, K.I., Lindgren, K.N., Bonaccorsy, C., Bleecker, M.L., 1991. Memory complaints in older adults. Fact or fiction? Arch Neurol 48 (1), 61–64.

Braak, H., Braak, E.V.A., 1995. Staging of Alzheimer's disease-related neurofibrillary changes. Neurobiol aging 16 (3), 271–278.

Brailean, A., Steptoe, A., Batty, G.D., Zaninotto, P., Llewellyn, D.J., 2019. Are subjective memory complaints indicative of objective cognitive decline or depressive symptoms? findings from the english longitudinal study of ageing. J psychiatr res 110, 143–151.

Brandt, J., 1991. The hopkins verbal learning test: development of a new memory test with six equivalent forms. Clin neuropsychol 5 (2), 125–142.

Brett, M., Anton, J.-L., Valabregue, R., Poline, J.-B., 2002. Region of interest analysis using an SPM toolbox. In: 8th international conference on functional mapping of the human brain, Sendai, Japan, p. 497.

Buckley, R.F., Hanseeuw, B., Schultz, A.P., Vannini, P., Aghjayan, S.L., Properzi, M.J., Jackson, J.D., Mormino, E.C., Rentz, D.M., Sperling, R.A., Johnson, K.A., Amariglio, R.E., 2017. Region-specific association of subjective cognitive decline with tauopathy independent of global beta-amyloid burden. JAMA Neurol 74 (12), 1455–1463.

Burmester, B., Leathem, J., Merrick, P., 2016. Subjective cognitive complaints and objective cognitive function in aging: a systematic review and meta-analysis of recent cross-sectional findings. Neuropsychol Rev 26 (4), 376–393.

Caballero, M.Á.A., Song, Z., Rubinski, A., Duering, M., Dichgans, M., Park, D.C., Ewers, M., 2020. Age-dependent amyloid deposition is associated with white matter alterations in cognitively normal adults during the adult life span. Alzheimers Dement 16 (4), 651–661.

Canty, A., Ripley, B., 2021. boot: Bootstrap R (S-Plus) functions. R package version 1, pp. 3–27.

Carp, J., Park, J., Polk, T.A., Park, D.C., 2011. Age differences in neural distinctiveness revealed by multi-voxel pattern analysis. Neuroimage 56 (2), 736–743.

Chen, X., Farrell, M.E., Moore, W., Park, D.C., 2019. Actual memory as a mediator of the amyloid-subjective cognitive decline relationship. Alzheimers Dement 11, 151–160.

Crary, J.F., Trojanowski, J.Q., Schneider, J.A., Abisambra, J.F., Abner, E.L., Alafuzoff, I., Arnold, S.E., Attems, J., Beach, T.G., Bigio, E.H., Cairns, N.J., Dickson, D.W., Gearing, M., Grinberg, L.T., Hof, P.R., Hyman, B.T., Jellinger, K., Jicha, G.A., Kovacs, G.G., Knopman, D.S., Kofler, J., Kukull, W.A., Mackenzie, I.R., Masliah, E., McKee, A., Montine, T.J., Murray, M.E., Neltner, J.H., Santa-Maria, I., Seeley, W.W., Serrano-Pozo, A., Shelanski, M.L., Stein, T., Takao, M., Thal, D.R., Toledo, J.B., Troncoso, J.C., Vonsattel, J.P., White 3rd, C.L., Wisniewski, T., Woltjer, R.L., Yamada, M., Nelson, P.T., 2014. Primary age-related tauopathy (PART): a common pathology associated with human aging. Acta Neuropathol 128 (6), 755–766.

Crumley, J.J., Stetler, C.A., Horhota, M., 2014. Examining the relationship between subjective and objective memory performance in older adults: A meta-analysis. Psychol aging 29 (2), 250.

Davison, A.C., Hinkley, D.V., 1997. Bootstrap methods and their application. Cambridge university press.

Dennis, N.A., Daselaar, S., Cabeza, R., 2007. Effects of aging on transient and sustained successful memory encoding activity. Neurobiol aging 28 (11), 1749–1758.

Desikan, R.S., Segonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31 (3), 968–980.

Dixon, R.A., Hultsch, D.F., Hertzog, C., 1988. The metamemory in adulthood (Mia) questionnaire. Psychopharmacol Bull 24 (4), 671–688.

Drouin, S.M., McFall, G.P., Dixon, R.A., 2020. In multiple facets of subjective memory decline sex moderates memory predictions. Alzheimers Dement 12 (1), e12089.

Edelman, K., Tudorascu, D., Agudelo, C., Snitz, B., Karim, H., Cohen, A., Mathis, C., Price, J., Weissfeld, L., Klunk, W., Aizenstein, H., 2017. Amyloid-beta deposition is associated with increased medial temporal lobe activation during memory encoding in the cognitively normal elderly. Am J Geriatr Psychiatry 25 (5), 551–560.

Eichenbaum, H., 2004. Hippocampus: cognitive processes and neural representations that underlie declarative memory. Neuron 44 (1), 109–120.

Erk, S., Spottke, A., Meisen, A., Wagner, M., Walter, H., Jessen, F., 2011. Evidence of neuronal compensation during episodic memory in subjective memory impairment. Arch Gen Psychiatry 68 (8), 845–852.

Farrell, M.E., Kennedy, K.M., Rodrigue, K.M., Wig, G., Bischof, G.N., Rieck, J.R., Chen, X., Festini, S.B., Devous Sr., M.D., Park, D.C., 2017. Association of longitudinal cognitive decline with amyloid burden in middle-aged and older adults: evidence for a dose-response relationship. JAMA Neurol 74 (7), 830–838.

Gardner, M.J., Altman, D.G., 1986. Confidence intervals rather than P values: estimation rather than hypothesis testing. Br Med J (Clin Res Ed) 292 (6522), 746–750.

Gutchess, A.H., Welsh, R.C., Hedden, T., Bangert, A., Minear, M., Liu, L.L., Park, D.C., 2005. Aging and the neural correlates of successful picture encoding: frontal activations compensate for decreased medial-temporal activity. J Cogn Neurosci 17 (1), 84–96.

Harrison, T.M., Maass, A., Adams, J.N., Du, R., Baker, S.L., Jagust, W.J., 2019. Tau deposition is associated with functional isolation of the hippocampus in aging. Nat commun 10 (1), 1–12.

Hayes, J.M., Tang, L., Viviano, R.P., van Rooden, S., Ofen, N., Damoiseaux, J.S., 2017. Subjective memory complaints are associated with brain activation supporting successful memory encoding. Neurobiol Aging 60, 71–80.

Hesterberg, T., 2011. Bootstrap. Wiley Interdiscip Reviews 3 (6), 497–526.

Ho, J., Tumkaya, T., Aryal, S., Choi, H., Claridge-Chang, A., 2019. Moving beyond P values: data analysis with estimation graphics. Nat Methods 16 (7), 565–566.

Hu, X., Uhle, F., Fliessbach, K., Wagner, M., Han, Y., Weber, B., Jessen, F., 2017. Reduced future-oriented decision making in individuals with subjective cognitive decline: A functional MRI study. Alzheimers Dement (Amst) 6, 222–231.

Huijbers, W., Schultz, A.P., Papp, K.V., LaPoint, M.R., Hanseeuw, B., Chhatwal, J.P., Hedden, T., Johnson, K.A., Sperling, R.A., 2019. Tau accumulation in clinically normal older adults is associated with hippocampal hyperactivity. J Neurosci 39 (3), 548–556.

Jack Jr., C.R., Bennett, D.A., Blennow, K., Carrillo, M.C., Dunn, B., Haeberlein, S.B., Holtzman, D.M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J.L., Montine, T., Phelps, C., Rankin, K.P., Rowe, C.C., Scheltens, P., Siemers, E., Snyder, H.M., Sperling, R.Contributors, 2018. NIA-AA Research framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement 14 (4), 535–562.
Jagust, W., 2013. Vulnerable neural systems and the borderland of brain aging and neurodegeneration. Neuron 77 (2), 219–234.
Kennedy, K.M., Rodrigue, K.M., Bischof, G.N., Hebrank, A.C., Reuter-Lorenz, P.A., Park, D.C., 2015. Age trajectories of functional activation under conditions of low and high processing demands: an adult lifespan fMRI study of the aging brain. Neuroimage 104, 21–34.
Kennedy, K.M., Rodrigue, K.M., Devous Sr., M.D., Hebrank, A.C., Bischof, G.N., Park, D.C., 2012. Effects of beta-amyloid accumulation on neural function during encoding across the adult lifespan. Neuroimage 62 (1), 1–8.
Kenney, J.W., Gould, T.J., 2008. Modulation of hippocampus-dependent learning and synaptic plasticity by nicotine. Molecular neurobiol 38 (1), 101–121.
Kim, H., 2011. Neural activity that predicts subsequent memory and forgetting: a meta-analysis of 74 fMRI studies. Neuroimage 54 (3), 2446–2461.
Koen, J.D., Rugg, M.D., 2019. Neural dedifferentiation in the aging brain. Trends Cogn Sci 23 (7), 547–559.
Kutner, M.H., Nachtsheim, C.J., Neter, J., Li, W., 2005. Applied linear statistical models. McGraw-Hill, Irwin New York.
Leal, S.L., Landau, S.M., Bell, R.K., Jagust, W.J., 2017. Hippocampal activation is associated with longitudinal amyloid accumulation and cognitive decline. Elife 6, e22978.
Leal, S.L., Yassa, M.A., 2015. Neurocognitive aging and the hippocampus across species. Trends neurosci 38 (12), 800–812.
Long, J.A., 2019. interactions: Comprehensive, User-Friendly Toolkit for Probing Interactions R package version 1.1.0.
Machulda, M.M., Pankratz, V.S., Christianson, T.J., Ivnik, R.J., Mielke, M.M., Roberts, R.O., Knopman, D.S., Boeve, B.F., Petersen, R.C., 2013. Practice effects and longitudinal cognitive change in normal aging vs. incident mild cognitive impairment and dementia in the Mayo Clinic Study of Aging. Clin neuropsychol 27 (8), 1247–1264.
McDonough, I.M., Festini, S.B., Wood, M.M., 2020. Risk for Alzheimer's disease: a review of long-term episodic memory encoding and retrieval fMRI Studies. Aging Res Rev, 101133.
Mitchell, A.J., Beaumont, H., Ferguson, D., Yadegarfar, M., Stubbs, B., 2014. Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: meta-analysis. Acta Psychiatr Scand 130 (6), 439–451.
Molinuevo, J.L., Rabin, L.A., Amariglio, R., Buckley, R., Dubois, B., Ellis, K.A., Ewers, M., Hampel, H., Kloppel, S., Rami, L., Reisberg, B., Saykin, A.J., Sikkes, S., Smart, C.M., Snitz, B.E., Sperling, R., van der Flier, W.M., Wagner, M., Jessen, F.Subjective Cognitive Decline Initiative Working, G., 2017. Implementation of subjective cognitive decline criteria in research studies. Alzheimers Dement 13 (3), 296–311.
Mormino, E.C., Brandel, M.G., Madison, C.M., Marks, S., Baker, S.L., Jagust, W.J., 2012. Abeta Deposition in aging is associated with increases in brain activation during successful memory encoding. Cereb Cortex 22 (8), 1813–1823.
Nisbett, R.E., Wilson, T.D., 1977. Telling more than we can know: Verbal reports on mental processes. Psychol rev 84 (3), 231.
O'Brien, J.L., O'Keefe, K.M., LaViolette, P.S., DeLuca, A.N., Blacker, D., Dickerson, B.C., Sperling, R.A., 2010. Longitudinal fMRI in elderly reveals loss of hippocampal activation with clinical decline. Neurology 74 (24), 1969–1976.
Ossenkoppele, R., Jagust, W.J., 2017. The complexity of subjective cognitive decline. JAMA Neurol 74 (12), 1400–1402.
Park, D.C., Polk, T.A., Park, R., Minear, M., Savage, A., Smith, M.R., 2004. Aging reduces neural specialization in ventral visual cortex. Proc Natl Acad Sci U S A 101 (35), 13091–13095.
Perrotin, A., Mormino, E.C., Madison, C.M., Hayenga, A.O., Jagust, W.J., 2012. Subjective cognition and amyloid deposition imaging: a Pittsburgh Compound B positron emission tomography study in normal elderly individuals. Arch Neurol 69 (2), 223–229.
Petersen, R.C., Wiste, H.J., Weigand, S.D., Rocca, W.A., Roberts, R.O., Mielke, M.M., Lowe, V.J., Knopman, D.S., Pankratz, V.S., Machulda, M.M., 2016. Association of elevated amyloid levels with cognition and biomarkers in cognitively normal people from the community. JAMA neurology 73 (1), 85–92.
Core Team, R, 2020. R: A language and environment for statistical computing [Internet]. Vienna: R Foundation for Statistical Computing 2020.
Rabin, L.A., Smart, C.M., Amariglio, R.E., 2017. Subjective cognitive decline in preclinical Alzheimer's disease. Annu Rev Clin Psychol 13, 369–396.
Radloff, L.S., 1977. The CES-D scale: A self-report depression scale for research in the general population. Applied psycholo measurement 1 (3), 385–401.
Robbins, T.W., James, M., Owen, A.M., Sahakian, B.J., McInnes, L., Rabbitt, P., 1994. Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. Dementia 5 (5), 266–281.
Rodda, J., Dannhauser, T., Cutinha, D.J., Shergill, S.S., Walker, Z., 2011. Subjective cognitive impairment: functional MRI during a divided attention task. Eur Psychiatry 26 (7), 457–462.
Rodda, J.E., Dannhauser, T.M., Cutinha, D.J., Shergill, S.S., Walker, Z., 2009. Subjective cognitive impairment: increased prefrontal cortex activation compared to controls during an encoding task. Int J Geriatr Psychiatry 24 (8), 865–874.
Rodrigue, K.M., Kennedy, K.M., Devous Sr., M.D., Rieck, J.R., Hebrank, A.C., Diaz-Arrastia, R., Mathews, D., Park, D.C., 2012. beta-Amyloid burden in healthy aging: regional distribution and cognitive consequences. Neurology 78 (6), 387–395.
Savalia, N.K., Agres, P.F., Chan, M.Y., Feczko, E.J., Kennedy, K.M., Wig, G.S., 2017. Motion-related artifacts in structural brain images revealed with independent estimates of in-scanner head motion. Hum Brain Mapp 38 (1), 472–492.
Sheather, S., 2009. A modern approach to regression with R. Springer Science & Business Media.
Slavin, M.J., Brodaty, H., Kochan, N.A., Crawford, J.D., Trollor, J.N., Draper, B., Sachdev, P.S., 2010. Prevalence and predictors of "subjective cognitive complaints" in the Sydney memory and ageing study. Am J Geriatr Psychiatry 18 (8), 701–710.
Snitz, B.E., Small, B.J., Wang, T., Chang, C.C., Hughes, T.F., Ganguli, M., 2015. Do subjective memory complaints lead or follow objective cognitive change? a five-year population study of temporal influence. J Int Neuropsychol Soc 21 (9), 732–742.
Song, Z., McDonough, I.M., Liu, P., Lu, H., Park, D.C., 2016. Cortical amyloid burden and age moderate hippocampal activity in cognitively-normal adults. Neuroimage Clin 12, 78–84.
Sperling, R., Mormino, E., Johnson, K., 2014. The evolution of preclinical Alzheimer's disease: implications for prevention trials. Neuron 84 (3), 608–622.
Sperling, R.A., Aisen, P.S., Beckett, L.A., Bennett, D.A., Craft, S., Fagan, A.M., Iwatsubo, T., Jack Jr., C.R., Kaye, J., Montine, T.J., Park, D.C., Reiman, E.M., Rowe, C.C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M.C., Thies, B., Morrison-Bogorad, M., Wagster, M.V., Phelps, C.H., 2011. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7 (3), 280–292.
Squire, L.R., 1992. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psycholog rev 99 (2), 195.
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15 (1), 273–289.
Wang, X., Huang, W., Su, L., Xing, Y., Jessen, F., Sun, Y., Shu, N., Han, Y., 2020. Neuroimaging advances regarding subjective cognitive decline in preclinical Alzheimer's disease. Mol Neurodegener 15 (1), 1–27.
West, M.J., Coleman, P.D., Flood, D.G., Troncoso, J.C., 1994. Differences in the pattern of hippocampal neuronal loss in normal ageing and Alzheimer's disease. Lancet 344 (8925), 769–772.
Zeileis, A., Hothorn, T., 2002. Diagnostic checking in regression relationships.
Zimprich, D., Kurtz, T., 2015. Subjective and objective memory changes in old age across five years. Gerontology 61 (3), 223–231.