

Supplementary Text For:

Alzheimer's disease pathologies affect dopaminergic neural mechanisms of memory

Abbreviated Title: AD pathology affects dopaminergic memory

Thomas M. Morin^{1,2}, Jordyn L. Cowan¹, Hsiang-Yu Chen¹, Jourdan H. Parent^{1,2}, Jennifer L. Crawford¹, Claire J. Ciampa¹, Vyoma D. Shah³, Ming Hsu⁴, William J. Jagust³, Anne S. Berry^{1*}

1. Department of Psychology, Brandeis University
2. A. A. Martinos Center for Biomedical Imaging, Mass. General Hospital
3. Department of Neuroscience, University of California Berkeley
4. Haas School of Business, University of California Berkeley

*Corresponding Author:

Anne S. Berry, Department of Psychology, Brandeis University, Lemberg Hall #101.
Waltham, MA 02453. (781) 736-3278

Email: anneberry@brandeis.edu

Supplementary Methods

fMRI Preprocessing with fMRIPrep

MRI preprocessing was performed using fMRIPrep (22.0.2) which is based on NiPype (1.8.5) (Esteban et al., 2019). Preprocessing steps included skull stripping, distortion correction using the phase-encoded EPI fieldmaps, co-registration of each subject's functional data with their anatomical scan using boundary-based registration with six degrees of freedom, estimation of head-motion parameters, slice-time correction, and spatial normalization of the subject's anatomical and functional data to standard template space (MNI152NLin2009cAsym template from templateflow) (Ciric et al., 2021). Full details of the fMRIPrep pipeline are described below. After minimal processing with fMRIPrep, we performed spatial smoothing (3mm FWHM gaussian kernel), EPI masking, and scaling so that each voxel time series had a mean of 100 using AFNI (Cox, 1996).

The following boilerplate text was produced by the fMRIPrep pipeline that was used to preprocess the MRI data in this study:

Results included in this manuscript come from preprocessing performed using fMRIPrep (22.0.2) which is based on Nipype (1.8.5).

Preprocessing of B₀ Inhomogeneity Mappings: A B₀ nonuniformity map for each subject (fieldmap) was estimated from the phase-drift map with two consecutive GRE (gradient-recalled echo) acquisitions. The corresponding phase-map was phase-unwrapped with 'prelude' (FSL 6.0.5.1). A B₀ nonuniformity map (fieldmap) was estimated based on two echo-planar imaging (EPI) references with 'topup' (FSL 6.0.5.1).

Anatomical Data Preprocessing: The T1-weighted (T1w) image for each subject was corrected for non-uniformity (INU) with 'N4BiasFieldCorrection', distributed with ANTs 2.3.3, and used as a T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a Nipype implementation of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as a target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM), and gray-matter (GM) was performed on the brain-extracted T1w using 'fast' (FSL 6.0.5.1). Brain surfaces were reconstructed using 'recon-all' (FreeSurfer 7.2.0), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray matter of Mindboggle. Volume-based spatial normalization to one standard space (MNI152NLin2009cAsym) was performed through using brain-extracted versions of both the T1w reference and the T1w template. The following template was used for spatial normalization: ICBM 152 Nonlinear Asymmetrical template version 2009c. (RRID: SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym)

Functional Data Preprocessing: For each of the four BOLD runs per subject (acquired during the Real Estate Selling Task), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated by aligning and averaging one single-band reference image (SBRef). Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) were estimated before any spatiotemporal filtering using 'mcflirt' (FSL 6.0.5.1). BOLD runs were slice-time corrected to 1.15s (0.5 of slice acquisition range 0s-2.3s) using '3dTshift' from AFNI. Slice onset times were determined from the "SliceTiming" field in the JSON sidecar file that was paired with each BOLD run. The BOLD time-series (including slice-time correction) were resampled onto their original, native space by applying the transforms to correct for head-motion. These resampled BOLD time-series will be referred to as 'preprocessed BOLD in original space' or just

‘preprocessed BOLD.’ The BOLD reference was then co-registered to the T1w reference using `bbregister` (FreeSurfer) which implements boundary-based registration. Co-registration was configured with six degrees of freedom. The BOLD-timeseries were resampled into standard space, generating a preprocessed BOLD run in MNI152NLin2009cAsym space. First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. All resamplings can be performed with a single interpolation step by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction, and co-registrations to anatomical output spaces). Gridded (volumetric) resamplings were performed using ‘`antsApplyTransforms`’ (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels. Many internal operations of fMRIPrep use Nilearn (0.9.1) mostly within the functional processing workflow. For more details of the pipeline see the section corresponding to workflows in fMRIPrep’s documentation: <https://fmriprep.readthedocs.io/en/latest/workflows.html>.

Supplementary Figures

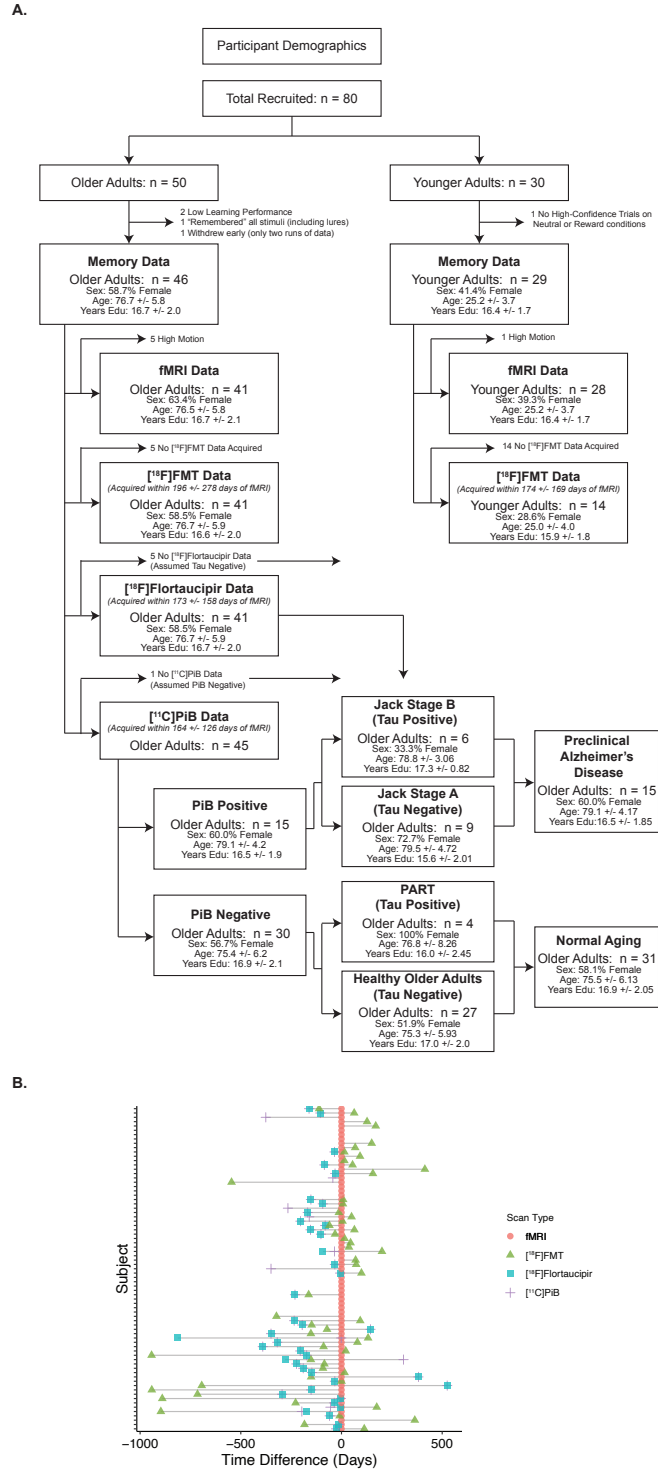


Figure S1. (A) Participant Attrition Flow Chart.

The complete sample consisted of 50 cognitively normal older adults and 30 cognitively normal younger adults. A quality control procedure was conducted to determine which data to

include/exclude in analyses. First, participants' memory data was assessed. For participants with good quality memory data, their available fMRI and PET imaging data was also assessed for quality and included/excluded as noted. Overall, we sought to include as much data as possible (e.g. if a participant had fMRI data, but not PET data, we included their fMRI data in fMRI analyses, but not in analyses that compared fMRI to PET measures). **(B)** Data collection timeline. All participants completed the real estate selling task during fMRI scanning and a follow-up memory test outside the scanner. A subset of participants also completed PET neuroimaging sessions to measure dopamine synthesis capacity (with [18F]fluoro-m-l tyrosine), tau burden (with [18F]Flortaucipir), and amyloid load (with [11C]Pittsburgh Compound-B).

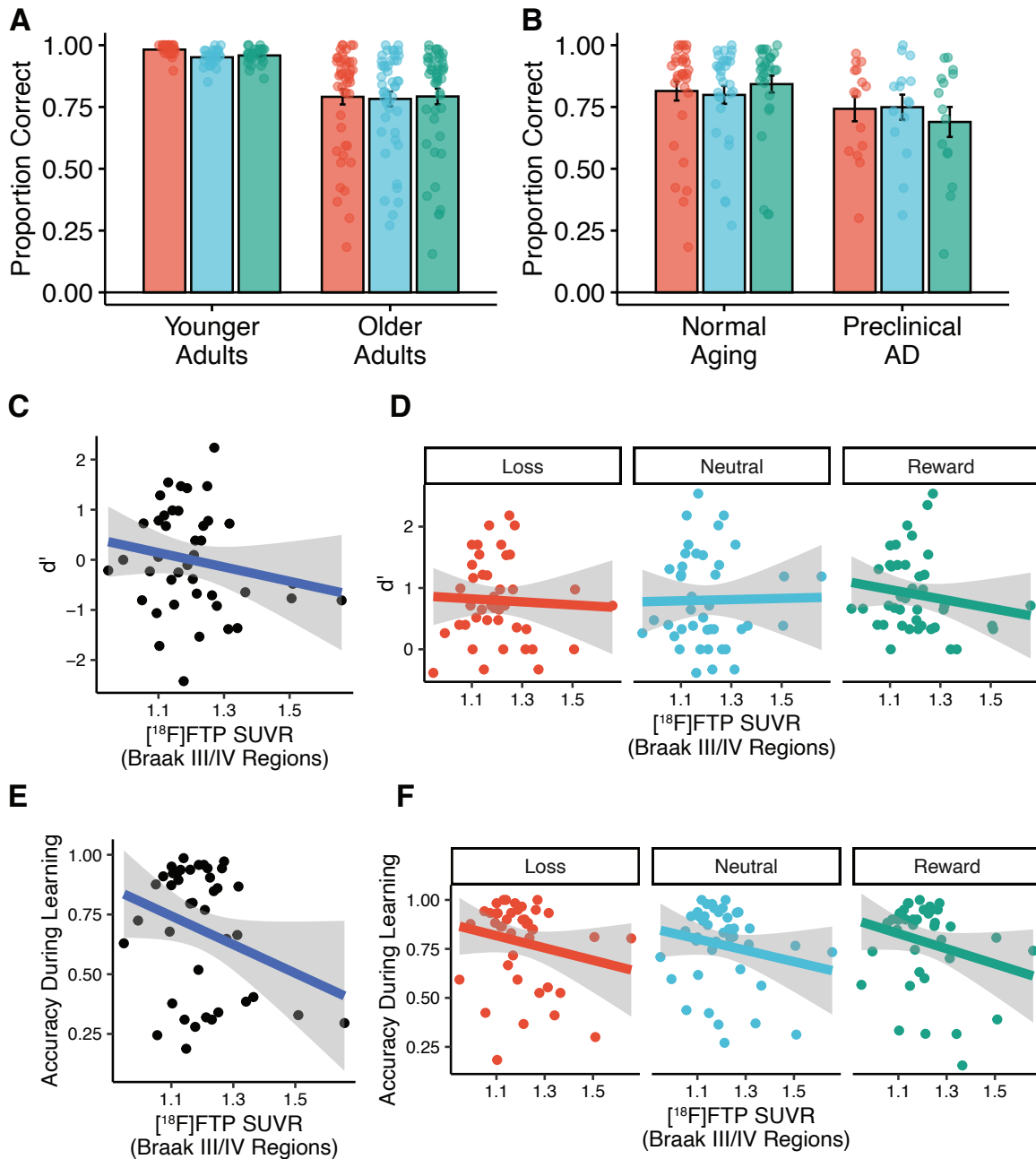


Figure S2. Supporting Analyses of Behavioral Data. **(A)** Analysis of performance during the learning phase of the task. We used a linear mixed effects model to compare performance across valences and age groups during the learning phase of the task [accuracy \sim age_group \times valence + (1 | subject)]. Overall, older adults showed worse learning performance compared to younger adults ($b = -0.19$, $T = -4.90$, $p < .001$). We did not observe a significant difference in performance between the reward and loss trials in either age group. (Younger Adults: $b = -0.024$, $T = 0.92$, $p = .22$; Older Adults: $b = 0.025$, $T = 1.02$, $p = .31$). **(B)** In a second linear mixed effects model, we examined the effect of AD-related pathology on learning performance in only the older adults. [accuracy \sim biomarker_group \times valence + age + sex + years_edu + (1 | subject)]. We did not

observe a significant difference in accuracy between normal aging and preclinical AD ($b = -0.020$, $T = -0.33$, $p = .74$). Bar height represents mean proportion correct for each condition. Error bars = standard error. Red = loss; Blue = neutral; Green = reward. **(C)** A linear model found no significant relationship between [18F]FTP SUVR in Braak III/IV regions and overall memory scores (d'). [$d' \sim \tau_burden + age + sex + years_edu$] ($b = -1.39$, $T = 1.26$, $p = .27$). **(D)** We used a linear mixed effects model to test for a relationship between [18F]FTP in Braak III/IV regions and memory across valences [$d' \sim \tau_burden \times valence + age + sex + yrs_edu + (1 | subject)$]. The model failed to detect any significant main effects of tau burden ($b = -0.12$, $t = -0.15$, $p = .89$) or trial valence (neutral: $b = -0.41$, $t = -0.60$, $p = .55$; reward: $b = 0.72$, $t = 1.05$, $p = .30$) on memory performance. **(E)** A linear model found no significant relationship between [18F]FTP SUVR in Braak III/IV regions and overall learning performance. [$total_learning \sim \tau_burden + age + sex + years_edu$] ($b = -0.46$, $T = -1.64$, $p = .11$). However, the model did find significant effects of age ($b = -0.016$, $T = -2.46$, $p = .02$) and sex ($b = -0.18$, $T = -2.44$, $p = .02$) on learning performance. **(F)** We used a linear mixed effects model to test for a relationship between [18F]FTP in Braak III/IV regions and learning across valences [$learning \sim \tau_burden \times valence + age + sex + years_edu + (1 | subject)$]. The model failed to detect a significant main effect of tau burden ($b = -0.22$, $T = -0.944$, $p = .35$) or valence (neutral: $b = -0.043$, $t = -0.23$, $p = .82$; reward: $b = 0.09$, $t = 0.48$, $p = .63$) and did not detect a significant tau burden by valence interaction. However, we did observe an effect of years of education ($b = 0.031$, $t = 2.16$, $p = .04$).

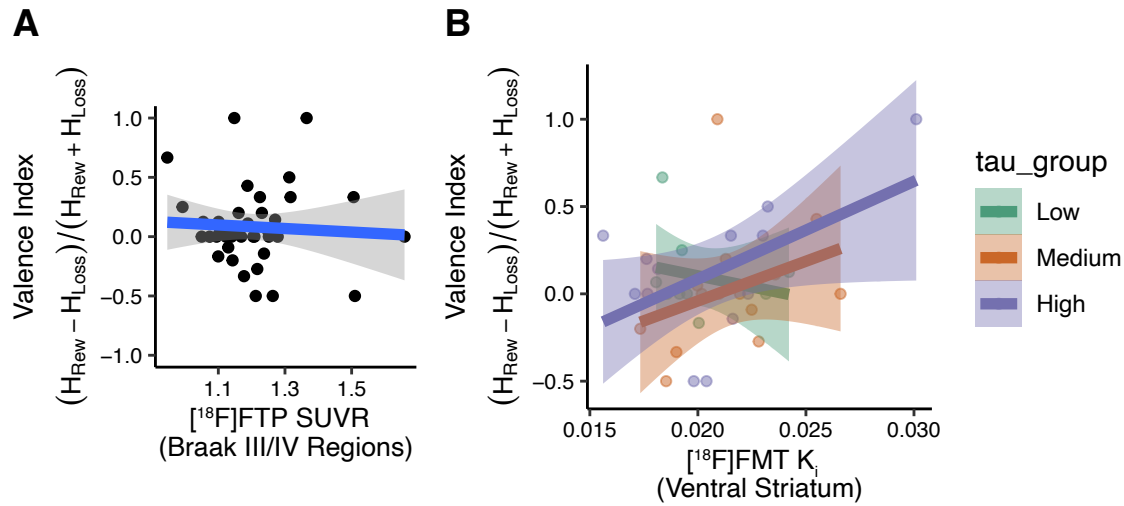


Figure S3. (A) Tau burden had no direct relationship with the valence index. Analyses showed that [¹⁸F]FTP SUVR in Braak III/IV regions was not directly associated with individual differences in the valence index for older adults [$\text{valence_index} \sim \text{ftp_suvr} + \text{age} + \text{sex} + \text{years_edu}$] ($b = -0.25$, $t = -0.612$, $p = 0.55$). (B) However, there was a significant interaction between tau burden and ventral striatal dopamine synthesis capacity on valence index [$\text{valence_index} \sim \text{ftp_suvr} + \text{age} + \text{sex} + \text{years_edu}$] ($b = 512.3$, $t = 2.63$, $p = .01$), such that participants with higher tau burden showed a significantly stronger positive relationship between dopamine synthesis capacity and valence index. This interaction effect remained significant in a model accounting for learning performance ($b = 453.8$, $t = 2.234$, $p = .03$).