Lower novelty-related locus coeruleus function is associated with Aβ-related cognitive decline in clinically healthy individuals

Prokopis C. Prokopiou1,9, Nina Engels-Domínguez1,2,9, Kathryn V. Papp3,4, Matthew R. Scott4,5, Aaron P. Schultz4,6, Christoph Schneider1, Michelle E. Farrell4, Rachel F. Buckley3,4,7, Yakeel T. Quiroz4,8, Georges El Fakhri1, Dorene M. Rentz3,4, Reisa A. Sperling3,4, Keith A. Johnson1,3,4 & Heidi I. L. Jacobs1,2

Animal and human imaging research reported that the presence of cortical Alzheimer’s Disease’s (AD) neuropathology, beta-amyloid and neurofibrillary tau, is associated with altered neuronal activity and circuitry failure, together facilitating clinical progression. The locus coeruleus (LC), one of the initial subcortical regions harboring pretangle hyperphosphorylated tau, has widespread connections to the cortex modulating cognition. Here we investigate whether LC’s in-vivo neuronal activity and functional connectivity (FC) are associated with cognitive decline in conjunction with beta-amyloid. We combined functional MRI of a novel versus repeated face-name paradigm, beta-amyloid-PET and longitudinal cognitive data of 128 cognitively unimpaired older individuals. We show that LC activity and LC-FC with amygdala and hippocampus was higher during novelty. We also demonstrated that lower novelty-related LC activity and LC-FC with hippocampus and parahippocampus were associated with steeper beta-amyloid-related cognitive decline. Our results demonstrate the potential of LC’s functional properties as a gauge to identify individuals at-risk for AD-related cognitive decline.
Alzheimer’s disease (AD), the most prevailing type of dementia, is manifested by gradually progressive memory problems. The neuropathologic hallmarks include the deposition of beta-amyloid (Aβ) plaques and neurofibrillary tangle tangles, which each emerge throughout the cortex in a distinct, predictable topographical manner, starting decades prior to clinical symptoms. Several in-vitro and human autopsy studies suggested that one of the earliest sites in the brain implicated in these AD-related proteinopathies is the locus coeruleus (LC), a subcortical nucleus providing norepinephrine to the entire brain. While many of these studies focused predominantly on the role of tau, LC neurons and their axonal terminals can accumulate soluble, oligomeric variants of Aβ early on, which interact with tau deposits in the LC and which subsequently trigger aggregation of soluble and extracellular Aβ into plaques in the remote cortex during the initial phases of AD.

As both the LC and Aβ undergo early pathologic alterations, there may be a common mechanism contributing to the initial clinical symptoms of AD. These initial symptoms emerge typically after age 60 when cortical Aβ is detectable, tau is omnipresent in the LC and has reached the hippocampus (HIPP). Recent animal work demonstrated that oligomeric Aβ in the LC has the capacity to dysregulate LC activity promoting early hyperexcitability, which is reminiscent to the previously reported Aβ-driven excitatory toxicity in the cortical and hippocampal networks. As the disease progresses and tau accrues, neuronal hyperexcitability was followed by neuronal silencing in transgenic mice or loss of hyperconnectivity in fMRI studies. Thus, a closer investigation of the effect of Aβ on activity of the LC and its functional connectivity (FC), in particular with the medial temporal lobe (MTL) could improve our understanding of the evolution and the early detection of AD-related cognitive decline and provide new anchor points for interventions.

LC neurons are known to discharge during conditions of novelty, arousal, and cognitive demand. Animal studies have shown that novel or unexpected stimuli elicit phasic spikes in LC neurons, leading to NE release that targets the task-relevant regions in the brain, such as the amygdala (AMYG) and HIPP in the MTL and the prefrontal cortex. Given that novelty detection is also an essential component of both learning and memory, tasks involving novelty detection may thus be well-suited to examine the vulnerability of the LC and the medial temporal pathways in AD-related cognitive decline. So far, few studies have looked at in vivo human LC function during novelty and its relationship with cognitive performance. A study by del Cerro et al. demonstrated greater connectivity between the LC and the rest of the brain during oddball trials as compared to standard trials, but the FC strength did not differ between healthy participants and mild cognitively impaired (MCI) patients. In contrast, Clewett et al. used an emotional arousal paradigm in young adults and showed that increased LC-FC with the insula and dorsolateral prefrontal cortex was associated with subsequent better memory performance for negative stimuli. These studies provide initial evidence that communication of the LC with the cortex contributes to cognition, but to the best of our knowledge, no in vivo study has investigated the impact of AD pathology on LC activity or FC, and its downstream effects on cognitive decline.

In this work, we set out to investigate associations between in vivo LC activity and LC-MTL connectivity during the encoding of novel associations in well-characterized clinically unimpaired older individuals of the Harvard Aging Brain Study (HABS). We also examined whether novelty-related LC activity and connectivity have downstream effects on cognitive decline over a 10-year period as a function of Aβ PET. Based on the staging of pathology, suggesting proliferation of cortical tau in these older individuals, and its association with activity patterns, we hypothesized that novelty-related LC activity and connectivity would be lower at higher levels of Aβ, and that this lower novelty-related activity would be associated with Aβ-related cognitive decline.

### Results

#### Characteristics of sample and design.

One hundred twenty-eight older individuals from HABS underwent imaging, as well as longitudinal neuropsychological evaluations over up to 10 years. Seventy-one participants (55.46%) were female. At baseline, the mean age of the participants was 70.07 ± 8.86 (SD) and the mean education level was 15.74 ± 2.67 (SD) years. In addition, all participants had no history of medical or psychiatric disorders and were clinically unimpaired at baseline: Mini-Mental State Examination (MMSE) > 25, Clinical Dementia Rating (CDR) = 0, and normal age- and education-adjusted scores on the Logical Memory delayed-recall test (Table 1).

Table 1: Characteristics of participants at baseline and follow-up time of neuropsychological evaluation sorted by PiB status.

| PiB status | n, No. (%) | Age (years) | Sex, No. (%) = M | Education (years) | PiB, PVC FLR (DVR) | MMSE (score) | GDS (score) | Logical Memory delayed-recall (score) | PACCs (score) | NP follow-up time (years) |
|------------|------------|-------------|------------------|-------------------|--------------------|--------------|------------|-------------------------------------|---------------|--------------------------|
| Aβ−        | 92 (71.9)  | 66.75 [62.69, 72.69] | 40 (43.5)        | 16.00 [14.00, 18.00] | 1.18 [1.14, 1.21] | 30.00 [29.00, 30.00] | 2.00 [1.00, 4.00] | 14.00 [12.00, 16.25] | 0.32 [−0.10, 0.57] | 4.10 [2.03, 8.23] |
| Aβ+        | 36 (28.1)  | 76.62 [71.00, 82.38]  | 17 (47.2)        | 16.00 [13.00, 18.00] | 1.84 [1.50, 2.16] | 29.00 [29.00, 30.00] | 2.00 [1.00, 4.00] | 15.00 [12.00, 17.00] | 0.03 [−0.32, 0.52] | 6.92 [3.92, 8.33] |
| P value     |            | <0.001       | 0.853            | 0.946              | <0.001             | 0.051        | 0.889      | 0.271                               | 0.13          | 0.025                    |

Data are presented as medians and (interquartile ranges (IQRs)) for continuous variables and proportions for dichotomous data. Two-tailed chi-square tests and Kruskal-Wallis tests were conducted to evaluate group differences.

DVR: distribution volume ratio, FLR frontal, laterotemporal and retrosplenial cortices, GDS Geriatric Depression Scale, M male, MMSE Mini-Mental State Examination, NP neuropsychological evaluation, PVC partial volume corrected, PiB Pittsburgh Compound-B, PACCs Preclinical Alzheimer Cognitive Composite.

*p < 0.05, ***p < 0.001.
The imaging assessments included both a Pittsburgh Compound-B (PiB) - positron emission tomography (PET) scan and a BOLD-fMRI session during which participants performed an encoding task of novel and repeated face-name associations, organized in blocks21 (Fig. 1). The novelty block consisted of unfamiliar faces that varied in age, sex, and ethnicity paired with common first names. The repetition block consisted of repeated familiar faces, which were presented to the participants in a familiarization practice run prior to the fMRI session. Because of the responsiveness of the LC to novelty, here we focus on the novel versus repeated face-names contrast (NvR).

The LC is a remarkably tiny structure, located near multiple vessels and the fourth ventricle, thereby exposing the LC to motion and physiological noise22,23. To account for the confounding effect of non-neural related contributions in our measurements, the BOLD-fMRI images acquired during each condition were pre-processed, including AROMA (Automatic Removal of Motion Artifacts) for denoising and a custom ellipsoid smoothing kernel to account for the shape of the LC, and entered into a general linear model (GLM) for detecting task-related brain activation and generalized psychophysiological interaction analyses (gPPI) for detecting task-related voxel-wise functional connectivity of the LC within predefined regions of interest (ROIs; see “Methods”). In addition, to account for differences in hemodynamics across brain regions and individuals, we estimated region- and subject-specific hemodynamic response functions (HRF)24. We restricted our analyses to a set of predefined ROIs that are involved in memory, face processing, novelty detection and arousal: the AMYG, HIPP, parahippocampal gyrus (PHG), entorhinal (EC), temporal fusiform (TFC) insular (INS) cortices, and brainstem (medulla,pons, and midbrain; Supplementary Fig. 1c). As the LC was the seed for the gPPI analyses, we excluded the brainstem from the target ROIs. To demonstrate the robustness of our findings, we also performed several sensitivity analyses, which included analysis of unsmoothed data, time-series extracted from an eroded version of our LC ROI and correction for gray matter density, as well as analyses with the Replication Dataset and Matched Dataset (see “Methods”).

Greater neuronal activity within predefined ROIs during Novelty versus Repetition. First, we aimed to verify the brain activation patterns associated with novelty. We performed voxel-wise linear mixed-effects (LME) models with cross-sectional NvR contrast estimates as outcome variable, and including age and sex as covariates, random intercepts for participants and random slopes for fMRI runs (see “Methods”). Consistent with previous reports, we observed greater activation during NvR in the HIPP, and temporal occipital fusiform (TOF) cortices21,26. In addition, we also observed greater NvR activation in the AMYG, INS and LC (Fig. 3a). Our sensitivity analyses reproduced these observations when the unsmoothed data (Supplementary Fig. 2) and the Replication Dataset (Supplementary Fig. 3) were used, as well as when gray matter density was included into the model as a covariate (Supplementary Fig. 4). We detected no significant sex or age contributions in our activity maps. Given the age difference observed between the Aβ+ and Aβ− groups (Table 1) we post-hoc also repeated the same analysis using the Matched Dataset. The results (Supplementary Fig. 5) revealed greater activation during NvR in similar areas as the results obtained for the entire cohort shown in Fig. 3a. Adding PiB as covariate to the model did not modify the patterns of NvR activity. In addition, PiB did not interact with NvR on brain activation. Furthermore, greater activation was observed during Novelty compared to Fixation (NvF; Supplementary Fig. 6), albeit less than compared to NvR. No activation was observed during Repetition versus Fixation (RvF).

Greater functional connectivity between locus coeruleus and amygada as well as hippocampus during Novelty versus Repetition. To investigate novelty-related coactivations between the LC and other voxels in the predefined set of ROIs, we employed gPPI analyses27. We performed LME models to
identify brain regions whose coactivation with the LC differs between novelty and repetition, using their contrast estimates as outcome variable, and including age and sex as covariates, random intercepts for participants and random slopes for fMRI runs. The resulting FC maps revealed greater NvR-related FC between the LC and both the bilateral AMYG and HIPP (Fig. 4a). Our sensitivity analyses reproduced these findings using BOLD time-series extracted from an eroded version of the LC ROI (Supplementary Figs. 7 and 8), unsmoothed data (Supplementary Fig. 9), as well as the Replication Dataset (Supplementary Fig. 10). We detected no significant sex or age contributions in the maps. Similar FC maps were obtained using the Matched Dataset (Supplementary Fig. 11) compared to the results obtained using our original dataset shown in Fig. 4a. Further, adding PiB as covariate to the model did not modify the patterns of NvR LC-FC and PiB did not interact with NvR on LC-FC. Also, greater FC was observed during both NvF and RVF between the LC and the bilateral AMYG and HIPP (Supplementary Fig. 12). However, FC during NvF was overall stronger and revealed more extended clusters of voxels within the AMYG and HIPP compared to RVF.

Associations between novelty-related LC activity and functional connectivity with cognition. Given that novelty processing promotes learning and memory28,29, we sought to examine (i) the relationship between both NvR activity and FC between the LC and the respective individual voxels within the predefined set of ROIs (LC-FC), with cognitive performance, and (ii) whether these relationships are modulated by Aβ burden.

Lower novelty-related activity in the LC is associated with Aβ-related PACC5 decline. First, we examined which anatomic regions exhibited activity during NvR that is related to baseline PACC5 (Preclinical Alzheimer Cognitive Composite) performance using a voxel-wise linear model analysis including age, sex, and years of education as covariates. We observed no significant associations under cluster-extent thresholding (number of participants n = 128; cluster defining threshold Z > 2.3, two-tailed p < 0.05, family-wise error (FWER)-corrected). However, we also performed explorative analyses using false discovery rate (FDR)-based correction (number of participants n = 128; Z > 2.3, P_{FDR} < 0.05). This showed that lower NvR activation in small clusters of voxels in the right HIPP and left TFC (Supplementary Fig. 13) was associated with lower PACC5 performance.

Subsequently, we examined which anatomic regions exhibited activity during NvR that is associated with prospective PACC5 decline using voxel-wise mixed-effects model analyses including baseline age, sex and years of education as covariates (number of participants n = 128, number of observations is 753). Random intercepts and slopes were used for participants and time, respectively. No region was associated with PACC5 decline under cluster-extent-based thresholding. Using FDR correction we observed that lower NvR activation in the bilateral LC was associated with PACC5 decline under cluster-extent-based thresholding. Using FDR correction we observed that lower NvR activation in the bilateral LC was associated with PACC5 decline (Supplementary Fig. 14; Z > 2.3, P_{FDR} < 0.05). Given that the PACC5 was developed as a sensitive measure of Aβ-related cognitive decline, we next aimed to uncover whether the associations between regions with NvR activity and PACC5 decline were modified by PiB.

To that end, we included the three-way interaction, NvR activity × time × PiB, in the linear mixed effect model. Using cluster-extent thresholding, we observed that lower NvR activation in the brainstem, including the right LC, and in the right PGH was associated with a steeper PACC5 decline, in particular when PiB was elevated (Fig. 5). The lateralization of these findings did not change under the less strict FDR correction (Supplementary Fig. 15). Similar results were obtained when PiB was used as a dichotomous rather than a continuous variable (Supplementary Fig. 16). To visualize these findings, we extracted the time-series from the right LC cluster (Fig. 5a) and plotted the simple slopes at mean and ±1 SD of LC activity for the two-way...
interaction (Fig. 5b, number of participants \( n = 128 \) and number of observations is 753; \( B = 0.05, t(623) = 1.66, p = 0.097, 95\% \) confidence interval (CI)[−0.009, 0.11]) and the three-way interaction (Fig. 5c, number of participants \( n = 128 \) and number of observations is 753; \( B = 0.20, t(621) = 3.37, p = 0.001, 95\% \) CI[0.09, 0.32]). Supplementary Fig. 17 illustrates the same result using dichotomous PiB. Post-hoc floodlight analyses revealed that the latter association is significant for PiB values equal to or above 1.44 DVR (\( p < 0.05 \) FDR corrected). We also investigated the Aβ-dependent associations between right PHG NvR activity and PACC5 decline (Supplementary Fig. 18) and observed that lower NvR PHG activity was associated with PACC5 decline when PiB values were equal to or above 1.62 DVR (\( p < 0.05 \) FDR corrected).

To examine whether the associations between LC NvR activity and (Aβ-related) PACC5 decline were driven by specific cognitive domains, we also investigated the subtests of the PACC5 and two other composite measures (Fig. 5d; Supplementary Tables 4 and 5). The largest effect sizes for the association between LC activation and Aβ-related cognitive decline were detected for the digit-symbol substitution and cognitive abilities test (verbal frequency).

**Lower novelty-related LC functional connectivity is associated with Aβ-related PACC5 decline.** To examine the relationship between LC-FC and PACC5, we took a similar approach as for the activation maps. We observed no significant associations between LC-FC and baseline PACC5 performance when correcting for multiple comparisons using cluster-extent-based thresholding (number of participants \( n = 128 \); cluster defining threshold \( Z > 3.1, \) two-tailed \( p < 0.05 \), FWER-corrected). However, using FDR-based correction (number of participants \( n = 128 \); \( Z > 2.3, P_{\text{FDR}} < 0.05 \)), we detected that lower FC between the LC and left AMYG, as well as left PHG are associated with lower PACC5 performance (Supplementary Fig. 19).

For the longitudinal data, we observed that lower novelty-related FC between the LC and left HIPP was associated with PACC5 decline (Fig. 6) at the cluster-extent thresholding levels. We then examined possible effect modification by PiB by including the three-way interaction in the LME model and observed that lower FC between the LC and bilateral HIPP and PHG are associated with steeper PACC5 decline in individuals with elevated PiB (number of participants \( n = 128 \) and number of observations is 753; cluster defining threshold \( Z > 3.1, \) two-tailed \( p < 0.05 \), FWER-corrected, Fig. 7a). Similar findings were observed when PiB was used as a dichotomous variable (Supplementary Fig. 20).

To visualize the associations between PACC5 decline and FC between the LC and areas in the MTL, we extracted the FC values from the voxels in the bilateral HIPP and PHG that survived the cluster-extent-based thresholding shown in Fig. 7a, and plotted the simple slopes at mean and ±1 SD of LC-FC for the two-way interaction (Fig. 7b, number of participants \( n = 128 \) and number of participants \( n = 128 \)).
Figure 4: Voxel-wise analysis of LC functional connectivity in predefined regions of interest during Novelty versus Repetition. a) Functional connectivity maps between the LC and the predefined ROIs obtained during NvR face-name associations: greater FC between the LC and the amygdala as well as hippocampus during NvR. Inference was performed using mixed-effects models including NvR LC-FC contrast estimates as outcome variable, age and sex as fixed effects, random intercepts for participants and slopes for fMRI runs. The FC maps were corrected for multiple comparisons using cluster-extent-based thresholding (number of participants n = 128; cluster defining threshold Z > 4.5, two-tailed p < 0.05, FWER-corrected). b) Boxplots of averaged gPPI parameter estimates (PE) for each participant and experimental condition in the bilateral hippocampus and amygdala. Vertical lines within boxes indicate the median. The left and right part of the boxes indicate the 25th and 75th percentile of the underlying PE distribution, respectively. Dots represent averaged PE values across runs (number of participants n = 128). The gPPI PE values obtained during Novelty were significantly larger than those during Repetition. The coordinates of the peak voxels of the detected clusters are provided in Supplementary Table 9. Abbreviations: AMYG amygdala, cond condition, HIPP hippocampus, Nov novelty, Rep repetition.

Discussion

AD's neuropathologic hallmarks consist of Aβ plaques and neurofibrillary tau formations. Neuronal hyperactivity has been linked to the emergence and progression of these proteinopathies, as well as to disease progression. Given the early involvement of the LC in AD's pathophysiology and the fact that both animal and human imaging studies showed that the LC is highly responsive to novelty leading to NE-release in the HIPP and AMYG, thereby contributing to learning, we set out to investigate whether novelty-related LC activity and connectivity are associated with cognitive decline over a 10-year period as a function of Aβ. To that end, we examined data from the well-characterized HABS cohort consisting of cross-sectional neuroimaging and longitudinal cognitive data.

Using dedicated processing methods to improve the measurement of the LC BOLD-fMRI signal and several sensitivity analyses confirming the robustness of our findings, we replicated animal work by showing that the LC shows higher activity during novelty and higher novelty-related FC with the bilateral AMYG and HIPP. We extended these results by demonstrating that both lower novelty-related LC activity and LC-MLT FC are associated with steeper Aβ-related cognitive decline. These findings are promising for the potential of LC's functional properties as a gauge to detect individuals at risk for AD-related processes. Interestingly, during the course of our study, ten participants progressed to MCI/AD, suggesting that our findings are also applicable to prodromal AD. Future studies with longer follow-up or a larger group of prodromal AD are needed to examine whether the relationship between LC function and Aβ-related cognitive decline varies as a function of disease stage.

Processing of novel stimuli is known to facilitate learning and memory. Animal and human pharmacological and imaging studies demonstrated that exposure to novel stimuli induces activity of the LC, releasing NE, and leading to reconfiguration of specific task-relevant networks, such as the salience or memory-related networks. Consistent with these observations, during processing of novel faces, we observed higher activation in areas relevant for saliency, face discrimination, and learning. In addition, we observed higher FC between the LC and both the AMYG and HIPP.
during novelty compared to repetition. Such a rearrangement for processing novel stimuli is thought to be important to reallocate cognitive resources for optimal performance, such as attentional shifts, learning, and action selection. In addition, the involvement of the hippocampus here aligns with the reported increase in hippocampal NE, which contributes to cellular mechanisms for effective learning, such as LTP.

Indeed, we observed that lower novelty-related bilateral LC activity and LC connectivity with the MTL were associated with worse performance and steeper cognitive decline. This agrees with recent cross-sectional MRI studies suggesting that lower LC-cortical FC is also associated with worse memory performance and that age-related reductions in LC structural integrity are associated with impaired cognitive function and worse memory performance. LC integrity has been also associated with tau pathology and longitudinal memory decline. Further exploration of the PACC5 subtests revealed that these LC-network changes that we observed were predominantly related to performance on the...
It is known that beyond the LC’s effects on learning, its putative function involves fast disengagement from specific tasks and amplification of attentional focus to the goal-relevant information. Additionally, allocation of attention has generally been ascribed to the right hemisphere, which aligns with the abundant involvement of attention in the digit-symbol substitution test and our observation of lower right-sided LC activity being associated with steeper Aβ-related cognitive decline. This right lateralization is also consistent with the hypothesis that the LC may represent an important biological substrate underlying cognitive reserve and its associated processes, such as arousal, attention, and novelty, which all have been related to activation of predominantly the right frontoparietal network. Previous imaging work showed lower connectivity between the LC and frontoparietal or salience networks resulting in greater distractibility in older individuals. Our results indeed demonstrated that individuals who are able to maintain optimal levels of novelty-related LC functional properties may be more resilient to cognitive decline, even in the presence of elevated Aβ. Together, these findings strengthen the role of the LC-NE system in modulating networks, promoting cognition and potentially supporting cognitive reserve.

Even though novelty processing declines gradually during AD, we did not find an association between LC activity or LC-MTL FC and Aβ. Hyperactivity has been associated with elevated Aβ inducing an excitatory toxic environment for disease progression. It may be hypothesized that Aβ affects neuronal activity and networks differently depending on the disease stage. In fact, several studies using a similar task argue for a nonlinear process. In clinically unimpaired older individuals, hippocampal activity during a face-name associative memory task was not different between individuals with low or elevated Aβ, which is consistent with our observations for the LC. However, Huijbers and colleagues reported modest differences in EC activity between low and elevated Aβ groups. In a study using the same fMRI task, hippocampal activity was higher in MCI individuals with elevated Aβ deposition, compared to those with low Aβ deposition. But, in AD patients presented with this face-name associative paradigm twice during six months, worse performance on the cognitive subscale of the Alzheimer’s Disease Assessment Scale was associated with decreased novelty-related cortical activity.

We speculate that the impact of Aβ on activity or FC may be dependent on the targeted circuit. Previous imaging work reported combinations of hyper and hypoactivity in relationship to predominantly Aβ or tau pathology, respectively. Work by Sepulcre et al. highlights that there may be regional differences in vulnerability, possibly dependent on the topography of AD pathology. It should be noted that our sample consisted of older individuals (age range 50–89 years; M = 70.07, SD = 8.86), and at that time in life presence of prefrontal material in the LC is ubiquitous. Unfortunately, we do not have information on the tau burden of our participants, but autopsy data suggests that it is very likely that the majority of our participants have Braak stage II pathology. In addition, given that 28% of our sample was classified with elevated Aβ, consistent with Thal phase II/III, it is presumed that these individuals bear at least Braak stage III-IV tau burden. Under this premise, we posit that the presence of tau may have obscured the impact of Aβ on neuronal activation. Animal work indicated that tau pathology, already when soluble non-aggregated, can dominate the effects of Aβ hyperactivity, resulting in suppression or even silencing of neuronal activity.

Consistent with a potential overriding effect of tau and the observation that tau is closely associated with cognition, we observed that lower novelty-related LC-MTL FC was associated with Aβ-related cognitive decline, at values below the GMM-derived threshold. Recent work demonstrated lower LC-cerebellar and LC-MTL FC patterns associated with reduced memory performance in offspring of patients with sporadic AD and MCI patients with possible AD. Our observations now indicate that lower novelty-related LC functional properties may identify clinically unimpaired individuals at risk of cognitive decline associated with an AD trajectory. Interestingly, we also note that individuals who are able to maintain optimal levels of novelty-related LC activity or FC may be resilient to cognitive decline, even in the presence of elevated Aβ. Which LC-related factors may confer resiliency to AD pathology are not yet clear and warrant further examination. Animal research has suggested that greater novelty-related LC activity may be a potentially important component mediating the cognitive effects promoting cognitive reserve via molecular mechanisms such as β-adrenergic enhanced neurogenesis and elevated expression of plasticity-related genes.

This study has limitations. First, as the LC is one of the first regions affected by tau, it would have been interesting to examine the relationship between FC and cortical tau deposition. Unfortunately, tau-PET imaging was recently introduced in HABS, adding analytical complexities in terms of varying time difference with the FMRI data. Second, imaging the LC is challenging due to its proximity to the 4th ventricle and its tiny size, making it prone to partial volume effects. However, pairwise Pearson’s correlation between BOLD-fMRI time-series extracted from the LC and 4th ventricle ROIs confirmed that our findings are not biased by partial volume effects (Supplementary Fig. 22). Similarly, we were not able to measure Aβ directly in the LC because of the low spatial resolution of PET imaging. Measuring LC function at 3T is challenging, due to the constraints on spatial resolution. To account for this, we implemented brainstem targeted pre-processing techniques including (i) weighted registration of the brainstem into the Montreal Neurological Institute (MNI)-152 space, (ii) nuisance regression including the average BOLD time series of the 4th ventricle, and (iii) special smoothing using an ellipsoid Gaussian kernel aiming to improve the spatial SNR and enhance detection of elongated structures within the brainstem, such as the LC. This ellipsoid smoothing brought the resolution of our data to a comparable and sometimes even better resolution.
resolution than other LC studies using spherical smoothing (Supplementary results 1). Furthermore, our sensitivity analyses performed using unsmoothed data (providing the highest spatial resolution), an eroded version of the LC ROI, and the Replication and Matched Datasets demonstrated the robustness and reproducibility of our imaging findings. The maps were corrected for multiple comparisons using cluster-extent-based thresholding (number of participants \( n = 128 \) and number of observations is 753; cluster defining threshold \( Z > 3.1 \), two-tailed \( p < 0.05 \), FWER-corrected).

**Fig. 7** Lower novelty-related FC between the LC and bilateral hippocampus as well as parahippocampal gyrus are associated with steeper Aβ-related PACC5 decline. **a** Voxel-wise analyses relating LC- region of interest FC, PiB, and longitudinal PACC5 measurements: lower NvR functional connectivity between the LC and the bilateral hippocampus and parahippocampal gyrus is associated with greater decline on the PACC5, in particular in individuals with elevated PiB. Inference was performed using mixed-effects models including PACC5 as outcome variable, NvR LC-FC contrast estimates, time, PiB, their interactions, age, sex, and years of education as fixed effects, random intercepts for participants, and slopes for time (number of years between baseline and follow-up cognitive assessments). The maps were corrected for multiple comparisons using cluster-extent-based thresholding (number of participants \( n = 128 \) and number of observations is 753; cluster defining threshold \( Z > 3.1 \), two-tailed \( p < 0.05 \), FWER-corrected). **b** Visualization of the association between PACC5 performance over time and NvR FC between the LC and the group of voxels within the bilateral hippocampus and parahippocampal gyrus shown in Fig. 7a. **c** Visualization of the interaction between NvR LC-FC and PiB on PACC5 slopes (number of participants \( n = 128 \)). The cyan box illustrates the range of PiB values at which lower NvR LC-hippocampus and parahippocampal FC is associated with PACC5 decline. In all line plots, the estimated marginal mean of the interaction terms is plotted at the mean (green), \(+1\) SD (yellow), and \(-1\) SD (black), but analyses were done continuously. Inference was performed using linear regression including PACC5 decline as outcome variable, and NvR LC-FC, PiB, their interaction, age, sex and years of education as predictor variables. Shaded areas around the fit lines show 95% CI. **d** Radar chart showing the magnitude of the associations (estimate/standard error) between NvR LC-hippocampus and parahippocampal FC and PiB-related cognitive decline on the subtests of the PACC5, as well as the executive function and memory composite scores (number of participants \( n = 128 \) and number of observations is 753). The inner orange line indicates \( t \)-value = 1.96. The outer black line indicates \( t \)-value = 10.00. More detailed results are provided in Supplementary Table 7. * Random effects were modeled using only a random intercept for each subject. Abbreviations: CAT Category Fluency Test, DSST Digit-Symbol Substitution Test, DVR Distribution volume ratio, FCSRT Free and Cued Selective Reminder Test, HIPP hippocampus, LM Logical Memory, MMSE Mini-Mental State Examination, PHG parahippocampal gyrus, PiB Pittsburgh Compound-B, PACC5 Preclinical Alzheimer Cognitive Composite and SD Standard Deviation.
In conclusion, we investigated the association between in vivo novelty-related LC activity or LC-MLT functional connectivity and Aβ or Aβ-related cognitive decline in clinically unimpaired older individuals. Our findings demonstrate that lower novelty-related LC activity and functional connectivity between the LC and HIPP and PHG were associated with steeper decline in cognition measured over 10 years, particularly in the presence of elevated Aβ deposition. These results emphasize the potential of functional properties of the LC as a gauge to differentiate individuals vulnerable for the AD-related trajectory from those carrying resilience against AD-related changes.

Methods
Participants. One hundred twenty-eight individuals from HABS were included in the present study (57 M/71 F; median age at baseline = 69.62, interquartile range (IQR): 63.69–76.81; years of education at baseline = 16, IQR: 14–18 years; Table 1). HABS is an ongoing longitudinal observational study of cognitively unimpaired individuals aimed to further our understanding of normative aging and preclinical AD. All participants underwent baseline task-IMRI and PiB-PET imaging (within one year of the MRI scan), and annual cognitive assessments (followed up for up to 10 years; median (years) = 4.25, IQR: 2.07–8.26). For the cognitive assessments, n = 125 participants completed 2 visits, n = 117 participants completed 3 visits, n = 89 participants completed 4 visits, n = 78 participants completed 5 visits, n = 60 participants completed 6 visits, n = 55 participants completed 7 visits, n = 50 participants completed 8 visits, n = 43 participants completed 9 visits and n = 8 participants completed 10 visits (Supplementary Fig. S3). To validate our results, we analyzed two different fMRI datasets. The first one, the Replication Dataset, consisted of fMRI data acquired from forty-one older individuals using an alternate version of the face-name associative task. Twenty-four individuals overlapped with the main cohort but were scanned four years later using an alternative version of the fMRI task. In total, twenty-one participants had completed PACC5 in HABS later in the study and their baseline imaging and cognitive measurements were not within one year from each other and were therefore excluded from the main sample. The characteristics of the Replication Dataset are provided in Supplementary Table 1. The other dataset, the Matched Dataset, consisted of a subset of 36 Aβ-individuals who were matched with 36 Aβ+ individuals based on the age, sex, and years of education distributions using propensity-based matching. The characteristics of the Matched Dataset are provided in Supplementary Table 2. The study complied with all ethical regulations and was approved by the Partners Human Research Committee at Massachusetts General Hospital (3D mode; 63 image planes; 15.2 cm axial field of view; 5.6 mm transaxial resolution; and 2.4 mm slice interval). Following radiosynthesis of 11C PiB, an injection of 8.5–15 mCi PiB was administered and dynamic data in 69 frames was obtained (90 s; 15 frames and 3 s; 57 frames). PiB-PET data were registered to the subject’s high-resolution anatomical MRI and converted into distribution volume ratio (DVR) using the Logan graphical method32.

PET data acquisition and pre-processing. PiB-PET data were acquired on a Siemens ECAT EXACT HR + PET system located at the Massachusetts General Hospital (3D mode; 63 image planes; 15.2 cm axial field of view; 5.6 mm transaxial resolution; and 2.4 mm slice interval). Following radiosynthesis of 11C PiB, an injection of 8.5–15 mCi PiB was administered and dynamic data in 69 frames was obtained (90 s; 15 frames and 3 s; 57 frames). PiB-PET data were registered to the subject’s high-resolution anatomical MRI and converted into distribution volume ratio (DVR) using the Logan graphical method32.

Cerebellar gray matter was used as the reference region36. The PET images were aligned to the high-resolution anatomical MRI images described below, and motion correction was applied using cross-modal alignment in SPM12 (Wellcome Department of Cognitive Neurology, Function Imaging Laboratory, UK). Partial-volume correction (PVC) was performed using the Geometrical Transfer Matrix approach implemented in FSL. PiB retention was assessed using a large ROI comprising the frontal, lateral temporal and retrosplenial (FLR) cortices. Classification into Aβ+/- groups was ascertained using a PiB cut-off value of 1.324 for the PVC data (1.20 for non-PVC), which was previously determined with a Gaussian mixture modeling approach on the entire HABS cohort18. Based on this cut-off value, 92 participants in this study were classified as low Aβ (Aβ-), and 36 participants (28.13% of the entire cohort) with elevated Aβ (Aβ+) at baseline. This is consistent with the estimated prevalence of Aβ+ individuals among cognitively unimpaired individuals ranging from 13% to 30%9. The median baseline PiB-PET imaging delay from the first neuropsychological evaluation was 0.29 years or 107 days (IQR, 0.20–0.46 years) and the median delay from the first MRI scan was 0.09 years or 35 days (IQR, 0.04–0.19 years).

MRI data acquisition and pre-processing. All data were collected on a 3T Trio Tim syno MR B17 scanner (Siemens Medical Systems) using 12-channel phased-array head coils for field localization located at the Athinoula A. Martinos Center for Biomedical Imaging in Charlestown, MA. Functional data were acquired using a T2*-weighted echo planar imaging (EPI) sequence sensitive to BOLD contrast. Sequence parameters: TR/TE (Repetition/Echo Time) = 2000/30 ms; Voxel size = 3.1 x 3.1 x 5.0; FA (Flip Angle) = 90°; 30 slices; Acquisition matrix = 200 x 200 x 179 mm. Each run comprised 127 volumes with slices acquired in an interleaved manner in a coronal orientation perpendicular to the anterior commissure-posterior commissure (AC-PC) plane. This orientation was chosen to maximize the in-plane resolution within the HIPP and brainstem21. In addition, a high-resolution T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo structural image was also acquired to aid registration of the PiB-PET and BOLD images to a common MNI space. Sequence parameters: TR/TE = 2300/2.93 ms; Voxel size = 1.1 x 1.1 x 1.2 mm; Inversion time = 900 ms; FA = 9°; 176 (sagittal oriented) slices; Acquisition matrix = 270 x 254 x 212 mm; 2x (GRAPPA) acceleration.

The high-resolution T1 structural images were pre-processed in F5 (version 6.0; http://freesurfer.net/) using the software package’s default automated reconstruction algorithm. This one included a familiarization voxel elimination step prior to the MRIs runs. The face-name pairs within each block were presented for 4.75 s and followed by a brief, randomly jittered white fixation crosshair, giving a total duration of approximately 40 s per block. Participants were asked to remember the name associated with each face, and to indicate with a button press whether or not they thought the name was a good match for the face. The latter was a purely subjective decision of each individual that was used to ensure engagement with the task26. The task comprised 6 functional runs, and each type of block was shown twice in each run in an interleaved fashion. In addition, visual fixation blocks were added: a 5-s fixation block was presented at the beginning and end of each run and a 25-s fixation block was alternated with the novelty and repetition blocks. We focused primarily on the novelty versus repetition contrast.

Cognitive performance. We employed the most recent version of the Preclinical Alzheimer’s Cognitive Composite score (PACC5)20,63. PACC5 is designed to track early Aβ-related cognitive decline. The PACC5 score consists of the average of the z-transformed (using baseline mean and standard deviation) scores of the Digit-Symbol Substitution Test (DSST)26; free and total recall elements of Free and Cued Selective Reminding Test (FCSRT)26; Logical Memory Delayed Story Recall66; Mini-Mental State Examination (MMSE)15, and Category fluency (CAT) tests to animals, fruits, and vegetables67. We allowed at most one missing subtest for PACC5 score calculation. Missing subtests were excluded from the calculation. In addition to PACC5, we also included a memory and an executive function composite score following factor analyses16. The memory composite score comprised z-transformations of the delayed recall scores of the 6-Trial Selective Reminding Test68, free recall element of the FCSRT66 and Logical Memory Delayed Story Recall66. The executive function composite score comprised z-transformations of the Trail Making Test Form B − A40. Letter Number Sequencing test71 and phonemic fluency FAS test52. The intraclass correlation coefficient (ICC)73 demonstrated adequate measurement reliability over time. For the PACC5, the ICC was 0.85, for the memory composite score 0.81, and for the executive function composite score 0.81.

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(2022)13:1571 | https://doi.org/10.1038/s41467-022-28986-2 | www.nature.com/naturecommunications
The pre-processing of the BOLD images was carried out using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library (FMRIB) Diffusion Toolbox (FDT). This included brain extraction, slice time correction, motion correction via volumetric realignment, normalization to the 2 mm3 MNI-152 EPI template, and further artifact detection and removal using ICA-AROMA. This included the derivation of root mean squared variance across voxels (DVARS). To improve the accuracy of the registration of the brainstem, we initially aligned the BOLD images to the high-resolution 1 mm3 T1 structural image of each subject using boundary-based registration. Subsequently, the T1 structural image was aligned with the MNI-152 template using a 3-step registration procedure: in the first step the T1 structural image was registered to the MNI-152 template using an affine, linear registration with 12 degrees of freedom. In the second step, this affine registration was refined using cost-function weighting input and reference volumes (Supplementary Fig. 24). The weighting volumes were constructed by assigning higher weights to the voxels within the 4th ventricle, midbrain, pons and medulla. In the third step, a nonlinear registration was performed, which was initialized using the transformation matrix obtained from the previous step. To mitigate artifacts from CSF flow, breathing motion and cardiac pulsatility of blood vessels in the brainstem, nuisance regressors were generated and removed from the data through linear regression. The nuisance regressors included three ROI time-series obtained as the mean across voxels in the 4th ventricle, lateral ventricles and white matter, the 6 motion parameters (MPs) generated during volume realignment, the derivatives of the 6 MPs, and the squares of all the aforementioned time-series. Finally, the BOLD images were spatially filtered using a custom ellipsoidal Gaussian kernel (Supplementary Fig. 24) in order to further enhance the estimation of the 4th ventricle, midbrain, pons and medulla. The third step performed, which was initialized using the transformation matrix obtained from the previous step. To mitigate artifacts from CSF flow, breathing motion and cardiac pulsatility of blood vessels in the brainstem, nuisance regressors were generated and removed from the data through linear regression. The nuisance regressors included three ROI time-series obtained as the mean across voxels in the 4th ventricle, lateral ventricles and white matter, the 6 motion parameters (MPs) generated during volume realignment, the derivatives of the 6 MPs, and the squares of all the aforementioned time-series. Finally, the BOLD images were spatially filtered using a custom ellipsoidal Gaussian kernel (Supplementary Fig. 24) in order to enhance the estimation of the 4th ventricle, midbrain, pons and medulla. The BOLD images were spatially filtered using a custom ellipsoidal Gaussian kernel (Supplementary Fig. 24) in order to enhance the estimation of the 4th ventricle, midbrain, pons and medulla.

To prevent overfitting, the order \( P \) of the BOLD signal model described by Eq. (3) was fixed to \( P = 2 \) for both experimental conditions (\( i = 1,2 \)). The selection of the model order was determined based on the Bayesian information criterion. Optimal values for \( a > 0 \) and \( r > 0 \) parameters were determined based on the minimum generalization error using a grid search. In voxel-wise analyses, performing grid search to determine optimal values for these parameters incurs heavy computational burden. To reduce this, the voxel-wise analysis was performed in two steps: in the first step, an optimal basis set \( B(\ell, M) \) was constructed for each subject based on each subject's BOLD signal estimate across all ROIs. To identify differences in the HRF curve shape between different experimental conditions and ROIs, we applied principal component analysis to the group of HRF estimates obtained across all participants, for each ROI and experimental condition. The HRF curve shape of each group was evaluated in terms of the first principal component, which accounted for most of the variance across all subject-specific HRF estimates contained within each group.

The second step, the optimal basis set \( B(\ell, M) \) that was constructed for each subject in the previous step was employed to obtain optimal voxel-specific HRF estimates for each experimental condition using Eq. (2).

The optimal voxel-specific HRF estimates obtained for each subject were used in the voxel-wise analysis to study neuronal activity in response to novel versus repetition. To this end, a GLM was constructed for each subject using three regressors: one constant term for modeling the intercept, and two regressors each of which associated with a different experimental condition. The time-course of each condition was initially convolved with the corresponding condition-dependent HRF estimate. Subsequently, the derived regressors were z-transformed and entered into a GLM analysis. A parameter estimate associated with each condition was obtained using ordinary least squares regression (OLSR). It should
be noted that this approach provides more accurate parameter estimates, which could not be extracted directly from the first part of the analysis (modeling the BOLD signal and HRF estimation) nor from the estimation of one hemisphere. The advantage of this approach for quantifying the strength of the hemodynamic response to novelty or repetition events is that it takes the entire HRF into consideration as illustrated in Supplementary results 2.

Generalized psychophysiological interaction (gPPI) fMRI analysis. In a second step, a whole-brain gPPI fMRI analysis was performed to study novelty-dependent FC of the LC ROI within our preselected ROIs (see section "fMRI data analysis")\(^2\). To this end, a GLM was constructed for each subject using a total of 5 regressors: one physiological, two psychological, and two interaction regressors\(^5\). The physiological regressor was constructed as the average of all voxels within the LC ROI (seed region). The analysis was also repeated using an eroded version (60% volume reduction) of the LC ROI (Supplementary Fig. 8). The psychological regressors were constructed by convolving each of the task-dependent block time-series with the group-level LC HRF, which is shown in Fig. 2a and derived as described in section fMRI data analysis. This was important in order to align the block time-series associated with each condition with the physiological regressor in time. The interaction regressors were calculated by multiplying each of the psychological regressors with the physiological regressor. A parameter estimate associated with each regressor was estimated using OLSR.

Statistical analyses. Statistical analyses were performed in R (version 4.0.1; https://www.r-project.org/). Group characteristics were summarized in medians and interquartile ranges (IQRs). Differences between or within the age, sex and subtest scores of the PACC5 battery, as well as the executive functioning and memory subtest scores (adjusted for multiple testing using FDR with a q-value of 0.05\(^5\)). Residual plots and QQ plots were examined for all models. All reported beta coefficients were unstandardized except in Figs. 5d and 7d, and P values were two-sided.

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The Harvard Aging Brain Study project is committed to publicly releasing its data. Baseline structural MRI, PiB-PET and cognitive follow-up data until year 5 is publicly available to the research community at http://nmr.mgh.harvard.edu/lab/ harvardagingbrain/data. Task-fMRI data are currently not yet publicly available but will be made available in future releases. Requests for material, currently available raw and processed data for all the datasets used in the study, and correspondence can be addressed to Dr. Spelke. Qualified investigators must abide by the Harvard Aging Brain Study online data use agreement, designed to protect the privacy of our participants. Source data are provided with this paper.

Code availability

All analyses were performed using the available toolboxes: R version 4.0.1 (http://www.r-project.org/), MATLAB R2018b (https://www.mathworks.com), FSL version 5.0.7 (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki), SPM12 https://www.fil.ion.ucl.ac.uk/spm/software/spm12/, FreeSurfer version 6 (http://freesurfer.net) and ANTs version 2.1.0 (http://stnava.github.io/ANTs/).

Received: 15 July 2021; Accepted: 23 February 2022; Published online: 23 March 2022.

References

1. Lane, C. A., Hardy, J. & Schott, J. M. Alzheimer’s disease. Eur. J. Neurol. 25, 79–90 (2018).
2. Braak, H. & Tredici, K. D. The pathological process underlying Alzheimer’s disease in individuals under thirty. Acta Neuropathol. 121, 171–181 (2011).
3. Weinschenker, D. Long road to ruin: noradrenergic dysfunction in neurodegenerative disease. Trends Neurosci. 41, 211–223 (2018).
4. Muresan, Z. & Muresan, V. Neuritic deposits of amyloid-beta peptide in a subpopulation of central nervous system-derived neuronal cells. Mol. Cell. Biol. 26, 4982–4997 (2006).
5. Muresan, Z. & Muresan, V. Seeding neuritic plaques from the distance: a critical role of soluble amyloid-beta for early hippocampal atrophy in patients with Alzheimer’s disease. Acta Neuropathol. 123, 223–228 (2018).
6. Busche, M. A. et al. Critical role of soluble amyloid-beta for early hippocampal hyperactivity in a mouse model of Alzheimer’s disease. Proc. Natl Acad. Sci. USA 109, 8740–8745 (2012).
7. Mather, M. & Harley, C. W. The locus coeruleus: essential for maintaining cognitive function and the aging brain. Trends Cogn. Sci. 20, 214–226 (2016).
13. Poe, G. R. et al. Locus coeruleus: a new look at the blue spot. Nat. Rev. Neurosci. 21, 644–646 (2020).
14. Haxby, J. V. The anatomy of the hippocampus-dependent memory is orchestrated by the locus coeruleus-noradrenergic system. Neural Plast. 2017, 2727602 (2017).
15. Lustberg, D. et al. Central norepinephrine transmission is required for stress-induced repetitive behavior in two rodent models of obsessive-compulsive disorder. Psychopharmacology 237, 1973–1987 (2020).
16. Del Cerro, I. et al. Locus coeruleus connectivity alterations in late-life major depressive disorder during a visual oddball task. NeuroImage Clin. 28, 20482 (2020).
17. Clewett, D., Schoeke, A. & Mather, M. Locus coeruleus neuromodulation of memories encoded during negative or unexpected action outcomes. Neurobiol. Learn Mem. 115, 65–70 (2014).
18. Dagley, A. et al. Harvard aging brain study: dataset and accessibility. NeuroImage 144, 255–258 (2017).
19. Folstein, M. F., Folstein, S. E. & McHugh, P. R. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198 (1975).
20. Morris, J. C. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 43, 2412–2414 (1993).
21. Sperling, R. A. et al. Encoding novel face-name associations: a functional MRI study. Hum. Brain Mapp. 11, 65–70 (2014).
22. Handwerker, D. A., Ollinger, J. M. & D. A. M. Functional network changes in the aging brain. Alzheimer’s Dement. 13, 1261–1269 (2017).
23. Del Cerro, I. et al. Disrupted functional connectivity of the locus coeruleus in healthy adults with parental history of Alzheimer’s disease. J. Psychiatr. Res. 123, 81–88 (2020).
24. Jacobson, H. L. et al. Relevance of parahippocampal–locus coeruleus connectivity to memory in early dementia. Neurobiol. Aging 36, 618–626 (2015).
25. Veyrac, A. et al. Novelty determines the effects of olfactory enrichment on memory and neurogenesis through noradrenergic mechanisms. Neuropsychopharmacology 34, 786–795 (2009).
26. Mather, M. Noradrenaline in the aging brain: promoting cognitive reserve or accelerating Alzheimer’s disease? Semin Cell Dev. Biol. 116, 108–124 (2021).
27. Li, B., Chohan, M. O., Grundke-Iqbal, I. & Iqbal, K. Disruption of microtubule transport in neurodegenerative diseases related locus coeruleus signal intensity differences. Acta Neuropathol. 113, 501–511 (2007).
28. Papp, K. V., Rentz, D. M., Orlovsky, I., Sperling, R. A. & Mormino, E. C. Optimizing the preclinical Alzheimer’s cognitive composite with semantic processing: the PACC5. Alzheimers Dement. 3, 668–677 (2017).
29. Mormino, E. C. et al. Early and late change on the preclinical Alzheimer’s disease pathology and cognitive decline. Nat. Med. 13, 1004–1012 (2017).
30. Wechsler, D. WAIS-III Manual: Wechsler Adult Intelligence Scale-revised (Psychological Corporation, 1981).
31. Grober, E., O’Cleirigh, K. & Terasi, J. A. The free and cued selective reminding test: evidence of psychometric adequacy. Psychol. Sci. Q. 51, 268–282 (2009).
32. Wechsler, D. Wechsler Memory Scale-revised (Psychological Corporation, 1987).
33. Wechsler, D. Wechsler Adult Intelligence Scale-revised (Psychological Corporation, 1997).
34. Reitan, R. M. Manual for Administration of Neuropsychological Test Batteries for Adults and Children (Neuropsychology Laboratory, Indiana University Medical Center, 1959).
35. Benton, A. L. et al. Contributions to Neuropsychological Assessment: A Clinical Manual (Oxford University Press, USA, 1994).
36. Nakagawa, S., Johnson, P. C. & Schizelth, H. The coefficient of determination R² and intra-class correlation coefficient from generalized linear mixed-effects models revisited and expanded. J. R. Soc. Interface 14, 20170213 (2017).
K.V.P. and D.M.R. aided in data collection, neuropsychological assessments, interpreted the results and reviewed the manuscript. N.E.D. and M.R.S. aided in data collection, study organization and data management. C.S. aided in methods development, interpreted the data and reviewed the manuscript. M.R.S., A.P.S., R.F.B. aided in MRI methods, data management and reviewed the manuscript. M.E.F and G.E.F. aided in PET methods, interpreted the results, and revised the manuscript. Y.T.Q. interpreted the results and revised the manuscript. R.A.S. and K.A.I. provided the participants, data analytic tools, aided in study design, interpreted results, and revised the manuscript. H.I.L.I., D.M.R., G.E.F. R.A.S., and K.A.I. acquired the financial support for the project leading to this publication. H.I.L.I. conceptualized this study, aided in study design, aided in methods development, aided in statistical analyses, interpreted data, revised the manuscript, and had the general supervision of the study.

Competing interests
K.V.P. is funded by NIA grant K23 AG053422-01 and the Alzheimer’s Association and has served as a paid consultant for Biogen. A.P.S. has been a paid consultant for Janssen, Biogen, Synapse, and NervGen. D.M.R. has done consulting for Biogen, Idec and Digital Cognition Technologies and served on the Scientific Advisory Board for Neurotrack. R.F.B. is funded by grants from the NIH K99/R00 (R00AG061238) and the Alzheimer’s Association. Y.T.Q is funded by grants from the NIH NIA (R01 AG054671, R01AG066823), the Alzheimer’s Association, and Massachusetts General Hospital ECOB, and has served as a paid consultant for Biogen. K.A.I. has served as paid consultant for Janssen, Genzyme, Novartis, Biogen, Roche, and AC Immune. He is a site co-investigator for Lilly/Avid and Janssen, and receives research support for clinical trials from Eisai, Lilly and Cerevea. K.A.I. received funding from NIH grants R01 EB048949, R21 AG038994, R01 AG206484, R01 AG03556, P50 AG0153421, U19 AG10483, P01 AG036694, R13 AG4201714210, R01 AG027435, and R01 AG37497 and the Alzheimer’s Association grant ZEN-10-174210. RAS has served as a paid consultant for AC Immune, Acumen, Alnylam, Biogen, Cytos, Genentech, Ionis, Janssen, JOMDD, Neuraly, Neurocentria, Oligomerix, Prothena, Renew, Roche, Shionogi and receives research support for clinical trials from Alzheimer’s Association, Eisai, Eli Lilly and Co. and NIA. She also receives research support from the following grant: P01 AG36694, U01 AG02438, U01 AG02494, R01 AG07497, R01 AG034556, K24 AG0350007, P50 AG015134, U19 AG10483, R01 AG027435, Fulfill Fideliosciences, Harvard NeuroDiscovery Center and the Alzheimer’s Association. These relationships are not related to the content in the manuscript. All other authors report no relevant conflicts.

Additional information
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41467-022-28986-2.
Correspondence and requests for materials should be addressed to Heidi I. L. Jacobs.
Peer review information Nature Communications thanks Arun Bokde, Jeremy Elman and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available.
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Acknowledgements
We would like to thank all the participants of the Harvard Aging Brain Study. This work was supported in part by the Gordon Center for Medical Imaging P41 EB001589, as well as shared instrumentation grants: S10OD018035, S10RR021110, S10OD10364, S10RR23401, S10RR023843, and 1S10RR01907. This research was supported by the Harvard Aging Brain Study P01 AG036694 (MPRs Reisa Sperling, MD and Keith Johnson, MD), NIH grant R01 AG042396 (PI Keith Johnson, MD), NIH grant T32 EB013180 (PI El Pakhri Georges, Ph.D), NIH grant R01AG062599 and R01AG080802 (PI Heidi Jacobo, PhD) and Deldker-Padget Dutch2USA Grant (Nina Engels-Dominguez).

Author contributions
P.C.P. and N.E.D. aided in study design, performed methods development, analyzed imaging data, performed statistical analyses, interpreted data, and wrote the manuscript. K.V.P. and D.M.R. aided in data collection, neuropsychological assessments, interpreted the results and reviewed the manuscript. N.E.D. and M.R.S. aided in data collection, study organization and data management. C.S. aided in methods development, interpreted the data and reviewed the manuscript. M.R.S., A.P.S., R.F.B. aided in MRI methods, data management and reviewed the manuscript. M.E.F and G.E.F. aided in PET methods, interpreted the results, and revised the manuscript. Y.T.Q. interpreted the results and revised the manuscript. R.A.S. and K.A.I. provided the participants, data analytic tools, aided in study design, interpreted results, and revised the manuscript. H.I.L.I., D.M.R., G.E.F. R.A.S., and K.A.I. acquired the financial support for the project leading to this publication. H.I.L.I. conceptualized this study, aided in study design, aided in methods development, aided in statistical analyses, interpreted data, revised the manuscript, and had the general supervision of the study.

The authors declare no competing interests.