Age-related Increase in Locus Coeruleus Activity and Connectivity with Prefrontal Cortex during Ambiguity Processing

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Abstract

Interpreting ambiguous environmental cues, like facial expressions, becomes increasingly challenging with age, especially as cognitive resources decline. Managing these challenges requires adaptive neural mechanisms that are essential for maintaining mental well-being. The locus coeruleus (LC), the brain's main norepinephrine source, regulates attention, arousal, and stress response. With extensive cortical connections, the LC supports adapting to cognitive demands and resolving conflicting cues from environment, particularly in later life. Previous research suggests that the LC interacts with the prefrontal cortex during high-conflict tasks. However, whether LC activity and its connectivity with the PFC support emotional ambiguity processing and contributes to emotional well-being in healthy aging remains unclear. To address this gap, we used 7T-MRI to examine LC function in 75 younger (25.8±4.02years, 35females) and 69 older adults (71.3±4.1 years, 35females) during facial emotion-recognition task morphed with varying ambiguity: anchor (unambiguous happy or fearful), intermediate-ambiguity (30% happy–70% fearful and 40%-happy–60% fearful expressions, in either direction), and absolute-ambiguity (50% happy-fearful). Behaviorally, participants had longer response times and lower confidence in the absolute-ambiguity condition, while older adults perceived ambiguous faces as happy more frequently than younger adults. Neuroimaging results revealed older adults exhibited greater LC activity and enhanced connectivity with dorsolateral PFC (dlPFC) during absolute-ambiguity compared to younger adults. This heightened connectivity in older adults was linked to better emotional resilience and mental well-being. These findings suggest greater LC activity supports managing cognitively demanding tasks, while enhanced LC-dlPFC connectivity helps maintain emotional well-being, underscoring the importance of this neural pathway for healthy aging.

Significance Statement

Understanding how the brain adapts to cognitive and emotional demands with age is key to promoting healthy aging. This study examined whether the locus coeruleus (LC), a brain region critical for regulating attention and arousal, undergoes adaptive changes with age, especially during emotional ambiguity task. Using ultra-high-field imaging, we explored younger and older adults recognize facial expressions with varying ambiguity levels. Our findings indicated that compared to young, older adults showed heightened LC activity and LC-dorsolateral prefrontal cortex (dlPFC) connectivity when processing absolute-ambiguous facial expressions, with enhanced connectivity linked to improved mental well-being. These results suggest higher LC activity supports cognitive demands of ambiguity processing with LC-dlPFC connectivity promoting emotional well-being and resilience, offering insights into mechanisms underlying healthy aging.

Introduction

Interpreting facial expressions is fundamental to everyday social interactions, yet often impaired in neurological and psychiatric conditions (Henry et al., 2016; Cotter et al., 2018). However, not all facial expressions convey a definitive emotional message. Ambiguity in facial expressions, such as a smile paired with furrowed brows, poses significant challenges in interpreting emotional intent (Berlyne, 1960; Zeki, 2004; Wang et al., 2017). Resolving such ambiguity necessitates sustained attention, arousal, and cognitive effort (FeldmanHall et al., 2016), processes essential for interpreting ambiguous signals and supporting mental well-being (Keller et al., 2019; Wolpe et al., 2024). While there are age-related differences in processing facial expressions with negative emotions (Ruffman et al., 2008; Ebner et al., 2012; Hayes et al., 2020), encoding ambiguous facial expression demands even greater cognitive effort from older adults. To navigate challenges associated with processing ambiguity, older adults tend to rely on adaptive neural mechanisms to mitigate age-related cognitive decline (Dexter & Ossmy, 2023), though these mechanisms remain largely unknown.

The locus coeruleus (LC), a small brainstem structure, plays a pivotal role in regulating key brain functions such as attention, arousal, autonomic activity, emotion, memory, and stress (Poe et al., 2020; Mather, 2016). Through its extensive projections to the prefrontal cortex (PFC; Chandler et al., 2014), particularly the dorsolateral prefrontal cortex (dlPFC) (Levinson et al., 2023; Sara, 2009), the LC-prefrontal connectivity underpins top-down regulatory mechanisms critical for resolving conflicting information (Grueschow et al., 2020), maintaining emotional balance and mental well-being (Morris et al., 2020; Ross & Vann Bockstaele, 2021; Watanabe et al., 2024). In late adulthood, structural and functional dynamics within LC and between LC-cortical regions tend to alter (Budygin et al., 2024), manifesting as a reduction in attentional focus (Lee et al., 2020) and episodic memory capacity (Dahl et al., 2023), while preserved LC structural integrity has been associated to superior episodic,

working memory and cognitive reserve (Clewett et al., 2016; Dahl et al., 2019). Additionally, elevated LC functional activity in response to emotionally salient stimuli, has also been linked to greater resilience against cognitive decline in later life (Clewett et al., 2018; Prokopiou et al., 2022; Ludwig et al., 2024). Moreover, the LC-prefrontal functional coupling supports inhibitory control among older adults (Tomassini et al., 2022), suggesting its role in compensatory adaptations for cognitive aging. Despite the significance of the LC-prefrontal pathway in cognitive performance (Mather & Harley, 2016), the specific role of this pathway in emotional processing – particularly in resolving ambiguity signals – and its association with mental well-being in late adulthood remains unexplored. Advances in neuroimaging techniques to delineate the LC with a 7-Tesla Magnetic Resonance Imaging (7T-MRI) provide a powerful tool for characterizing the LC, offering insights into adaptive processes that might ease age-related cognitive and emotional challenges during healthy aging.

The current study addresses this gap and investigates age-related differences in the LC activity and LC-prefrontal connectivity during emotional ambiguity processing and their role in promoting emotional resilience and mental well-being in healthy aging. Using ultra-high field 7T-MRI, we examined responses to an emotion recognition task among healthy younger and older adults. The task required recognition of facial expressions ranging from unambiguous (100%-fearful or 100%-happy) to varying levels of ambiguity in morphed facial expression (30% happy–70% fearful and 40% happy–60% fearful expressions, in either direction), and an absolute-ambiguous faces (50%-fearful/50%-happy). Based on prior work on age-related differences in the LC activity during emotionally salient, novelty processing and cognitively demanding tasks (Prokopiou et al., 2022; Ludwig et al., 2024), we hypothesized that older, compared to younger, adults would exhibit heightened LC responses to ambiguous expressions. While evidence is limited, based on the LC-prefrontal coupling associated with better inhibitory control (Tomassini et al., 2022), we anticipated higher connectivity between LC-

prefrontal areas during emotional ambiguity processing among older adults, and expected that this connectivity would link with mental well-being, emphasizing this pathway's relevance in promoting mental health in late adulthood.

Materials and Methods

Participants

To determine the minimum sample size required to detect a moderate-to large-sized age effect (f = .33) with 85% power (α = 0.01), our power analyses revealed that we required a minimum of 70 participants in each age category. Eighty younger and 75 older adults were recruited and scanned as part of the Trondheim Aging Brain Study (TABS). However, due to incomplete behavioral data sets, technical issues during data collection, and excessive head motion (mean framewise displacement >0.5 mm) in five young and six elderly participants, the final sample included a total of 144 participants, including 75 younger (mean age = 25.8 years, SD = 4.02; 35 females) and 69 older adults (mean age = 71.27 years, SD = 4.07; 35 females). Participants were recruited from the local community through paper flyers and online advertisements. Exclusion criteria included the presence of metallic implants, claustrophobia, or a history of neurological (e.g., neurodegenerative diseases), psychiatric disorders (major depression) or autism spectrum disorder. All participants were right-handed, had normal or corrected-to-normal vision, and reported normal hearing abilities. All older participants underwent cognitive screening using the Mini-Mental State Examination (MMSE; Folstein et al., 1975), conducted either in person or via phone using the 22-point Braztel-MMSE (REF), and participants scored above the respective thresholds of 24 and 15, confirming lack of cognitive deficits. As shown in Table 1, younger and older adults had comparable scores in cognitive and emotional empathy scores, however, older adults reported better mental well-being and higher emotional resilience, with lower scores on self-reported measures of depression, stress, and anxiety, and

performed better on the social cognitive tasks such as the Reading the Mind in the Eyes Test (RMET), compared to younger adults. In contrast, younger adults outperformed older adults in working memory, IQ, verbal fluency, and trail-making tests. All participants provided written informed consent and received compensation of 500 Norwegian Kroner in gift cards for their participation. This study was approved by the regional Ethics Committee.

Experimental design

The experimental paradigm was developed and executed using MATLAB R2017b (The MathWorks) in conjunction with the Psychtoolbox extension (http://psychtoolbox.org). The task design was adapted from the Wang and colleagues work (2017). Facial expression stimuli were generated by morphing prototypical fearful and happy faces along a continuous gradient using the Delaunay tessellation function. This method involved selecting control points on the face manually, which were then used to guide the transformation. The pixel values and their spatial locations were interpolated through piecewise cubic-spline transformation, ensuring smooth transitions between facial features across the morphing continuum (Wang et al., 2017). The process allowed for the creation of highly realistic expressions that captured varying degrees of emotional intensity and ambiguity facilitating nuanced experimental manipulation of facial stimuli. The stimuli were created at seven distinct levels of emotional intensity, ranging from 100% fear to 100% happiness. Ambiguity levels spanned from 30% fearful - 70% happiness to 70% fearful - 30% happiness, with increments of 10%, including a 50% fearful - 50% happiness condition (Fig. 1b). Low-level image properties, including Fourier amplitude spectra, mean luminance, contrast, and histogram specifications, were equalized using the SHINE toolbox (Willenbockel et al., 2010) to ensure perceptual visual quality. In total, a sample of four young and four elderly individuals (4 males and 4 females in each group) sourced from the FACES database (Ebner et al., 2010). Faces were matched for attractiveness

and distinctiveness with no difference between males and females within each emotional categories (attractiveness: $M_{male\ happy}$ = 46.29 (SD = 7.90), $M_{female\ happy}$ = 47.60 (SD = 7.15), $M_{male\ fearful}$ = 28.83 (SD = 7.84), $M_{female\ fearful}$ = 30.73 (SD = 8.62; Distinctiveness: $M_{male\ happy}$ = 45.45 (SD = 3.72), $M_{female\ happy}$ = 44.86 (SD = 4.20), $M_{male\ fearful}$ = 42.35 (SD = 3.29), $M_{female\ fearful}$ = 42.41 (SD = 5.09)). An online pilot study was conducted to gauge responses to each facial expression and ambiguity levels created for this study. Seventy-four participants (40 females) were shown morphed faces and asked to indicate emotional expressions as well as intensity of the facial expression on a 1 to 10 Likert scale. Findings of the pilot study indicated higher intensity rating for anchor images, such as happy and fearful (M = 7.57, SD = 0.80), followed by intermediate ambiguity (M = 5.86, SD = 1.05) and ambiguous faces (M = 5.02, SD = 0.83), confirming the effect of interest for ambiguity processing from FACES dataset.

The task design (Fig. 1a) was event-related where a face was presented for 1 second, followed by a question asking participants to identify the emotional expression of the face. Participants indicated their decisions (fearful or happy) by pressing a button within 2 seconds followed by a confidence rating block. Participants rated their confidence level by pressing buttons: 1 for "very sure," 2 for "sure," or 3 for "unsure.", within 2 seconds. Following confidence response rating, a cross was presented as the inter-trial intervals, which was jittered randomly, with a uniform distribution between 1 to 3.5 seconds within each run. Each participant completed a total of 168 trials with a total time of ~21 minutes across three runs. The order of runs was counterbalanced between participants and order of faces within each run was pseudorandomized, ensuring no more than two consecutive faces shared the same emotional expression, identity, or age category. Behavioral responses were collected through an MR-compatible button box.

For subsequent analyses, the conditions were grouped based on their level of ambiguity: 100% fearful and 100% happy facial expressions were categorized as an anchor condition, the 50% happy - 50% fear morphed face as an absolute-ambiguous condition, and the remaining morphed facial expression (30, 40, 60, and 70) as an intermediate-ambiguity condition. This grouping was strategically chosen to examine the age-related differences underlying the processing of different ambiguous emotional expressions.

Cognitive and emotional well-being measurements

As part of the TABS, participants completed a comprehensive series of behavioral and neuropsychological tests outside the scanner, designed to evaluate executive functioning, empathy, theory of mind, and overall mental well-being. The behavioral testing session was completed within two to four days following the imaging session followed by 7-days daily sampling method, which are not reported here. Descriptives and inferential statistics of cognitive and emotional measures are reported in Table 1. Executive control functioning was assessed using a battery of tests, including the Stroop test (Jensen & Rohwer, 1966), the Trail Making Test (both A and B parts, Reitan & Wolfson, 2004), and the Phonemic and Semantic Verbal Fluency Task (Newcombe, 1969). Theory of Mind and empathy were measured using the Reading the Mind in the Eyes Task (RMET; Baron-Cohen et al., 2001) and the Interpersonal Reactivity Index (IRI; Davis, 1980), respectively. The abbreviated version of Raven's Progressive Matrices (Raven, 1940) was used for measuring general intelligence. Emotional and mental well-being were evaluated using several validated questionnaires, including the Depression, Anxiety, and Stress Scale (DASS-21; Lovibond & Lovibond, 1995), the Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004), the General Health Questionnaire (GHQ-28; Goldberg, 1979), the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), the Connor-Davidson Resilience Scale (CD-RISC; Connor

& Davidson, 2003), the Intolerance of Uncertainty Scale (IUS; Freeston et al., 1994; Buhr & Dugas., 2002), the Perceived Stress Scale (PSS; Cohen et al., 1983) and the State-Trait Anxiety Inventory (STAI; Spielberger, 1983).

Emotional well-being factor analysis

Participants were assessed on multiple emotional and cognitive measures using established scales, and Principal Component Analysis (PCA) was applied to reduce data dimensionality for both cognitive and emotional assessments separately. This resulted in the identification of two primary indices: the 'Emotional Resilience Index', which captures the multidimensional construct of emotional resilience and mental well-being, and the 'Cognitive Function Index', representing performance on cognitive tasks. Sampling adequacy for the Emotional Resilience Index was confirmed with a high Kaiser-Meyer-Olkin (KMO) value of 0.918, while Bartlett's test of sphericity indicated strong correlations among variables ($\chi^2_{(142)} = 105$, $p < 0.001$) (Masullo et al., 2021). For the Cognitive Function Index, a moderate KMO value of 0.67 was observed, with Bartlett's test similarly confirming strong correlations among variables ($\chi^2_{(142)} = 21$, $p < 0.001$). PCA components were considered significant if their eigenvalues exceeded 1. The Emotional Resilience Index loaded on two significant components, explaining 63.94% of the variance in total, with the first component explaining 57.05% of variance. In contrast, the Cognitive Function Index loaded on three significant components, accounting for 72.69% of the total variance, with the first and second component explaining 37.26% and 20.06%, respectively. Composite scores for both indices were calculated as weighted sums of the factor scores, with weights determined by the variance explained by each factor (Antony & Rao, 2007). The Emotional Resilience Index reflects an individual’s ability to feel, manage and regulate emotional responses, along with adapting to uncertain situations. The Cognitive Function Index serves as a comprehensive measure of cognitive performance, encompassing

key domains such as verbal ability (assessed through COWAT Phonemic and Semantic tasks), working memory (evaluated via forward and backward digit span tests), and inhibitory control (measured using the Stroop task). To enhance interpretability, scores for the Emotional Resilience Index were inverted, indicating higher values for better emotional resilience.

Behavioral data analyses

Behavioral results are presented in Figure1. Response bias, response times (RT) and confidence rating were analyzed separately. Given that the ambiguity responses do not have any correct responses, we included all responses for behavioral analyses. For statistical analysis, a 2 (age group: young, old) by 3 (ambiguity level: anchor, intermediate, absolute-ambiguous) repeated-measures analysis of variance (ANOVA) was conducted, with RT and confidence rating as dependent variables. This analysis allowed for the evaluation of both between-group differences in age and ambiguity level, as well as the interaction between factors.

The responses to faces were analyzed using a logistic function to generate the smooth psychometric curves shown in Fig. 1c similar to Wang et al. (2017):

$$P(x) = \frac{P_{\infty}}{1 + e^{-\alpha(x - x_{\mathrm{half}})}}$$

where P represents the percentage of trials where faces were judged as fearful, $\boldsymbol{x}$ is the morph level, P_{∞} is the maximum value as $\boldsymbol{x}$ approaches infinity, $\boldsymbol{x}_{\mathrm{half}}$ is the curve's midpoint, and α indicates curve steepness. These parameters (P_{∞}, $\boldsymbol{x}_{\mathrm{half}}$ and α) were fitted to each subject's data from the emotion perception task. Flatter curves (lower α) indicate reduced sensitivity to emotion changes, while steeper curves (higher α) indicate greater sensitivity.

MRI acquisition and analyses

Image acquisition

MR scans were acquired on a 7T Siemens MAGNETOM Terra scanner with a 32-channel head coil at the Norwegian 7T MR Center at St. Olav's Hospital. First, high-resolution anatomical T1-weighted (T1w) images were acquired using a MP2RAGE sequence (Marques et al., 2009; voxel size = 0.75 mm^3, with 224 slices, repetition time (TR) = 4300 ms, echo time (TE) = 1.99 ms, flip angles = 5°/6°, field-of-view (FOV) = 240 x 240 x 175 and slice thickness = 0.75 mm). To achieve high-resolution imaging of the LC, we employed a magnetization transfer-weighted turbo flash (MT-TFL) sequence (Priovoulos et al., 2018), which is sensitive to LC contrast and utilizes a multi-shot 3D readout (voxel size = 0.4 × 0.4 × 0.5 mm, with 60 slices, TR = 400 ms, TE = 2.55 ms, flip angle = 8°). The FOV for the MT-TFL sequence was positioned approximately perpendicular to the pons, encompassing the region between the inferior colliculus and the inferior border of the pons. Whole-brain functional images were collected using $T2^*$-weighted echo-planar image sequence (90 interleaved slices, TR = 2s, TE = 35 ms, voxel size = 1.25 mm^3, slice thickness = 1.25mm, multiband factor = 2, flip angle = 80°, FOV = 200 x 200 x 112.5 mm).

Template creation and LC delineation

The procedure of the LC delineation is shown in Figure 2. The MT-TFL and whole-brain T1w images were utilized to create a study-specific template using the *antsMultivariateTemplateConstruction2.sh* function from Advanced Normalization Tools (ANTs). This process employed default parameters, with the exception that rigid-body registration was enabled. Prior to template construction of T1w, intensity non-uniformity was corrected using the *N4BiasFieldCorrection* method within ANTs (Tustison et al., 2010). To

delineate LC structure, we followed the methodology outlined by Van Egroo et al. (2021, 2023; Fig. 2). Briefly, individual MT-TFL images were intensity-normalized by dividing each image by the subject-specific mean intensity measured within a 10x10 voxel region of interest (ROI) located in the pontine tegmentum (PT). For each individual participant, the PT-ROI was consistently placed in the axial slice containing the highest intensity LC voxel identified by the first author (Fig. 2b). Subsequently, a study-specific template was constructed from these intensity-normalized MT-TFL images (Fig. 2c) using the *antsMultivariateTemplateConstruction2* function in ANTs (Avants et al. 2010), with the transformation model and similarity metric set to greedy SyN and cross-correlation, respectively. The LC was manually delineated on the resulting template (Fig. 2d, step 1) based on voxel intensities and anatomical characteristics using ITK-SNAP (by first author). This segmentation was repeated four weeks later by the first author, and only voxels identified in both sessions were included in the final segmentation (Jacobs et al., 2020).

Spatial transformation of LC

To facilitate spatial transformations across scans acquired at different resolutions, LC-sensitive structural images and LC segmentations were resampled to match the isotropic voxel resolution of the T1w images using the *mri_convert* function in FreeSurfer (Version 7.1; https://surfer.nmr.mgh.harvard.edu/, Martinos Center for Biomedical Imaging, Charlestown, Massachusetts). This resampling minimized interpolation errors and ensured accurate alignment during subsequent registration steps.

All spatial transformations were conducted using the deformable SyN algorithm in ANTs (Klein et al., 2009), known for its high precision and flexibility. First, the study-specific MT-TFL template slab (Fig. 2d) was linearly registered to the whole-brain study-specific T1w template using the *antsRegistrationSyN* function (Step 2 – red arrow). The T1w template served

as an intermediate bridge to facilitate the transformation of MT-TFL images into MNI space. Next, the whole-brain study-specific T1w template (Fig. 2e) was non-linearly registered to MNI space (Fig. 2f) using the *antsRegistrationSyN* function (Step 3 – green arrow). The transformation matrices obtained from step 2 and 3 during registration steps (Fig. 2e and Fig. 2f) were then applied to transform the LC segmentations, delineated on MT-TFL LC-sensitive structural scans into MNI space using *antsApplyTransforms* in a single step (Fig. 2g). Individual LC segmentations were transformed using the nearest neighbor option to avoid creating ambiguous voxels during the interpolation process (Yi et al., 2023), ensuring clear association with the original LC segmentation.

fMRI analyses

Analyses of fMRI data during preprocessing and statistical modeling steps were conducted using fMRIPrep version 22.0.2 (Esteban et al. 2019) and Statistical Parametric Mapping 12 (SPM12; Wellcome Centre for Human Neuroimaging, University College, London, UK, 2012), respectively. The raw DICOM data were converted to NIfTI format, preserving the original imaging parameters. The initial three volumes were discarded to eliminate transient effects in the MR signal. Preprocessing of the functional data was performed using the default fMRIPrep pipeline (Esteban et al. 2019), which includes slice timing correction, realignment, co-registration with the T1w image using boundary-based registration (FreeSurfer; Greve and Fischl 2009), normalization to MNI standard space. Due to small size of the LC, smoothing was performed with a 2mm FWHM Gaussian kernel, following the recommendation to use a kernel of at least 1.5 times the native voxel size (Worsley and Friston, 1995; Yi et al., 2023). The choice of using a 2mm smoothing kernel was to ensure maintaining spatial precision to avoid signal blurring (Yi et al., 2023).

The first-level analysis was performed using SPM12 in Matlab (Mathworks). For each participant, contrast images were modeled in the framework of the general linear model (GLM) for each of the seven conditions. Each event was modeled based on trial onset of faces and to control for potential confounding factors, head motion parameters were included as regressors minimizing the influence of motion-related artifacts. The regressors of interest were convolved with the hemodynamic response function (HRF). Additionally, five aCompCor regressors were used to account for noise in the data (Behzadi et al., 2007), as physiological measurements (e.g., cardiac and respiratory signals) were not available. To minimize the impact of movement artifacts, which high-resolution functional images are particularly susceptible to (Havsteen et al., 2017), we excluded subjects with severe motion (mean framewise displacement $\geq$ 0.5mm, Power et al., 2011). This conservative approach allowed for a more accurate modeling of neural activity associated with each condition (Siegele et al., 2013). The main effects of each condition were examined to identify the activation of ROI by different levels of emotional ambiguity. Group data were analyzed in a random-effects model that differentiated between conditions and parametric maps were generated using *t* statistics. All results are reported in MNI space. One-sample *t*-tests were used to analyze group-level effects across age for anchor, intermediate and absolute-ambiguity conditions, while two-sample *t*-tests compared neural responses between young and older adults' groups. For analyses of the LC, an inclusive brainstem mask (Beissner et al., 2013) was applied. Voxels were thresholded at $p<0.005$ and reported significant after surviving a family-wise error (FWE) corrected level of $p<0.05$. Given the small size of the LC, we applied small volume correction (SVC) to evaluate significant activations in the second-level analyses (Fig. 2g).

All analyses were performed with gender and years of education as a covariate and a gray matter mask was used for whole-brain analyses (Fonov et al., 2011). Cortical and subcortical

regions were defined using anatomical masks extracted from the AAL3 atlas (Rolls et al., 2020).

Functional connectivity analyses

To further explore the connection between the LC and prefrontal areas, we conducted functional connectivity (FC) analyses. The regions of PFC such as dlPFC and dmPFC were selected as regions of interest due to their well-established roles in conflict resolution (Grueschow et al., 2020; Sun et al., 2023). Additionally, we performed control analyses with other ROIs, including the ventromedial prefrontal cortex (vmPFC), insula, and anterior cingulate cortex (ACC), given their involvement in conflict processing, processing emotional ambiguity and decision-making (Sun et al., 2017; Suzuki & Tanaka, 2021; Wu et al., 2021; Ince et al., 2023).

We employed Generalized Psychophysiological Interaction (gPPI) analysis using the CONN toolbox (v22.a, Nieto-Castanon & Whitfield-Gabrieli 2022). These analyses were guided by our initial hypothesis regarding age-related changes in the LC connectivity with broader cortical PFC regions. The gPPI approach examines condition-specific changes in connectivity by modeling the interaction between psychological variables (e.g., task conditions) and the physiological time series extracted from the seed region. For the current analyses, the LC was selected as the seed region, while the dlPFC, dmPFC, vmPFC, insula and ACC were chosen as the target ROIs. The connectivity profiles of LC (seed) and target ROIs were assessed across each of the seven emotional conditions, which ranged from absolute fear to absolute happiness (anchor), several intermediate conditions and absolute ambiguity levels. The gPPI model included all conditions, generating beta coefficients that reflect the strength of connectivity between the seed and target ROIs under each condition. Additionally, gPPI measures represent the level of task-modulated connectivity between two ROIs (i.e., changes in functional

association strength covarying with the external or experimental factor). gPPI is computed using a separate multiple regression model for each target ROI timeseries (outcome). Each model includes as predictors: a) all the selected task effects (main psychological factor in PPI nomenclature); b) each seed ROI-BOLD timeseries (main physiological factor in PPI nomenclature); and c) the interaction term specified as the product of (a) and (b) (PPI term; Nieto-Castanon, 2020). Results were thresholded using a combination of a cluster-forming $p<0.05$ connection threshold, and a familywise corrected $p_{FDR}<0.05$ cluster-size threshold (Chumbley et al., 2009). To investigate age-related differences in ambiguity processing, the conditions were grouped based on their ambiguity levels: 100% fearful and 100% happy were classified as the anchor condition, 50-50 fearful/happy as the absolute-ambiguity condition, and 30%, 40%, 60%, and 70% fearful/happy as the intermediate ambiguity condition.

Results

Behavioral

Age-Related performance during emotional ambiguity processing

Analyses on behavioral responses using two sample *t*-test revealed significant lower x_{half} value among older adults (x_{half} = 49.45 ± 6.03) compared to younger counterparts (x_{half} = 53.08 ± 6.05, Fig. 1c), indicating that older adults were more inclined to perceive ambiguous faces as happy ($t_{(142)}$ = -3.06, p = 0.0004, d = -0.60). However, the steepness of the psychometric curve (α) did not show a significant difference between the two age groups ($t_{(142)}$ = 1.33, p = 0.186, d = 0.21), suggesting that while older adults were more likely to perceive ambiguous faces as happy, the overall sensitivity to changes in emotional intensity was similar to younger adults.

A 2 (age group: young and old) by 3 (ambiguity level: anchor, intermediate, and absolute-ambiguous) repeated-measures analysis of variance (ANOVA) was conducted with RT as the dependent variable. The analysis revealed no significant main effect of age group, $F_{(1, 142)}$ =

0.31, $p = 0.572$, $\eta^2 = 0.002$, but a significant main effect of ambiguity level, $F_{(2, 284)} = 79.36$, $p = 4.156 \times 10^{-28}$, $\eta^2 = 0.5$ (Fig. 1f). Follow-up analyses revealed that RTs were significantly longer for absolute-ambiguous faces compared to intermediate ambiguous ($t_{(142)} = 7.08$, $p = 1.41 \times 10^{-11}$, Hedge's g = 0.39) and anchor faces ($t_{(142)} = 9.95$, $p = 1.11 \times 10^{-18}$, Hedge's g = 0.96) regardless of age. Additionally, no significant interaction between age group and conditions were observed, $F_{(2, 284)} = 0.33$, $p = 0.71$, $\eta^2 = 0.002$, indicating that the effect of different ambiguity levels on RT was similar across younger and older adults.

A similar ANOVA analysis with confidence ratings as the dependent variable revealed significant main effects for both age group, $F_{(1, 142)} = 10.48$, $p = 0.0015$, $\eta^2 = 0.07$ with post hoc analysis suggesting lower confidence in older compared to younger adults regardless of ambiguity condition ($t_{(142)} = -11.84$, $p = 1.02 \times 10^{-11}$, Hedge's $g = -0.17$). Additionally, significant main effect of ambiguity level was also observed $F(2, 284) = 441.78$, $p = 1.26 \times 10^{-87}$, $\eta^2 = 0.75$ with post hoc analyses indicating that absolute-ambiguity resulted in significantly lower confidence compared to unambiguous conditions ($t_{(142)} = 40.88$, $p = 4.01 \times 10^{-12}$, Hedge's $g = 1.09$) and intermediate ambiguity condition ($t_{(142)} = 15.37$, $p = 4.01 \times 10^{-12}$, Hedge's $g = 0.32$) regardless of age. The interaction between age group and ambiguity level did not reach significance, $F_{(2, 284)} = 2.36$, $p = 0.097$, $\eta^2 = 0.16$, indicating that the effect of ambiguity levels on confidence was similar for both younger and older adults.

Age-related improvement in emotional well-being

Our analysis of emotional well-being revealed that older adults had significantly better 'Emotional Resilience Index' derived from the PCA analysis ($t_{(142)} = -8.32$, $p < 0.001$, $d = 1.40$), indicating greater emotional well-being compared to younger adults. In contrast, PCA of Cognitive Function Index showed that younger, compared to older, adults performed better in

cognitive tasks ($t_{(142)}$ = 6.382, p < 0.001, d = 1.07), All individual measurements and differences between two age groups are reported in Table 1.

fMRI results

Neural underpinnings of emotional ambiguity processing across age

First, we examined emotional ambiguity processing across age groups using a one-sample *t*-test. The results revealed significant activation in several key regions: bilateral middle frontal gyrus, bilateral inferior frontal gyrus, bilateral superior frontal gyrus, bilateral insula, bilateral superior temporal gyrus, bilateral middle temporal gyrus, bilateral postcentral gyrus, bilateral precentral gyrus, bilateral angular gyrus, and bilateral putamen.

Age-related differences during emotional absolute-ambiguity processing

Next, to examine our primary hypothesis on the age-related differences during ambiguity processing, a two-tailed *t*-test was conducted. Younger, compared to older adults, exhibited significantly greater activation in regions associated with sensory processing, cognitive control, and emotional regulation, including the left postcentral gyrus, bilateral insula, bilateral middle frontal gyrus, bilateral inferior frontal gyrus, right dorsolateral superior frontal gyrus, right angular gyrus, left hippocampus, right caudate, left precentral gyrus, and right superior medial gyrus (Table 2a). In contrast, older adults demonstrated greater activation in the right fusiform gyrus, right lingual gyrus, and left thalamus, compared to younger adults (Table 2b).

Although not the primary focus of this study, we examined age-related differences in brain activation during the anchor and intermediate conditions. For the anchor condition, younger adults exhibited heightened recruitment in regions such as the bilateral insula and left postcentral gyrus compared to older adults (Extended Table 2-1a). Conversely, older adults

demonstrated greater activation in posterior and visual regions, including the bilateral fusiform gyrus, posterior cingulate cortex, bilateral calcarine cortex, and bilateral precentral gyrus compared to younger adults (Extended Table 2-1b). For the intermediate condition, younger adults showed increased engagement in areas such as the left postcentral gyrus, mid cingulate cortex, bilateral insula, bilateral supramarginal gyrus, left hippocampus, and right middle frontal gyrus compared to older adults (Extended Table 2-2a). In contrast, older adults exhibited greater activation in regions such as the bilateral caudate, thalamus, and occipital fusiform gyrus compared to younger adults (Extended Table 2-2b).

Higher LC activation in older compared to younger adults during emotional absolute-ambiguity processing

In line with our second hypothesis, during the absolute-ambiguity condition, we observed significant higher activity in the left LC among older adults compared to younger adults [Fig. 3a; t = 3.51, P_{FWE} = *0.024, cluster size = 6,* MNI-coordinates of peak voxel, x = -5; y = -38; z= -24]. However, we did not find any age-related significant differences in LC activity in neither anchor nor intermediate condition, all ps > 0.05.

Next, we investigated the relationship between LC activity and RTs during absolute-ambiguity condition. The results revealed a significant positive correlation between the LC activity and RTs during absolute-ambiguity processing in older adults (Fig. 3b; r = 0.27, p = 0.032, 95% CI = [0.02, 0.49]), indicating heightened LC activation was associated with longer RTs during ambiguous condition. The relationship was not significant among younger adults (r = -0.10, p = 0.401, 95% CI = [-0.33, 0.14]).

Furthermore, we correlated the LC activity with emotional well-being measures. Our results showed a positive correlation between self-reported stress scores and LC activity (Fig. 3c) in

both younger adults (r = 0.37, p = 0.001, *95% CI* = [0.15, 0.55]) and older adults (r = 0.28, p = 0.026, 95% CI = [0.04, 0.50]), indicating the association between LC activation and greater reported stress levels regardless of age. Outliers for LC activation were assessed using the Interquartile Range (IQR) method, and all data points were found to fall within the range of -3 to +3, indicating no outliers. A bootstrapped correlation analysis using 1,000 iterations confirmed the robustness of these findings, showing consistent results for both RT [*95% CI*: 0.018, 0.504; mean r = *0.278*] and stress scores [*95% CI:* 0.027, 0.475; mean r = 0.252] in older adults. Additionally, our post-hoc analyses revealed no significant correlation between LC activity and 4th ventricles (r = -0.01, p > 0.8, uncorrected), ensuring the reliability of our findings.

Higher LC-dlPFC in older compared to younger adults during emotional absolute-ambiguity processing

To address our third hypothesis and further investigate age-related differences in the LC connectivity with PFC regions, we compared LC connectivity patterns between younger and older adults during the absolute-ambiguity condition. Notably, older adults demonstrated stronger connectivity between the LC and right dlPFC compared to younger adults (β = 0.12, t = 2.26, p = 0.024, P_{FDR} = 0.045), indicating an age-related increase in the LC-dlPFC connectivity (Fig. 4). In contrast, no significant age-related differences were found for the LC-left dlPFC connectivity (β = 0.09, t = 1.40, p = 0.16) and LC-dmPFC connectivity on either side (right: β = 0.10, t = 1.40, p = 0.16; left: β = 0.11, t = 1.11, p = 0.27). Similarly, no significant age-related differences were found for the LC connectivity with other areas such as the vmPFC, insula, or ACC (all ps > 0.05) in absolute-ambiguity condition, suggesting specificity of LC-dlPFC connectivity during ambiguity processing. Lastly, no significant differences in LC

connectivity with the dmPFC, dlPFC, vmPFC, insula, or ACC were observed during the anchor or intermediate ambiguity conditions (all *p*s > 0.05).

Higher LC-dlPFC connectivity links with emotional resilience among older adults

To investigate our final hypothesis regarding age-related differences in the LC-dlPFC connectivity during the ambiguity condition and its association with emotional resilience and well-being, we examined whether the observed LC-dlPFC connectivity correlated with emotional well-being outcomes. Among older adults, stronger left LC and right dlPFC connectivity was significantly associated with reduced stress level (Fig. 4d; r = -0.34, p = 0.006, 95% CI = [-0.54, -0.10]) and lower anxiety level (Fig. 4e; r = -0.34, p = 0.006, 95% CI = [-0.54, -0.11]). Additionally, this higher LC-dlPFC connectivity was linked to better emotional resilience (Fig. 4c; r = 0.26, p = 0.042, 95% CI = [0.01, 0.47]). In contrast, no significant associations were observed between the LC-dlPFC connectivity and emotional well-being measures among younger adults for stress (r = -0.11, p = 0.370, 95% CI = [-0.33, 0.12]), anxiety (r = 0.09, p = 0.442, 95% CI = [-0.14, 0.31]), or emotional resilience (r = -0.11, p = 0.355, 95% CI = [-0.33, 0.12]).

Additional analyses were conducted using the cognitive function index, which incorporates cognitive and executive control measures (reported in Table 1). No significant associations were observed for both older adults (r = 0.24, p = 0.059, 95% CI = [-0.01, 0.46]) and younger adults (r = -0.19, p = 0.114, 95% CI = [-0.40, 0.04]) with LC-dlPFC connectivity.

Discussion

The present study investigated age-related differences in the LC activity and LC-PFC connectivity during emotional ambiguity processing. Our findings revealed heightened LC activity and stronger connectivity with the dlPFC in older compared to younger participants,

specifically in absolute-ambiguity condition. Notably, this enhanced LC-dlPFC connectivity associated with greater emotional resilience and mental wellbeing in older adults, indicating the importance of this pathway for maintaining mental wellbeing in healthy aging.

Positivity bias and better emotional resilience among older adults

Behaviorally, both younger and older adults showed increased RTs when processing ambiguous faces, but only older adults exhibited a positivity bias, interpreting ambiguous faces as happy more frequently than fearful. This aligns with the socioemotional selectivity theory observed in aging populations (Petro et al., 2021; Carstensen & DeLiema, 2017). The positivity bias is consistent with findings in attention (Kim & Barber, 2022), memory (Charles et al., 2003; Ziaei et al., 2016), emotion recognition (Ziaei et al., 2015, 2016), and empathy (Ziaei et al., 2021). Older adults also demonstrated higher emotional resilience, suggesting their better mental well-being may reflect their tendency to interpret ambiguous signals more positively. The longer RTs for both groups indicate greater cognitive demands in processing ambiguous expressions (Kaminska et al., 2020), while lower confidence ratings during ambiguous trials highlight the task's difficulty compared to unambiguous or intermediate conditions (Wang et al., 2017).

Age-related enhanced LC activity during absolute-ambiguous condition

Neuroimaging results revealed that older adults exhibited elevated LC activity compared to younger adults during the processing of emotional ambiguity. This heightened LC activity in older adults associated with longer RTs, indicating greater cognitive effort required to process emotionally ambiguous stimuli. Supporting this interpretation, prior studies have shown that longer RTs are often linked to greater cognitive demands during tasks involving the resolution of conflicting information (Neto et al., 2021; Parr et al., 2023). In addition, this finding corroborates previous research that highlights the role of the LC-NE system in ambiguity

resolution, particularly in supporting cognitive processes required to manage uncertainty in decision making (Payzan-LeNestour et al., 2013).

Furthermore, the observed elevated LC activity among older adults aligns with the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH). According to this hypothesis, older adults recruit additional neural resources to maintain cognitive functioning under increasing cognitive demands, compared to younger adults (Reuter-Lorenz & Cappell, 2008). Given that aging is accompanied by widespread changes in the brain's structural and functional connections (Grady, 2012; Schulz et al., 2022; Kim & Kim, 2023; Jauny et al., 2024), older adults may employ adaptive neural mechanisms to maintain attention and arousal to resolve conflicting stimuli, in tasks such as processing emotional ambiguity.

In the context of the current study, the LC-NE system plays a critical role in adaptive processes during healthy aging by enhancing task-relevant neural activity (Aston-Jones & Cohen, 2005). For example, the LC's involvement in tasks such as the emotional Stroop-task where participants must resolve conflicting demands of words and emotional expressions, demonstrated its essential role in cognitive control and attentional flexibility (Grueschow et al., 2020). Recent studies have also highlighted higher LC activity among older adults during emotionally salient tasks such as reversal reinforcement learning task (Ludwig et al., 2024) and during novel face encoding (Prokopiou et al., 2022). We extended these findings by demonstrating that older adults exhibit higher LC activity during emotional ambiguity processing. This higher LC activity, compared to younger adults, enables older individuals to allocate additional cognitive resources to manage the heightened demands of resolving ambiguous stimuli, highlighting the critical role of the LC-NE system in supporting cognitive functions during healthy aging.

The enhanced engagement of the LC-NE system is also closely linked to cognitive reserve, which allows older adults to sustain cognitive performance despite age-related neural changes (Stern, 2009; Mather, 2016). The NE released during cognitively demanding tasks provides neuroprotective benefits that help to mitigate inflammation and neurodegenerative disorders in late life (Heneka et al., 2010). In the context of ambiguity processing, attention, arousal, cognitive effort, and exposure to novelty associated with emotional ambiguity processing might enhance the LC activation, ultimately supporting cognitive functions critical for resolving ambiguous signals in older compared to younger adults. This aligns with previous studies which demonstrate that enhanced LC activity is essential for maintaining cognitive functions in healthy aging (del Cerro et al., 2020; Prokopiou et al., 2022; Ludwig et al., 2024). Previously, higher activations among older adults have been reported as a compensation of declining cognitive capacity (Aron et al., 2022). However, contrasting findings of no age-related difference in LC activity have also been noted (Berger et al., 2023). From the conceptual standpoint, heightened LC activity in late adulthood may stem from region's high metabolic demand, which makes it particularly susceptible to reactive oxygen species and other toxins generated as byproducts of its activity with increasing age (Kelly et al., 2021; Matchett et al., 2021). These stressors can affect LC function, prompting the remaining neurons to compensate by increasing their activity to sustain optimal cognitive function (Szot et al., 2016). Additionally, individual differences in vascular characteristics, such as in LC blood supply, may contribute to variability in the LC activation and cognitive performance among older adults observed previously (Bekar et al., 2012; Giorgi et al., 2020). Future studies are needed to further explore mechanisms underlying this neuronal compensation in the LC especially in the context of healthy aging.

Age-related enhanced LC-dlPFC connectivity and emotional well-being

Our results also revealed higher functional connectivity between the LC and dlPFC among older compared to younger adults during processing of absolute-ambiguous facial expressions. This finding supports the hypothesis that processing emotional ambiguity becomes increasingly cognitively demanding with age (Liebherr et al.,2017; Gaubert et al., 2023) requiring additional neural connections to compensate for age-related cognitive decline. The role of dlPFC is well-established as a key region for cognitive effort and conflict resolution (Kane & Engle, 2002; Rahnev, 2016). Previous studies in aged monkeys have shown that the LC-NE system plays a crucial role in maintaining the stability of dlPFC functioning. This is achieved through the phasic release of norepinephrine, which enhances the dlPFC's connectivity with the LC and supports working memory performance in aging (Arnsten et al., 2012; Cools & Arnsten, 2021). Consistent with these findings, our study suggests that stronger functional connectivity between the LC and the right dlPFC in older adults' aids in processing ambiguity and resolving ambiguous signals compared to young individuals. The observed laterality can be attributed to the functional specialization of the dlPFC, with the right dlPFC being more attuned to visual affective content and the left dlPFC primarily involved in processing verbal content (White et al., 2023).

Importantly, LC-dlPFC connectivity was associated with better emotional wellbeing in older adults, evidenced by lower anxiety and stress scores, and higher emotional resilience. This suggests that the LC-dlPFC pathway plays a crucial role in maintaining emotional stability with age. The results are in line with the autonomic compensation model that posits age-related norepinephrine hyperactivity and its connectivity with PFC aids emotional well-being in late life (Mather, 2024). Additionally, the dlPFC established role in stress and anxiety regulation (White et al., 2023), executive functions, such as cognitive control and emotional regulation (Chen et al., 2023; Nejati et al., 2021) supports this interpretation that the LC-dlPFC connectivity reflects top-down control mechanism, buffering against negative emotional states

and promoting emotional resilience in later life. Future research should examine whether the LC-dlPFC connection persists during stress-related tasks and its role in regulating emotional distress in real-life scenarios. Additionally, investigating the directionality of this connection could provide novel insights into the neural mechanisms underlying emotional regulation in aging populations. Lastly, no age-related differences were observed in the dmPFC, vmPFC, insula, or ACC, underscoring the LC-dlPFC connection's unique role in processing emotional ambiguity and its link with mental well-being in healthy aging.

Limitations

This study has limitations. First, using static facial expressions may not fully reflect the complexity of real-life emotional processing or the ambiguity in emotional situations (Trautmann et al., 2009). Dynamic facial expressions could offer a more ecologically valid assessment of emotional ambiguity and better insights into LC activity during real-life processing. Second, the LC's proximity to the 4th ventricle makes it susceptible to physiological artifacts, such as cardiac pulsatility and respiratory fluctuations. While aCompCor was used to regress noise from white matter and cerebrospinal fluid, future studies should include physiological measures to further minimize noise. Notably, our post-hoc analyses revealed no significant correlation between LC activity and the 4th ventricle, supporting the reliability of our findings.

In summary, our study highlights the pivotal role of LC activity and its connectivity with the dlPFC during emotional absolute-ambiguous task, and its link with better emotional resilience and mental well-being in older adults. Our findings revealed heightened LC activity and stronger LC-dlPFC connectivity in older adults compared to younger individuals, highlighting the importance of this neural pathway in managing cognitively demanding tasks while maintaining emotional wellbeing in healthy aging. By emphasizing the significance of this

functional connectivity in promoting healthy aging, our results open avenues for future research into targeted interventions aimed at enhancing cognitive functions, and emotional well-being in late adulthood.

Footnotes

- We would like to thank radiographers and MR physicists at the 7T MR center at NTNU for their help during this project. We also would like to thank our participants for their time and effort during the experiment. We thank Jørgen Østmo-Sæter Olsnes, Stian Framvik, Avneesh Jain, Jae Hong, and Karina Tømmerdal for their help during data collection. This project was funded by Kavli Foundation and was partially supported by the Research Council of Norway through its Centers of Excellence scheme, project number 332640.
- The authors declare no competing financial interests

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- Data availability: Behavioral data, ROI signals and the stimuli can be found in the Open Science Framework from this link: https://osf.io/7v2ez

Tables

Table 1: Participant Demographics, Cognitive Behavioral Task Performance, and Self-Reported Measures for Younger and Older Adults

Measurement	**Younger adults**		**Older adults**		**Older>Younger**
	Mean	***SD***	***Mean***	***SD***	***Independent t-test***
Demographic					
Age	25.80	4.02	71.30	4.11	67.59**
Gender	40M, 35F	-	34M,35F	-	-
Years of Education	16.79	4.11	12.05	4.62	-6.43**
Cognition					
Trail Making (B-A)	26.67	15.62	42.63	41.75	3.01*
Raven's Progressive Matrices	0.77	0.16	0.49	0.26	-8.60**
Digit Span - forward	6.15	1.32	5.23	1.38	-4.06**
Digit Span - backward	5.19	1.14	3.91	1.17	-6.62**
Stroop effect	0.21	0.15	0.31	0.16	3.90**
COWAT - Phonemic	12.60	3.68	15.50	4.56	4.56*
COWAT - Semantic	15.57	4.06	15.66	3.58	-0.40
RMET	0.66	0.12	0.60	0.11	-3.26**
Well-being measurements					
DASS - Depression	9.97	9.17	2.43	3.12	-6.49**
DASS – Anxiety	8.72	6.48	2.14	2.84	-7.77**

DASS - Stress	13.23	7.99	5.33	5.66	-7.36**
DERS	80.59	17.44	67.03	9.58	-5.71**
GHQ28 – somatic symptoms	13.00	3.46	10.32	2.07	-5.58**
GHQ28 - Anxiety/Insomnia	12.93	3.86	10.33	2.52	-4.74**
GHQ28 – Social Dysfunction	13.79	2.89	13.26	1.57	-1.34
GHQ28 – Severe Depression	10.25	3.99	7.51	1.22	-5.48**
HADS – Depression	4.51	3.58	1.46	1.47	-6.57**
HADS – Anxiety	6.75	3.51	2.88	2.33	-7.70**
CD-RISC	68.97	14.33	76.62	9.28	3.77**
PSS	1.63	0.65	1.05	0.38	-6.30**
IUS	59.08	15.90	46.61	14.18	-4.95**
IRI Cognitive empathy	34.56	8.84	32.01	6.92	-1.91
IRI Perspective Taking	18.61	4.33	18.78	3.78	0.22
IRI Fantasy Scale	15.94	6.44	13.24	5.13	-2.79**
IRI Emotional empathy	30.50	7.73	31.94	6.62	1.21
IRI Empathic concern scale	18.98	4.77	20.42	4.32	1.91
IRI Personal distress scale	11.53	5.19	11.52	4.15	-0.01
STAI-state anxiety	34.92	10.20	27.8	6.30	-5.19**
STAI-trait anxiety	35.53	9.30	25.0	5.20	-8.71**

PCA Composite Scores					
Emotional Resilience Index	-0.54	1.03	0.60	0.49	-8.32**
Cognitive Function Index	0.45	0.71	-0.49	1.03	6.38**
Task performance					
RT (milliseconds)					
Anchor	0.60	0.10	0.63	0.11	-0.24
Intermediate Ambiguity	0.69	0.12	0.68	0.14	0.09
Absolute-Ambiguity	0.75	0.14	0.72	0.20	0.12
Response bias					
Ratio of happy responses	49.45	6.03	53.08	6.05	-3.60**
Confidence rating					
Anchor	1.60	0.69	1.76	0.73	-1.32
Intermediate	1.94	0.81	2.23	0.71	-2.33*
Absolute-Ambiguity	1.37	0.65	1.51	0.70	-1.22

*Note: Stroop Effect (a measure of cognitive interference measured by response time in incongruent trials – response time in neutral trials)/response time in neutral trials); COWAT (Controlled Oral Word Association Test); RMET (Reading the Mind in the Eyes Test); DASS (Depression Anxiety Stress Scales); DERS (Difficulties in Emotion Regulation Scale; GHQ (General Health Questionnaire), HADS (Hospital Anxiety and Depression Scale); CD-RISC (Connor-Davidson Resilience Scale), PSS (Perceived Stress Scale); IUS (Intolerance of Uncertainty Scale); IRI (Interpersonal Reactivity Index); STAI (State-Trait Anxiety Inventory); PCA (Principal component Analysis);*p<0.05, **p<0.001.*

678 **Table 2:** Peak coordinates for significant clusters from whole-brain analyses during emotional
679 ambiguity condition
680

Region	Hemisphere	BA	MNI coordinates	*t*-value	Cluster Size
a. Younger > Older adults					
Postcentral gyrus	L	2	[-66 -21 26]	6.30	611
Superior frontal gyrus-dorsolateral	R	39	[24 22 55]	5.88	258
Middle frontal gyrus	L	9	[-48 8 46]	5.40	85
	R	9	[40 10 45]	5.00	197
Inferior frontal gyrus	L	48	[-54 -12 13]	4.69	40
	R	47	[44 22 -11]	4.82	65
Insula	L	48	[-40 1 10]	5.04	52
	R	48	[44 -12 6]	4.73	84
Caudate	R	25	[10 22 4]	4.94	95
Precentral gyrus	L	20	[-35 -18 45]	4.77	69
Superior Medial Gyrus	R	32	[1 34 34]	4.76	93
Hippocampus	L	-	[-25 -39 5]	4.93	55
Angular gyrus	R	39	[52 -52 26]	4.35	41
b. Older > Younger adults					
Thalamus	L	-	[-14 -25 8]	4.35	72
Occipital fusiform gyrus	R	19	[34 -82 4]	4.42	50

Lingual gyrus	R	18	[11 -90 -7]	4.30	48

BA = Broadman Areas; MNI = Montreal Neurological Institute; L = left; R = right; p<.001 cluster size ≥ 40 voxels

Figures

Figure 1

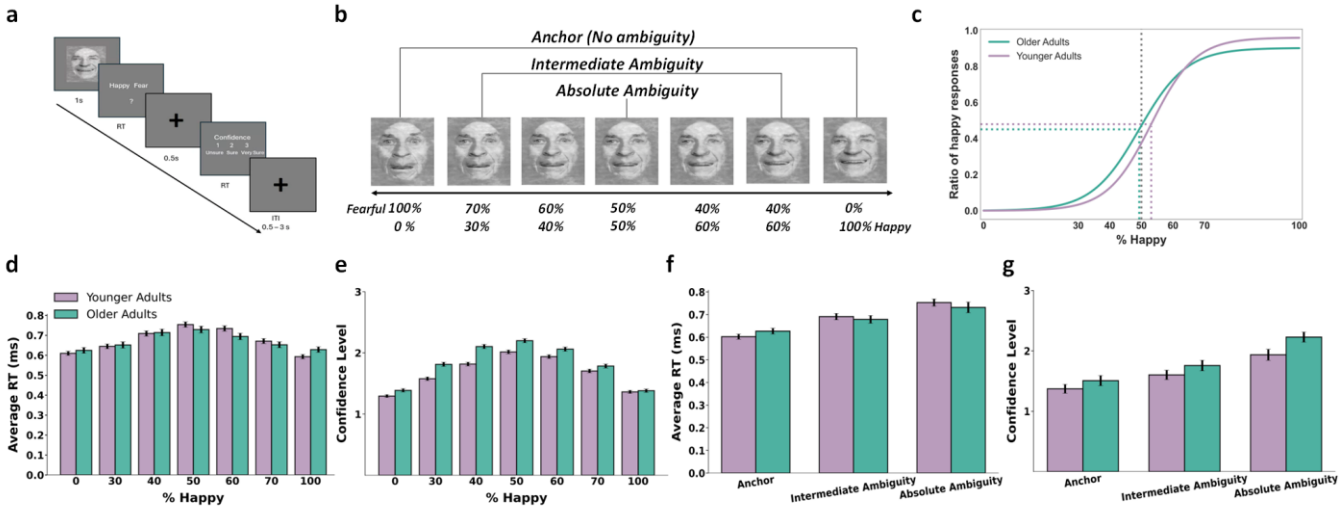


Figure 2

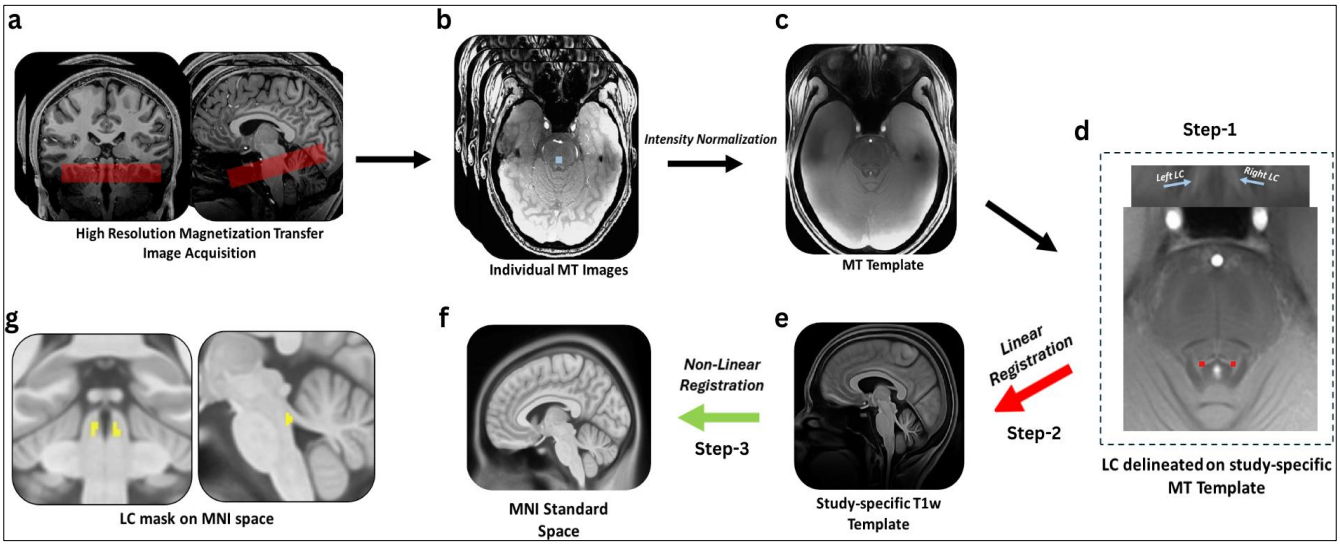


Figure 3

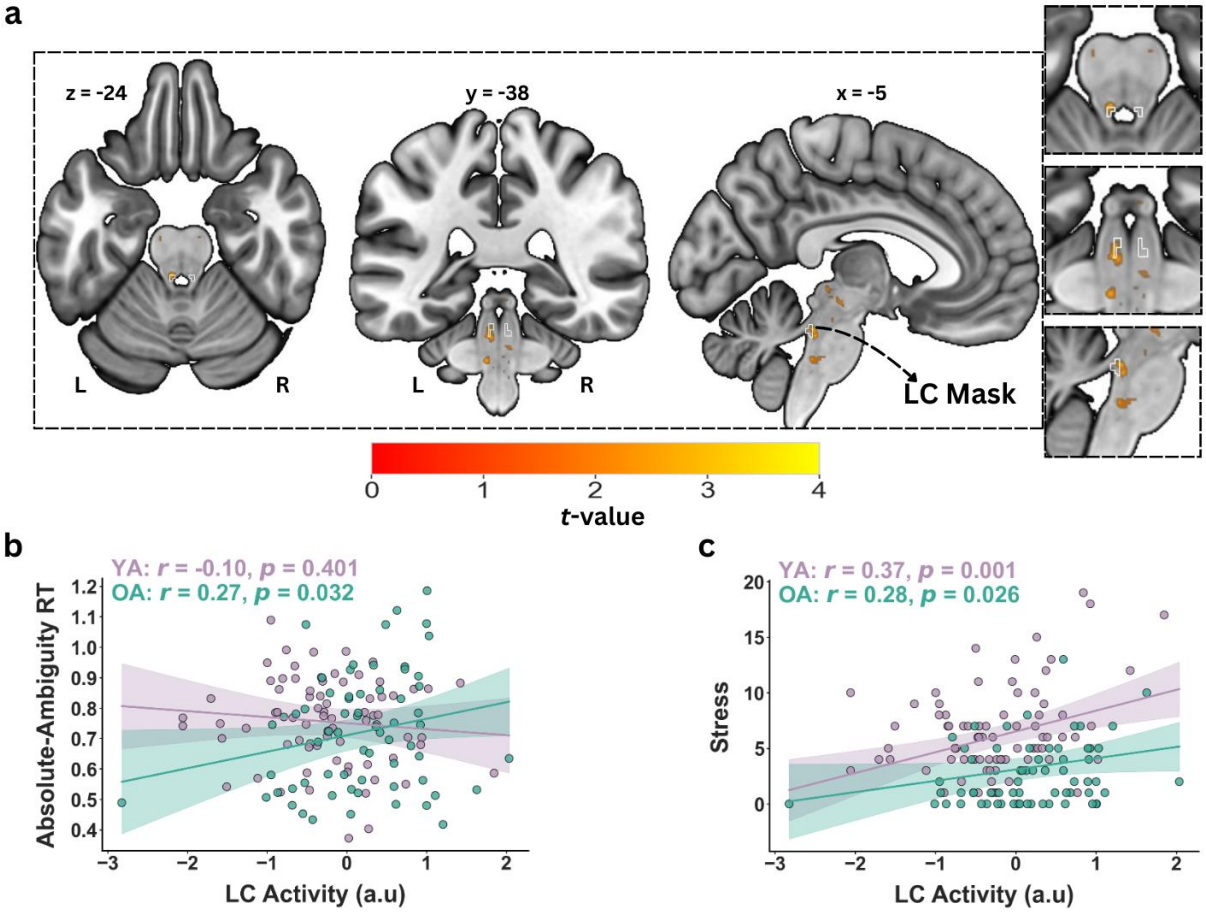
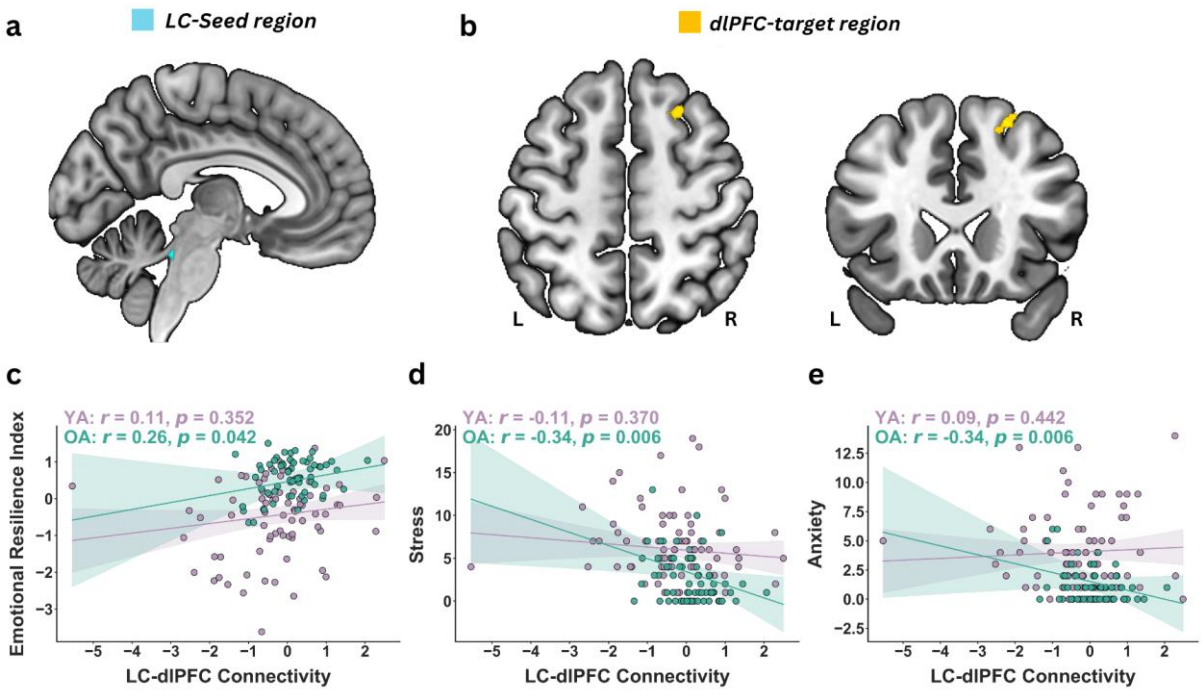

a
z = -24
y = -38
x = -5
L
R
L
R
LC Mask
0
1
2
3
4
t-value
b
YA: r = -0.10, p = 0.401
OA: r = 0.27, p = 0.032
Absolute-Ambiguity RT
LC Activity (a.u)
c
YA: r = 0.37, p = 0.001
OA: r = 0.28, p = 0.026
Stress
LC Activity (a.u)

Figure 4


a
LC-Seed region
b
dlPFC-target region
L
R
L
R
c
YA: r = 0.11, p = 0.352
OA: r = 0.26, p = 0.042
Emotional Resilience Index
LC-dlPFC Connectivity
d
YA: r = -0.11, p = 0.370
OA: r = -0.34, p = 0.006
Stress
LC-dlPFC Connectivity
e
YA: r = 0.09, p = 0.442
OA: r = -0.34, p = 0.006
Anxiety
LC-dlPFC Connectivity

Captions

Figure 1: Experimental task and behavioral results. panel (a) shows an example of experimental Trial. A face was displayed for 1 second, after which participants were prompted to identify the facial emotion as either fearful or happy. Following a 500-millisecond cross, they were asked to rate their confidence by selecting '1' for very sure, '2' for sure, or '3' for unsure. Panel (b) shows sample stimuli of one male ranging from 0% fear to 100% happy derived from FACES database (Ebner et al., 2010). (c-g) Behavioral results. Panel (c) depicts the group average of psychometric curves of both young and older adults showing the proportion of trials judged as happy normalized to 0 and 1 as a function of morph levels (ranging from 0% fearful to 100% happy). Panel (d) and (f) show response time (RT) comparison as a function of % happy and combined ambiguity level between younger and older subjects, respectively. Panels (e) and (g) depict confidence level comparison as a function of % happy and combined ambiguity level between younger and older subjects, respectively. Error bar denotes one standard error of mean (s.e.m) across subjects/sessions. ***Images of faces were derived from the FACES database (Max Planck Institute for Human Development). Used with permission under the terms of the database's copyright policy.***

Figure 2: Locus Coeruleus delineation pipeline. MT-TFL pre-processing and spatial transformation pipeline. (a) High resolution MT-TFL images acquired by positioning the approximately perpendicular to the pons, encompassing the region between the inferior colliculus and the inferior border of the pons. Panel (b) shows an example of individual MT-TFL images acquired using this sequence with 10x10 voxel (blue) placed on pons. Panel (c) demonstrates a study-specific MT-TFL template created after intensity normalizing the individual MT-TFL images. Panel (d) shows left and right LC delineated on subject-specific MT-TFL template using ITK-SNAP. Panel (e) depicts study-specific T1w template created to act as a bridge to transform LC mask to MNI space, red arrow indicates MT template and was rigidly registered to the whole-brain study-specific T1w template. Panel (f) shows MNI space

where T1w template was non-linearly registered (green arrow). Panel (g) depicts left and right LC mask transformed to MNI space after using the transformation matrices obtained from step-2 and step-3.

Figure 3: LC activation and behavioral correlation. (a) Higher Locus Coeruleus (LC) activation in older (OA) > younger adults (YA) during absolute-ambiguity condition. Significant activation thresholded with P_{FWE}<0.05 within LC mask (white). Panel (b) illustrates LC activity and its link with response time (RT) during absolute-ambiguity condition for both YA and OA. Panel (c) shows LC activity and its link with self-reported stress measures in YA and OA. FWE = family wise error

Figure 4: LC-dlPFC connectivity and behavioral correlation. Absolute-ambiguity elicits greater LC-dlPFC connectivity in older adults (OA) compared to younger adults (YA). Panel (a) shows the Locus coeruleus (LC) seed- region shows greater connectivity with panel (b) showing the right dorsolateral prefrontal cortex (dlPFC) target regions in ROI-to-ROI analysis using generalized psychophysiological interaction. Panel c to e illustrate the relationship between LC-dlPFC connectivity and mental well-being measures in OA: Panel (c) depicts that higher LC-dlPFC connectivity is positively associated with greater emotional resilience, while panel (d) shows that it is negatively associated with stress, and panel (e) with anxiety scores. These significant associations are observed in OA, but not in YA.

Extended Table 2-1: Peak coordinates of significant clusters for anchor ambiguity condition contrast: younger > older adults and older > younger adults (whole brain analysis)

Region	Hemisphere	BA	MNI coordinates X Y Z	*t*-value	Cluster Size
a. Younger > Older adults					
Postcentral gyrus	L	2	[-65 -20 26]	7.98	299
Insula	L	48	[-40 2 10]	6.74	42
	R	48	[40 6 10]	6.80	47
b. Older > Younger adults					
Fusiform gyrus	L	19	[-35 -15 -65]	5.75	205
	R	19	[32 -48 -17]	6.94	472
Posterior Cingulate Cortex		30	[5 -45 -18]	4.32	45
Calcarine Cortex	L	17	[-8 -75 -16]	5.02	77
	R	17	[17 -65 12]	6.47	373
Precentral gyrus	L	44	[-43 1 29]	4.65	148
	R	44	[40 9 33]	5.39	204

BA = Broadman Areas; MNI = Montreal Neurological Institute; L = left; R = right; p<.001 cluster size ≥ 40 voxels

763 **Extended Table 2-2:** Peak coordinates of significant clusters for intermediate ambiguity
764 condition contrast: younger > older adults and older > younger adults (whole brain analysis)

Region	Hemisphere	BA	MNI coordinates X Y Z	*t*-value	Cluster Size
a. Younger > Older adults					
Postcentral gyrus	L	2	[-39 -18 49]	11.20	387
Mid Cingulate Cortex	R	24	[2 -2 44]	10.19	1091
Supramarginal gyrus	L	48	[-65 -19 26]	12.30	3433
	R	48	[58 -42 30]	8.91	255
Insula	L	48	[-48 -4 4]	7.95	440
	R	48	[41 4 6]	9.16	199
Hippocampus	L	-	[-30 -38 0]	9.64	219
Middle temporal gyrus	R	42	[60 -30 20]	7.73	165
b. Older > Younger adults					
Thalamus	L	-	[-5 -20 5]	5.66	153
	R	-	[11 -28 6]	7.39	382
Occipital Fusiform gyrus	L	19	[-28 -82 -6]	7.61	82
	R	19	[30 -80 10]	7.94	223
Caudate	L	-	[-15 8 16]	5.40	97
	R	-	[18 1 20]	5.55	96

765 *BA = Broadman Areas; MNI = Montreal Neurological Institute; L = left; R = right; p<.001*
766 *cluster size ≥ 40 voxels*

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