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Curvilinear locus coeruleus functional connectivity trajectories over the adult lifespan: a 7T MRI study

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ABSTRACT

The locus coeruleus (LC) plays a crucial role in modulating several higher order cognitive functions via its widespread projections to the entire brain. We set out to investigate the hypothesis that LC functional connectivity (FC) may fluctuate nonlinearly with age and explored its relation to memory function. To that end, 49 cognitively healthy individuals (19–74 years) underwent ultra high-resolution 7T resting-state functional magnetic resonance imaging and cognitive testing. FC patterns from the LC to regions of the isodendritic core network and cortical regions were examined using region of interest–to–region of interest analyses. Curvilinear patterns with age were observed for FC between the left LC and cortical regions and the nucleus basalis of Meynert. A linear negative association was observed between age and LC-FC and ventral tegmental area. Higher levels of FC between the LC and nucleus basalis of Meynert or ventral tegmental area were associated with lower memory performance from age of 40 years onward. Thus, different LC-FC patterns early in life can signal subtle memory deficits. Furthermore, these results highlight the importance of intact interactions between neurotransmitter systems for optimal cognitive aging.

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1. Introduction

The locus coeruleus (LC), a tiny nucleus at the lateral edge of the fourth ventricle, plays a modulatory role in many cognitive functions via its extensive noradrenergic projections to the entire brain, including the neocortex and most subcortical areas such as the hippocampus or amygdala (Berridge and Waterhouse, 2003; Sara, 2009).

Structurally, the LC undergoes several changes during aging. With aging, the concentration of noradrenaline reduces in several brain regions (Arnsten and Goldman-Rakic, 1985). This reduction in noradrenalin turnover correlates with loss of neurons in the LC. At around 45 years of age, there is on average 40% of cell loss in the LC (German et al., 1988; Manaye et al., 1995; Mann and Yates, 1979). With aging, loss of neurons in the LC occurs most prominently in the rostral parts of the LC, the parts that connect to the cerebral cortex and forebrain structures, and almost no cell loss has been observed in the caudal portions, the part projecting to the spinal

cord (German et al., 1988; Manaye et al., 1995). Interestingly, histological studies noted an accumulation in neuromelanin-positive cells with aging. No or only minimal neuromelanin cells are observed in the LC of newborns, but their count increases linearly until around the age of 50–60 years, after which they progressively decline (Mann and Yates, 1979). Neuromelanin, resulting from the oxidation of noradrenaline, has both neuroprotective and neurotoxic effects, as it chelates toxins, but can also promote neuroinflammatory responses (Zecca et al., 2004).

Recently, postmortem reports suggested that the LC might be the initial site of tau pathology accumulation, one of the neuropathological hallmarks of Alzheimer's disease (AD) (Braak and Del Tredici, 2011; Braak et al., 2011; Ehrenberg et al., 2017). About half of the cases below 30 years of age showed evidence of early tau lesions in the LC, suggesting that the LC is not only affected by age-related atrophy of noradrenergic cells, but may also receive a second hit from AD-related pathology already very early in life.

The LC is part of the isodendritic core network (Theofilas et al., 2015) consisting of several subcortical nuclei with ascending projections to the cortex regulating behavior via aminergic and cholinergic neurotransmitters. These neurotransmitter systems have largely overlapping complex widespread projections

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throughout the brain. Interactions between these systems remain unclear but have been shown to be important for optimal cognitive performance (Aston-Jones and Cohen, 2005). The LC together with the cholinergic and serotonergic systems form the ascending arousal system projecting to the hypothalamus, thalamus, amygdala, hippocampus, and neocortex and regulates attention to salient stimuli. The dopaminergic system from the ventral tegmental area (VTA) has mesolimbic and mesocortical pathways to the nucleus accumbens and cortex and is a key component of the reward system (Paxinos and Mai, 2004). Considering the LC's widespread projections, its modulation of neuronal activity, metabolism and cognition, and its early involvement in AD pathology, structural and pathological changes of the LC can have important repercussions for brain systems and cognitive functioning of the individual.

Only a handful of studies have examined the functional connectivity (FC) pattern of the LC in vivo in animals or humans during rest. Cell recordings in rats have shown an age-related decline in the spontaneous firing rate of LC cells (Olpe and Steinmann, 1982). In young human adults between the age of 18 and 49 years, the FC between the LC and the angular gyrus, middle frontal gyrus, and cerebellum correlated positively with age, but negative correlations with age were observed for FC between the LC and the precuneus, cuneus, parahippocampus, and parietal-occipital fissure (Zhang et al., 2016). Interestingly, in older individuals (65–80 years old), we confirmed these positive correlations between the LC and the cerebellum and frontal gyrus (Jacobs et al., 2014). But, in contrast to Zhang et al., we observed a positive correlation between the right LC and the lingual gyrus and parahippocampal gyrus, suggesting that the interaction between certain regions may vary with aging and that there may be an age-related asymmetry among these interactions. The fact that the LC-parahippocampal connectivity correlated positively with episodic memory performance in healthy older individuals and was reduced in patients with prodromal AD (Jacobs et al., 2014) suggests that such age-varying dynamics in FC may reflect compensatory mechanisms for cognitive performance.

The observations of these studies highlight the importance of investigating the entire adult lifespan, to also consider nonlinear age relationships and to explore whether these FC age patterns have relevance for cognitive performance. Furthermore, in our previous study, we observed different FC patterns for the left and right LC, whereas Zhang et al. (2016) combined left and right. To examine whether LC connectivity shows age-related asymmetry, we decided to investigate the left and right LC separately. Whole-brain functional magnetic resonance imaging (fMRI) at 3T involving the LC is limited by the relatively low spatial resolution. We will therefore, for the first time, examine age associations of FC between the LC and the cortex or the isodendritic core network at ultrahigh-field 7T MRI providing 4 times the best resolution at 3T MRI. Because of the important role of the LC in the earliest stages of AD, these findings can contribute in developing a biomarker for early AD-related memory changes.

2. Methods

2.1. Participants

Forty-nine individuals (mean age: 44.12 years [standard deviation {SD}: 19.38]) recruited from the general community via advertisements participated in this observational study. Participants were stratified into 3 age groups (20–30 years old [$n = 18$], 40–50 years old [$n = 15$], and 60–80 years old [$n = 16$]). These age groups were chosen because prior research indicated that brain changes are most prominent in these phases of life (Fjell et al., 2013) and because cognitive neuroscience studies have shown that memory performance stays relatively stable until the age of 40–50 years and then declines linearly with age (Grady and Craik, 2000;

Hedden and Gabrieli, 2004), indicating that this scheme provides a reasonable sampling of important milestones of brain-behavior differences across the lifespan while reducing the sampling error for these crucial phases.

Participants were included if they met the following criteria: no evidence of cognitive deficits on neuropsychological screening, no presence of any major neurological or psychiatric disease, no psychoactive medication use, no abuse of alcohol or drugs, no contraindications for 7T MRI scanning, Dutch mother tongue, and participants had to be able to give informed consent. All participants were right-handed. The study was carried out at Maastricht University, Faculty of Psychology and Neuroscience and the Faculty of Health, Medicine and Life Sciences. The Ethical Review Board from the Faculty of Psychology and Neuroscience approved the study. Written informed consent was provided by all participants.

2.2. Procedure

All participants underwent a brief cognitive screening and 7T MRI session. The cognitive screening included the Mini-Mental State Examination (Folstein et al., 1975), the 15-word learning memory task to measure episodic memory (learning after 5 trials and delayed recall) (Van der Elst et al., 2005), the Stroop Color Word Task (Van der Elst et al., 2006b) to measure executive functions, and verbal fluency (categories: animals, professions, and words starting with M) (Van der Elst et al., 2006a). In addition, all participants were asked to fill in the Hamilton Depression Rating Scale (Hamilton, 1960) to screen for depressive symptoms.

All MRI data were acquired on a MAGNETOM 7T whole-body magnet scanner (Siemens Healthineers, Erlangen, Germany) with a 32-channel head coil (Nova Medical, Wilmington, MA, USA) and using dielectric pads positioned at the temples to improve the signal around the temporal lobes (Haines et al., 2010).

A high-resolution anatomical magnetization prepared 2 rapid acquisition gradient echoes image was acquired (Marques et al., 2010) for coregistration of the functional data. The whole-brain anatomical image was acquired with the following parameters: repetition time = 5000 ms, echo time = 2.47 ms, 240 slices, 0.7 mm isotropic voxel size, field of view = 224 mm, flip angle = $5^\circ/3^\circ$, inversion time = 900/2750 ms, and acquisition time = 9 minute 42 second. The high-resolution resting-state scan was acquired with the Center for Magnetic Resonance Research multi-band (MB, <https://www.cmrr.umn.edu/multiband> [Moeller et al., 2010]) package with the eyes open, asking participants to think about nothing in particular while looking at a fixation cross with the following parameters: repetition time = 1400 ms, echo time = 19 ms, 90 slices, 1.25 mm isotropic voxel size, field of view = 200 mm, flip angle = 70° , interleaved, a multiband generalized autocalibrating partial parallel acquisition acceleration factor of 3 and acquisition time = 6 minute 28 second (180 volumes).

2.3. Definition of regions of interest

The LC seed was identified using a high-resolution binary template map (0.5-mm isotropic voxel size) previously validated in vivo (Keren et al., 2009) in standard neuroimaging space (Montreal Neurological Institute [MNI]), which we have also applied successfully in our previous work (Jacobs et al., 2014). This template was also validated with ex vivo imaging and histology (Keren et al., 2015). We recently developed an ultrahigh-field MRI sequence to visualize the LC in vivo (Priovoulos et al., 2018). While the data acquisition for this project was almost finished at that time point, we were able to acquire this sequence in 3 individuals to show the spatial reliability of our LC seed (see Supplemental Fig. 1). The other brainstem nuclei, the VTA, dorsal and median raphe nucleus, and

the pedunculopontine nucleus were localized using the Harvard Ascending Arousal Network Atlas (Edlow et al., 2012). This atlas was generated using histological ex vivo data, diffusion data, and cross-correlation to the Paxinos Human brainstem atlas. All regions of interest were traced in MNI space. The nucleus basalis of Meynert (NBM) was localized from a stereotaxic probabilistic anatomical map of the so called region Ch4 (cholinergic), which corresponds to the NBM. This map was derived from histological analyses in nonhuman primates and human postmortem brains (Zaborszky et al., 2008). Finally, all supratentorial regions (cortical and subcortical) were based on the AAL atlas available within the Conn toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012). As the AAL atlas is an anatomical parcellation, we also performed ROI-to-ROI connectivity analyses between the LC and supratentorial regions using functionally defined parcellations. These functional parcellations were generated with an independent component analyses on 497 healthy control participants (293 females), part of the Human Connectome Project (<http://www.humanconnectome.org>). These parcellations include in total 32 functionally defined regions of 12 intrinsic networks. All ROIs were warped to each individual's native T1 image using the high-dimensional symmetric diffeomorphic normalization transformation of the Advanced Normalization Tool (Philadelphia, USA) warping first the MNI template to each native T1 image and consequently using the transformation model to warp the ROI to each T1 image (Klein et al., 2009).

2.4. Resting state fMRI preprocessing

All functional magnetic resonance images were preprocessed using the Conn Toolbox version 17a under SPM12 (Wellcome Trust Center of Neuroimaging, University College London, UK). The first 10 volumes were discarded to account for T1 saturation effects and obtain steady-state magnetizations.

Preprocessing included slice-time correction (because of the multiband acquisition, slice timing is nontrivial and the slice timing matrix was obtained via AFNI's 3dinfo-slice_timing tool), realignment to the mean image to compensate for motion, coregistration of functional and structural images, and tissue segmentation of the structural images into gray matter, white matter, and cerebrospinal fluid (CSF). Functional images were smoothed as part of the processing pipeline with a 1.5-mm full width at half maximum isotropic Gaussian kernel, but the ROI-to-ROI analyses were performed on the nonsmoothed images. The outliers of the fMRI time series were determined with Artifact Detection Tool (global signal Z value = 3, motion = 0.5 mm, and discarding the first 3 volumes). The principal components from white matter and CSF, including the CSF signal from the fourth ventricle (Bianciardi et al., 2016), were determined following the Conn-implemented CompCor strategy (Behzadi et al., 2007). Denoising involved regressing out the outliers, the CompCor noise components, the 6 motion parameters and their first first-order derivatives, and a linear term regressor (to model linear trends). The CompCor strategy improves the sensitivity and specificity of positive correlations and can reveal non-artifactual anticorrelations without global-signal removal. After preprocessing, the images were bandpass filtered to 0.008–0.09 Hz.

Because we have no information on respiration or other physiological noise sources, we added person-specific global correlations as a covariate to our models, as this will guard against false positives (Saad et al., 2013). We additionally ran an independent component analyses on the cleaned data in Conn and with FSL's (FMRIB Software Library [FMRIB = Functional Magnetic Resonance Imaging of the Brain]) MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) toolbox (www.fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC, see Supplemental Fig. 2). This revealed no additional components reflecting potential artifacts.

To correct for the influence of age-related brain atrophy on FC, we calculated the normalized brain volume for each participant with SIENAX of the FMRIB Software library version 5.0.1 (Smith et al., 2007).

2.5. Seed-to-voxel across the entire group, independent of age

We first performed seed-to-voxel analyses to explore the FC patterns of the left and right LCs, independent of age. The LC ROI was on average 58 mm³ for the left and 56 mm³ for the right LC. Correlation maps were generated by correlating the average blood-oxygen-level dependent time course from the seed with the blood-oxygen-level dependent time series of each voxel throughout the brain. These correlation coefficients were converted to normally distributed scores using Fisher's transformation. Individuals' maps were fed into the second-level analyses using a 1-sample *t*-test, covarying for age, education, sex, estimated normalized brain volume, and global correlation. We also performed a paired *t*-test to compare left and right FCs between the LC and the cortical regions. Voxelwise statistics were performed at the uncorrected *p*-level (*p* < 0.005) before nonparametric false discovery rate (FDR) correction was applied at the cluster level (*p* < 0.05). Performing seed-to-voxel analyses from the LC to the brainstem is associated with lower effect sizes than those obtained in the cortex. In addition, performing a cluster-wise correction on tiny brainstem regions such as the VTA is too stringent. We therefore decided to perform ROI-to-ROI analyses.

2.6. ROI-to-ROI analyses: age-related differences in FC between LC and subcortical/cortical regions

To assess the age-related differences in FC of the LC with other subcortical regions, we applied ROI-to-ROI analyses with either the left or the right LC as seed ROI with the linear Pearson correlation coefficient *r*. As the signal in the cortex is generally stronger than that in the brainstem (Dobromyslin et al., 2012), separate analyses were performed for the ROI-to-ROI analyses between the LC and the brainstem (subcortical) regions (median and dorsal raphe nucleus, VTA, left and right pedunculopontine nucleus, and the left and right NBM) and between the LC and the supratentorial regions (105 regions). Posthoc, we investigated whether these FC patterns can be replicated with ROI-to-ROI analyses consisting of all regions. Left and right were analyzed separately. The cross-correlation at lag 0 between the LC and each ROI was calculated. The *r*-coefficient (can be positive or negative), indicating the strength of connectivity between the LC and each ROI, was normalized with a Fisher's *Z*-transform for further analyses.

2.7. Statistical analyses

As previous studies provided evidence for a curvilinear relationship of age with FC, we used polynomial regression analyses up to maximum 3 degrees. The higher order polynomial term was compared with the linear fit using the *F*-statistic for nested models and using the Predictive Residual Error Sum of Squares—statistic that can give a more reliable indication of the model fit using leave-one-out cross-validation for small samples (smaller is better and indicates that the model is not overly sensitive to any single data point) (McKeown et al., 2003). We have also calculated the change in *R*² for the linear, quadratic, and cubic terms. In all models, education, sex, estimated normalized brain volume, and global correlation were added as covariates. The supratentorial and subcortical ROI-to-ROI analyses were each corrected for multiple comparisons using the FDR-adjusted *p*-values. We report the unstandardized beta coefficients for the polynomial term of interest, and the bias corrected

and accelerated nonparametric bootstrapped confidence interval ($n = 2000$) is provided in [Supplemental Tables 2 and 3](#).

Posthoc, we aimed to examine the relationship between memory performance and FC. We therefore focused on the results that survived the FDR correction in the previous analyses and performed linear regression models with the interaction “age by FC” on memory performance (total learning or delayed recall on the 15-word learning task). Age, sex, education, normalized brain volume, and global correlation were also entered as covariate. Analyses were corrected for multiple comparisons using the FDR approach. The Johnson-Neyman technique ([Bauer and Curran, 2005; Johnson and Fay, 1950](#)) was used to determine with precision the region of significance of possible moderation effects by calculating the value where the moderator produces the α -value of 0.05. To ensure the consistency of these results, we also performed linear regression analyses including group (instead of continuous age) in the model.

Group characteristics are represented in mean and SD. Age relationships with cognitive measures were tested using simple linear regression models. Statistical analyses were done in R version 3.3.0 (www.r-project.org).

3. Results

3.1. Group demographics

Participants were on average 44.12 years old (SD: 19.38), had an education level of 5.06 (scale 0–8, SD: 1.52), and 59% of the participants were female. The mean Mini-Mental State Examination score was 29.41 (SD: 0.79). Participants scored on average 1.65 on the Hamilton Depression Rating Scale (SD: 2.39). Mean performance on the cognitive tests is listed in [Table 1](#).

3.2. Seed-to-voxel analyses independent of age

The left and right LC seeds were each positively correlated with the bilateral medial-lateral frontal regions, precuneus, cingulate cortex, angular gyrus, occipital regions, and lateral temporal cortices. There were no negative correlations with any of the cortical voxels (see [Supplemental Table 1](#) and [Fig. 1](#)). There were no significant differences between the left and right LC seed connectivity with the cortical regions.

3.3. Age relationships with FC between the LC and brainstem/subcortical ROIs

Functional connectivity between the left or right LC and the VTAs shows a negative linear relationship with age ($\beta = -1.32$,

Table 1
Group characteristics

	Mean (SD)
Age (y)	44.12 (19.38) range [19–74]
Sex (n, % Females)	29, 59%
Educational level	5.06 (1.52)
Mini-Mental State Examination (score)	29.41 (0.79)
WLT Learning (number of words)	52.18 (8.85)
WLT delayed recall (number of words)	11.35 (2.72)
SCWT card 1 (s)	45.57 (9.27)
SCWT card 2 (s)	55.49 (10.04)
SCWT card 3 (s)	87.17 (21.34)
Fluency animals (score)	26.33 (6.25)
Fluency professions (score)	17.65 (4.72)
Fluency letter M (score)	16.57 (5.73)
Hamilton depression rating scale (score)	1.65 (2.39)

A standardized 8-point scale was used to indicate educational level (range 1 = primary school to 8 = university).

Key: SCWT, stroop color word test; SD, standard deviation; WLT, word learning test.

$t = -3.18$, $p = 0.0028$, $p_{FDR} = 0.021$; $\beta = -1.28$, $t = -3.61$, $p = 0.0008$, $p_{FDR} = 0.012$, respectively), whereas the FC between the left or right LC and the left NBM showed a nonlinear, cubic relationship with age ($\beta = 0.86$, $t = 2.73$, $p = 0.009$, $p_{FDR} = 0.044$; $\beta = 0.84$, $t = 2.64$, $p = 0.012$, $p_{FDR} = 0.044$, respectively). No other significant associations were observed (see [Fig. 2](#)).

3.4. Age relationships with FC between the LC and supratentorial ROIs

No age associations were observed for the FC patterns between the right LC and any of the regions of the AAL atlas. But a positive linear age relationship was found for FC between the left LC and the right postcentral gyrus ($\beta = 1.25$, $t = 2.94$, $p = 0.005$, $p_{FDR} = 0.042$). Nonlinear age relationships were observed between the left LC and the right frontal pole ($\beta = 0.93$, $t = 2.93$, $p = 0.006$, $p_{FDR} = 0.045$), left and right superior frontal gyrus ($\beta = 1.15$, $t = 3.14$, $p = 0.003$, $p_{FDR} = 0.033$; $\beta = 1.16$, $t = 3.60$, $p = 0.0008$, $p_{FDR} = 0.015$, respectively), left and right temporal pole ($\beta = 1.31$, $t = 3.28$, $p = 0.002$, $p_{FDR} = 0.027$; $\beta = 1.07$, $t = 2.80$, $p = 0.007$, $p_{FDR} = 0.045$, respectively), left and right anterior ($\beta = 1.24$, $t = 3.05$, $p = 0.004$, $p_{FDR} = 0.038$; $\beta = 1.27$, $t = 3.94$, $p = 0.0003$, $p_{FDR} = 0.015$, respectively) and posterior middle temporal gyri ($\beta = 0.99$, $t = 3.30$, $p = 0.002$, $p_{FDR} = 0.027$; $\beta = 0.84$, $t = 2.77$, $p = 0.008$, $p_{FDR} = 0.044$, respectively), left and right anterior-inferior temporal gyrus ($\beta = 1.30$, $t = 4.32$, $p = 0.00009$, $p_{FDR} = 0.010$; $\beta = 1.03$, $t = 3.24$, $p = 0.002$, $p_{FDR} = 0.027$, respectively), left and right angular gyri ($\beta = 0.987$, $t = 3.60$, $p = 0.0009$, $p_{FDR} = 0.015$; $\beta = 1.12$, $t = 3.71$, $p = 0.0006$, $p_{FDR} = 0.015$, respectively) and the left and right orbital frontal cortices ($\beta = 1.06$, $t = 2.95$, $p = 0.005$, $p_{FDR} = 0.045$; $\beta = 0.92$, $t = 3.77$, $p = 0.0005$, $p_{FDR} = 0.015$, respectively) (see [Fig. 3](#)). For each of these associations, the curvilinear model was a better fit than the linear model (see [Supplemental Table 2](#)). Combining subcortical and supratentorial regions in 1 model and correcting for multiple comparisons revealed the same patterns with age, confirming their robustness. More statistical information, including the Predictive Residual Error Sum of Squares, change in R^2 , F-statistics, and the bootstrapped confidence intervals for these analyses, are provided in [Supplemental Tables 2 and 3](#) and [Supplemental Fig. 3](#).

3.5. Age relationships with FC between the LC and functionally defined cortical ROIs

A positive linear age relationship was found for FC between the left LC and the right lateral sensorimotor network ($\beta = 1.11$, $t = 2.81$, $p = 0.007$, $p_{FDR} = 0.034$). Nonlinear age relationships were observed between the left LC and the left ($\beta = 0.94$, $t = 2.85$, $p = 0.007$, $p_{FDR} = 0.034$) and right posterior cingulate cortex of the frontoparietal network ($\beta = 0.98$, $t = 2.84$, $p = 0.007$, $p_{FDR} = 0.034$) and the left ($\beta = 0.88$, $t = 2.99$, $p = 0.005$, $p_{FDR} = 0.034$) and right inferior frontal gyrus ($\beta = 0.70$, $t = 2.82$, $p = 0.007$, $p_{FDR} = 0.034$) and the left ($\beta = 0.93$, $t = 2.90$, $p = 0.006$, $p_{FDR} = 0.034$) and right posterior superior temporal gyrus ($\beta = 0.83$, $t = 3.02$, $p = 0.004$, $p_{FDR} = 0.034$) of the language network (see [Supplemental Table 3](#) and [Fig. 4](#)).

3.6. Correlates to memory performance

No main effects of FC on memory learning or delayed recall were observed (additionally controlled for age, all $p > 0.05$). We found that a negative relationship between age and learning score on the 15-word learning task was present when the FC between the left LC and VTA was positive ($\beta = -0.41$, $t = -2.99$, $p = 0.005$, $p_{FDR} = 0.019$; the relationship between the right LC and VTA did not survive multiple comparison correction ($p = 0.036$, $p_{FDR} = 0.072$). Applying

Fig. 1. Locus coeruleus–cortical connectivity independent of age. One-sample t-test assessing voxelwise left (A) or right (B) locus coeruleus FC with cortical regions ($p < 0.005$ with nonparametric FDR cluster correction at $p < 0.05$). No negative correlations were observed. The color bar indicates the magnitude of the effects (t-value). Abbreviations: FC, functional connectivity; FDR, false discovery rate; L, left; R, right. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

the Johnson-Neyman technique showed that left LC-ventral tegmental FC was positively associated with memory for individuals below 42.69 years ($t = 2.02$, $p = 0.05$). In addition, for learning, we observed a significant interaction between age and FC between the left LC and the left NBM ($\beta = -0.55$, $t = -2.56$, $p = 0.014$, $p_{\text{FDR}} = 0.038$). Applying the Johnson-Neyman technique showed that the left LC-NBM connectivity was negatively associated with memory for individuals above 62.84 years ($t = 2.02$, $p = 0.05$).

For the delayed recall performance on the 15-word learning task, the negative relationship between age and performance was dependent on positive correlations between the left LC and the left NBM ($\beta = -0.24$, $t = -3.01$, $p = 0.004$, $p_{\text{FDR}} = 0.019$; Johnson-

Neyman: from 39.72 years onward ($t = -2.02$, $p = 0.05$) (see Fig. 5).

While several age-dependent associations between LC-frontotemporal FC and memory were observed, none of these associations survived multiple comparison correction for learning or delayed recall performance. When running these interactions with group instead of age, our findings did not change (see Supplemental Table 4 and Supplemental Fig. 4).

4. Discussion

We aimed to examine age associations of FC patterns from the LC across the adult lifespan using 7T resting-state fMRI and their

Fig. 2. Associations between FC between the LC and subcortical regions during aging. The line graphs depict the association between FC of the LC with the VTA or NBM and age (estimated marginal means). The connectivity ring depicts the effects that survived correction for multiple comparisons. Warm colors (red) show positive t-values and cold (blue) colors show negative t-values. The color bar indicates the magnitude of the effects (t-value). Shaded regions display the 95% confidence interval. Abbreviations of the regions are explained in Supplemental Table 5. Abbreviations: FC, functional connectivity; LC, locus coeruleus; NBM, nucleus basalis of Meynert; VTA, ventral tegmental area. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Fig. 3. Associations between FC between the LC and cortical regions during aging. The line graphs depict the association between FC of the LC with the cortical regions (AAL atlas) and age that survived correction for multiple comparisons (estimated marginal means). Shaded regions display the 95% confidence interval (connectivity ring is available as [Supplemental Fig. 3](#)). Abbreviations of the regions are explained in [Supplemental Table 5](#). Abbreviations: FC, functional connectivity; LC, locus coeruleus. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

relevance for memory functioning that is inherently changing during aging. Consistent with previous work, we observed widespread bilateral connectivity between the LC and cortical regions independent of age ([Zhang et al., 2016](#)). Our results now extend the current literature by showing that LC FC with frontal, temporal, and parietal regions ([Zhang et al., 2016](#)), and the NBM varies nonlinearly with aging. The same regional cortical effects with age were observed when using the functional parcellations. For the LC connectivity to the cortical regions, there may be a left-sided age-related vulnerability. Furthermore, our correlations with memory highlight the importance of intact interactions between the aminergic and cholinergic neurotransmitter systems to maintain optimal cognitive performance. Increased positive FC between the LC and NBM after the age of 40 years might reflect aberrant neuronal firing and indicate underlying pathology affecting the memory network in the brain.

Ample studies investigated age-related differences in intrinsic networks during resting-state fMRI ([Betzel et al., 2014](#); [Cao et al., 2014](#); [Chan et al., 2014](#); [Damoiseaux, 2017](#); [Fjell et al., 2015](#); [Huang et al., 2015](#); [Wang et al., 2012](#)). These studies reported an inverted U-pattern in FC measures. Longitudinal internetwork FC analyses showed increased FC from age 65–70 years ([Ng et al., 2016](#)), suggestive for a more cubic relationship between aging

and FC. Although our sample size is limited, we provided evidence for nonlinear associations between age and FC between the left LC and several cortical regions. For most of the cortical regions, we consistently observed a sharp increase from age 20–25 years—possibly reflecting brain maturation ([Dosenbach et al., 2010](#))—after which a slow continual decrease of FC was noted from the age of 25 years to around 60 years (negative correlations), followed by increases in FC.

The interpretation of these fluctuations in FC across the lifespan is complex. Neurons of the LC can discharge phasic bursts of activity or can fire at more tonic rates ([Rajkowski et al., 1994](#)). Phasic bursts are elicited by novel stimuli, whereas tonic activity fluctuates according to arousal levels and behavioral states. The low-frequency fluctuations measured with resting-state fMRI potentially reflect tonic activity, as there are no cognitive demands. Allocating fluctuations in these low-frequency activities to either tonic or phasic activity is difficult, but it can be speculated that negative correlations between the LC and cortical regions (also referred to as anti-correlations) reflect attempts of the LC system to reduce interference of emotional or cognitive information from the cortical regions ([Wermke et al., 2008](#)). Future studies could try to explore the additive effects of other neurobiological and physiological processes, such as the influence of arousal on these FC fluctuations.

work showed associations between amyloid deposition and increased FC (Cirrito et al., 2005; Sepulcre et al., 2017) and between amyloid deposition and nucleus basalis of Meynert volume (Kerbler et al., 2015; Teipel et al., 2014), suggesting that the age window for the association between memory and LC-NBM FC tracks with increased amyloid deposition. Lifespan studies including amyloid PET measures will be able to confirm this hypothesis.

Thus, these patterns suggest that increased FC signals aberrant processes. Postmortem correlations to noradrenergic metabolites also showed an inverse relationship between neuronal count in the LC and levels of these metabolites (Hoogendijk et al., 1999),

suggesting that remaining neurons increase their activity, potentially stemming from neuronal nonfunctional sprouting or random firing.

The correlation between the VTA and LC showed a steady linear decline during aging. Positive LC-VTA correlations are positively related to learning in the youngest. Corelease of noradrenalin and dopamine are important for memory formation (Lemon and Manahan-Vaughan, 2012). Integrity of the VTA, a source of dopamine, has been related to regulating encoding of hippocampal-dependent memories (Martig and Mizumori, 2011). Novel information detected by the hippocampus elicits a dopaminergic response in the VTA. Aging has been associated with a decline in dopamine availability and a lower density of dopaminergic receptors (Backman et al., 2000; Goldman-Rakic and Brown, 1981), which suggests that older individuals are less sensitive to reward or that novel reward learning is impaired (Eppinger et al., 2012; Samanez-Larkin et al., 2014). We speculate that the strong correlation between the LC and the VTA in younger adults reflects a combination of novelty and reward-related processes optimizing their memory performance. In older adults, in whom reward processing is affected, learning might be supported by unexpected novelty, providing some compensatory margin. A recent animal study showed that blocking ventral tegmental neurons has no effect on memory performance, suggesting that LC neurons can indeed mediate encoding (Takeuchi et al., 2016). As our data do not provide information on which system is different in the older individuals as compared to the younger, it could also be speculated that in older individuals, the dopaminergic system is compensating for the affected LC system (Guiard et al., 2008). These hypotheses can explain why the negative relationship between positive LC-VTA FC and learning was not significant in older individuals: it could point toward a role for the dopaminergic system in delaying age-related memory deficits. Consistent with this suggestion is the observation that monkeys treated with a dopaminergic agonist showed reduced decline on memory tasks (Arnsten and Goldman-Rakic, 1985).

While we observed age-related differences in the FC between the left LC and left parahippocampal gyrus (at an uncorrected alpha level), we did not see a relationship with memory performance in the total sample or older individuals. The fact that we were not able to replicate our previous study (Jacobs et al., 2014) may relate to sex differences. In our previous study, we only included males, whereas now, we included both males and females. Males have higher LC connectivity (Zhang et al., 2016), higher LC signal intensity (Clewett et al., 2016), and are more vulnerable to stress-related cognitive deficits (Bangasser et al., 2017).

It is intriguing that all age-related FC patterns for the cortical and functional network ROIs were observed with the left LC as a seed and not the right. The noradrenergic release from the LC, triggered by novelty, may be related to a right-lateralized frontoparietal network (Robertson, 2014). Upregulation of the noradrenergic system with reboxetine, a selective noradrenergic reuptake inhibitor, induced mainly right-sided effects, suggesting that the right has more compensatory abilities and stays stable much longer during aging (Grefkes et al., 2010).

This study has some limitations. First, the sample size, although it spans the entire range from 20 to 80 year olds, remains limited. Future studies should try to replicate these findings in large sample sizes, preferably also covering individuals older than 80 years and incorporating individuals with memory deficits. We did not see associations between FC of the LC and cortical regions and memory. This may be a consequence of our smaller sample size. However, our LC subcortical FC with memory correlations survived the multiple comparison correction suggesting a close relationship between behavior and brainstem physiology, one that may precede functional alterations in the cortex and reflect ongoing pathological

processes (Theofilas et al., 2015). In addition, given that cognition changes nonlinearly with age (Grady and Craik, 2000; Hedden and Gabrieli, 2004), future studies with larger sample sizes will have the power to investigate nonlinear interactions between age effects and LC FC on cognition (Hong et al., 2015).

Second, localization of the LC was based on an existing high-resolution template (Keren et al., 2009). To ensure anatomical accuracy, we implemented diffeomorphic registration methods to our high-resolution fMRI images, providing an increase in almost 14 times the spatial resolution of standard 3T fMRI. Templates for the localization of the LC can still introduce some error in mis-attributing some voxels, and therefore, it will be better in the future to combine high-resolution fMRI with neuromelanin imaging. We recently developed a 7T methodology to visualize the LC at high resolution (Priovoulos et al., 2018).

Finally, we did not acquire physiological data, such as respiration or heart rate variability. Although we cleaned the data in the best possible way, the brainstem region is prone to physiological artifacts, and we cannot exclude the possibility that these sources may have obscured our signal.

Disclosure statement

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.neurobiolaging.2018.05.021>.

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