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Research paper

Examining the role of the Noradrenergic Locus Coeruleus for predicting Attention and Brain Maintenance in healthy old age and disease: an MRI structural study for the Alzheimer's Disease Neuroimaging Initiative*.

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Abstract: The noradrenergic theory of Cognitive Reserve (Robertson, 2013-2014) postulates that the upregulation of the Locus Coeruleus - Noradrenergic System (LC-NA) originating in the Brainstem might facilitate cortical networks involved in attention, and protracted activation of this system throughout the lifespan may enhance cognitive stimulation contributing to Reserve.

To test the above-mentioned theory, a study was conducted on a sample of 686 participants (395 controls, 156 Mild Cognitive Impairment, 135 Alzheimer's Disease) investigating the relationship between LC volume, attentional performance and a biological index of brain maintenance (Brain-PAD – an objective measure which compares an individual's structural brain health, reflected by their voxel-wise grey matter density, to the state typically expected at that individual's age). Further analyses were carried out on Reserve indices including education and occupational attainment. Volumetric variation across groups was also explored along with gender differences. Control analyses on the Serotoninergic (5-HT), Dopaminergic (DA) and Cholinergic (Ach) systems were contrasted with the Noradrenergic (NA) hypothesis. The antithetic relationships were also tested across the neuromodulatory subcortical systems.

Results supported by bayesian modelling showed that LC volume disproportionately predicted higher attentional performance as well as biological brain maintenance across the three groups. These findings lend support to the role of the noradrenergic system as a key mediator underpinning the neuropsychology of Reserve, and they suggest that early prevention strategies focused on the noradrenergic system (e.g. cognitive-attentive training, physical exercise, pharmacological and dietary interventions) may yield important clinical benefits to mitigate cognitive impairment with age and disease.

Keywords: Locus Coeruleus; Reserve; Brain Age; Visual Attention; Alzheimer's Disease; Mild Cognitive Impairment; normal Aging; Neuroimaging; Voxel Based Morphometry

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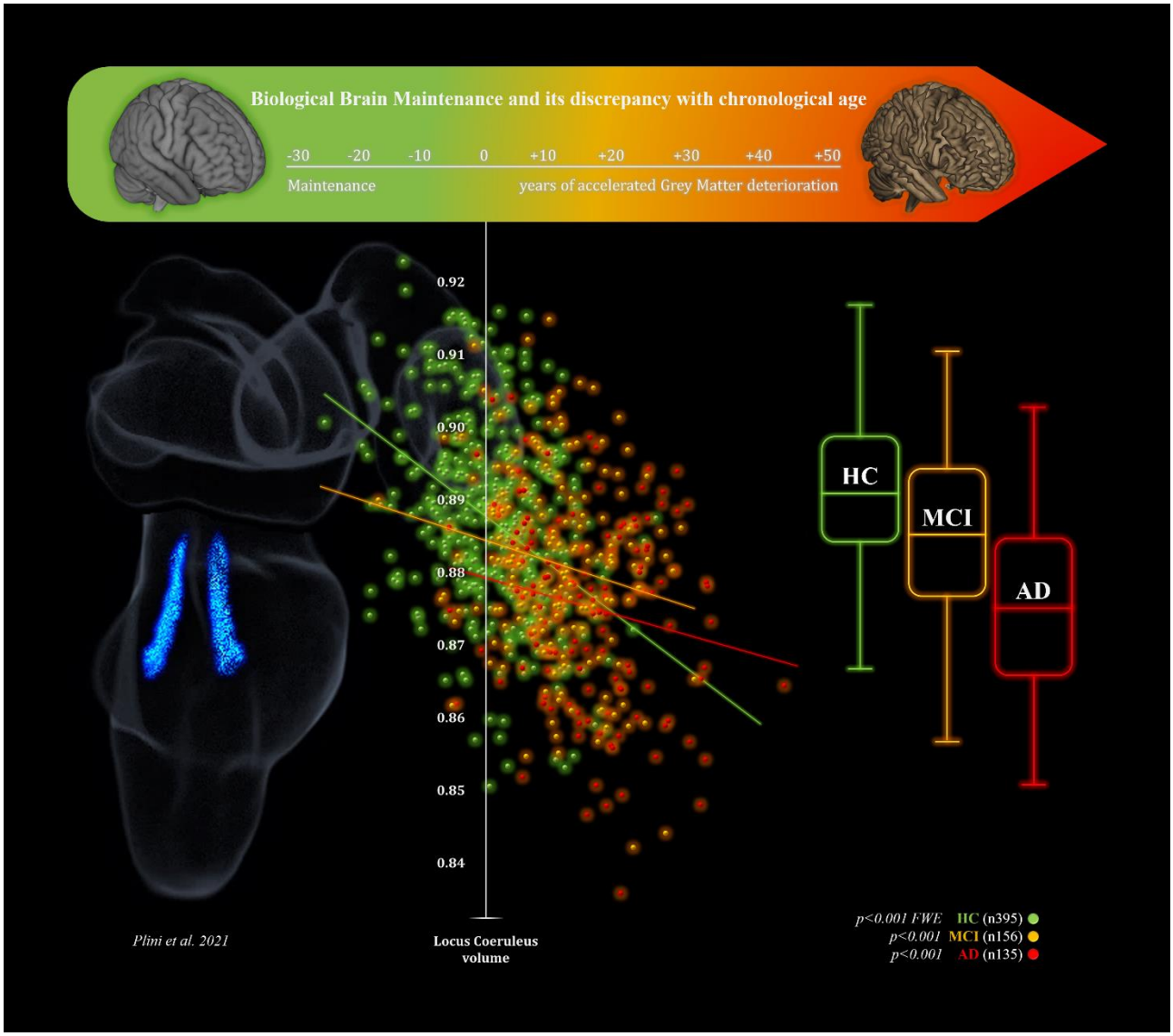
Graphical Abstract:



1. Introduction

Neurodegeneration does not always affect cognitive impairment and daily life functioning to the same extent [1, 2, 3]. In fact, some individuals even with marked brain deterioration present relatively preserved cognitive function compared to healthy individuals. The observation that the extent of brain deterioration does not reliably or linearly predict the severity of cognitive dysfunction and symptomatology can be viewed as a "cognition-pathology gap" [4]. This phenomenon has been partly explained by the role of compensatory neural processes, underscored by genetic and/or environmental factors that help mitigate the effects of advancing pathology. This resilience to brain damage has been conceptualised by Yaakov Stern (2002) [5] as a model of reserve that moderates between the degree of neural pathology and clinical outcome. Reserve is conceived as a protective factor shaped by cumulative improvement of neural resources due to genetic and environmental factors over a lifetime. In the earlier stages of the development of this construct, it has been differentiated as Cognitive Reserve and Brain Reserve respectively [6]. Cognitive Reserve refers broadly to a person's adaptability (i.e., efficiency, capacity, flexibility of cognitive processes) that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult [8]. Cognitive Reserve is often represented by I.Q., educational level, occupational complexity and cognitive performance on tests of attention, memory and executive functioning. By contrast, Brain Reserve is quantified at the neurobiological level in terms of, for example, brain volume, and the degree of functional and structural connectivity between diverse brain regions. However, the current consensus is moving towards a broader and more comprehensive concept of Reserve, since neural and cognitive components are deeply integrated with each other. Accordingly, the current terminology, referring to Reserve as the cumulative improvement due to genetic and environmental factors, pertains to both neurobiological and cognitive levels of Reserve [8]. Two important sub-components of Reserve are maintenance and compensation [9]. Maintenance is considered to reflect how well a brain is preserved in structural and functional terms, and compensation is the capacity to recruit existing resources with greater efficiency or to employ alternative neural networks in response to cognitive demand. These two sub-components are therefore measured in different ways [8]. First, an index of brain maintenance has been developed to assess the degree of brain deterioration relative to chronological age (Brain Predicted Age Difference – BrainPAD or Brain Gap Estimation - BrainAGE) in order to address a more precise value of maintenance than just brain volume alone [10, 11, 12]. Based on the brain deterioration in optimal normal ageing, BrainPAD is a cross-sectional measure which compares an individual's structural brain health, reflected by their voxel-wise grey matter density, to the state typically expected at that individual's age. Therefore, higher discrepancies between the biological brain age and chronological age are indices of abnormal ageing and lower Reserve with respect to the brain maintenance sub-component. Second, compensation can be indexed by upregulation of a particular neural network or by alternative patterns of functional connectivity during a task, yielding a beneficial behavioural outcome [8, 9]. Thus, it can be inferred that such patterns of activation or re-organisation serve compensatory processes.

The evidence of the last decades has shown that the most common and well addressed predictors of reserve – higher education, I.Q., cognitive stimulation, social interaction and physical activity – are related to reduced risk of dementia, better cognitive functioning and overall greater brain mass [13]. Moreover, these factors mediate the gap between brain pathology and cognitive functioning. In the extensive review by Livingstone and

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colleagues [13], it was estimated that among the 35% of the modifiable risk factors of dementia, high education has a mitigating impact of 8% on disease severity, which increases resilience. Although progress has been made in identifying the contribution of these genetic and/or life experience variables to the accumulation of Reserve, the neurobiological substrate underpinning Reserve and the extent to which it can mitigate neurodegeneration is not yet understood.

In this regard, Robertson [1, 2] proposed the noradrenergic theory of Cognitive Reserve, arguing that the continuous upregulation of the noradrenergic system throughout the lifetime can be a key component of Cognitive Reserve. The Noradrenergic (NA) system originates in a small bilateral nucleus of the pons of the brain stem named Locus Coeruleus (LC). LC synthesizes approximately 70% of Noradrenaline (NA) in the brain and is responsible of the 90% of the total brain efflux of NA [14]. NA is one of the most diffusely distributed neurotransmitters in the brain and underpins arousal, alertness and attention [14, 15, 16, 17]. Furthermore, several studies of neurodegeneration have found that NA supply and LC integrity are significantly reduced in Alzheimer's disease [18, 19, 20, 21]. Tau pathology in the LC has been found earlier than in other brain regions during the preclinical stages of the disease [22, 23, 24, 20, 31, 101], and reduced volume of the LC has been associated with the extent of beta-amyloid and tau pathologies [25, 26, 27], suggesting it as possible biomarker of neurodegenerative diseases [28]. In a post-mortem study on 165 individuals, Wilson et al. [29] found that higher neural density in the LC was significantly associated with better baseline cognitive functioning and with slower cognitive decline. There is also evidence that the LC exhibits neural loss up to 80% greater in Alzheimer's patients than in controls [30]. Comparatively, both neuroimaging and histopathological human and animal studies also report that lower LC volume was associated with increased beta-amyloid and tau pathologies across the brain and with increased overall brain deterioration and inflammation [31, 32, 26, 27, 33, 34, 35, 36]. Furthermore, murine models demonstrate that NA promotes phagocytosis of beta-amyloid plaques, suggesting that the LC-NA system may offer protection against the development of these plaques in the human brain [37].

Robertson's theory links the recent evidence concerning the LC-NA involvement in neurodegeneration with its primary role in attention, learning and memory consolidation. The key cognitive reserve factors (higher IQ and education, life-long social and cognitive stimulation and physical exercise) are components which require activation of the LC in producing and releasing NA [1, 2, 13, 38]. These reserve proxies require arousal modulation and attentional processing in response to problem solving and novelty. In Robertson's theoretical framework, the continuous protraction of these activities, on a regular basis throughout life-time, can lead to an overall higher noradrenergic tone, facilitating more active cognition and building more resilient neurobiological networks in the face of age- and disease-related decline. The ability to sustain attention and the arousal in response to cognitive engagement and novelty may increase general awareness and mental stimulation, both of which positively contribute to the construct of Reserve. Therefore, the proposed neurobiological mechanism behind the protective action of reserve indices may in part be explained by the properties of a more active noradrenergic system, which optimises structural and functional brain connectivity providing greater resistance to neurodegeneration. NA has been known for its neuroprotective effects [39, 40, 41], which reduce brain inflammation and promote neurogenesis and synaptogenesis increasing brain derived neurotrophic factor (BDNF), which could increase the number of brain cells [42, 43, 44, 45, 46, 47]. This noradrenergic system may therefore be critical in to reduce the brain's vulnerability to both the normal ageing process and pathological neurodegeneration via a more active attentional system [1, 2, 48]. Therefore, in this theoretical framework greater LC volume is proposed to reflect a greater noradrenergic tone, conversely, lower LC vol-

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ume is associated with lower NA levels compromising cognition and brain heath, according to previous studies [17, 18, 20, 21, 22, 26, 28, 31, 32, 35, 46, 48, 101, 102, 103, 104, 105, 106, 128, 129, 137, 139, 172, 176, 177].

The main aim of this study was to test the hypothesized relationship between the structural integrity of the LC and indices of reserve and attention in healthy older controls (HC), and patients with Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD). To this end, we adopted a neuroimaging voxel-based morphometry (VBM) approach utilizing 3T T1-weighted structural MRI scans from 686 subjects [n=395 (HC), n=156 (MCI), and 135 (AD)] provided by Alzheimer's Disease Neuroimaging Initiative – ADNI (ADNI2 and ADNI3 phases) [49, 50]. Structural volumetric analyses on 3T T1-weighted MRIs with this methodology have been already carried out by several studies showing accurate reliability investigating the integrity of the Brainstem [51, 52, 53, 54], the LC also in the ADNI [55, 56, 57, 58] and the other neuromodulators' seeds such as the Raphe Nuclei [59, 60, 61, 62], the Ventral Tegmental Area (VTA) [63, 64, 65, 66] and the Nucleus Basalis of Meynert (NBM) [67, 68, 69, 70, 71, 72, 73, 74]. The main objectives of this study were threefold. First (1st branch of VBM analyses), to examine the relationship between LC integrity and cognitive function measured by the Trail Making Test A (TMT-A), which is a clinical tool sensitive to basic attentional efficiency, visual search and motor processing speed [79, 169, 170]. We anticipated that greater LC volume would be negatively associated with TMT-A completion time in seconds, according to previous findings [29, 48, 55] and consistent with Robertson's theory [1, 2]. TMT part A has been chosen over the part B since the latter was not completed by all the selected participants included in the ADNI (specifically in the Alzheimer's group), and also because it is considered to evaluate more structured cognitive processes such as cognitive flexibility and divided attention [75, 76]. Second (2nd branch of VBM analyses), to examine the extent to which LC integrity mediates the relationship between BrainPAD and attentional efficiency. We tested the hypothesis that higher LC volume would be associated with both higher brain maintenance and better cognitive performance as postulated by Robertson [1, 2]. It was expected that higher LC volume would predict more negative values of BrainPAD reflecting 'younger' brain age. These analyses investigated the potential compensatory role of the LC-NA system in mediating the relationship between brain maintenance and cognitive performance. Third (3rd and 4th branches of VBM analyses), to analyse the potential relationships between LC integrity and putative indices of reserve, namely, educational level and occupational status held by people throughout their lifetime. It was anticipated that greater LC volume would be associated with both higher levels of education and occupational complexity demands. Indeed, in Robertson's theory, jobs with higher cognitive demands require greater stimulation of the noradrenergic system contributing to the reserve component [1, 2].

As a control procedure, each of the above analyses were repeated testing the opposite relationships as hypothesized, namely lower LC volume related to better cognition and brain health [77, 78, 79]. Furthermore, the analyses were repeated for brainstem nuclei of the serotoninergic, dopaminergic and cholinergic systems in order to compare the Noradrenergic hypothesis to the other main neuromodulators involved in cognition. Finally, the analyses were also performed on a ROI drawn in the ventro-rostral portion of the Pons, which to the best of our knowledge is without anatomical nuclei projecting neuromodulators to the cortex, and can therefore be considered a "neuromodulator-free" control region.

Secondary objectives of the study were to investigate: which of the above-mentioned neuromodulators showed the greatest covariance with cognitive decline across the three groups (5th branch of VBM analyses); and explore the differential volumetric variation of the neuromodulators due to gender at different stages of cognitive decline (6th branch of VBM analyses).

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2. Materials and Methods

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

2.1. Neuroimaging

3Tesla T1-weighted images in Nifti format of ADNI 2 and ADNI 3 phases [49, 50] were downloaded from IDA (image data archive powered by LONI - https://ida.loni.usc.edu/). Baseline T1-images of all subjects were selected and organised according to diagnosis: Cognitive Normal (CN/HC), Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD). Diagnostic criteria of the ADNI are described by Petersen et al. 2010 [80]. A rigorous manual quality control of the images was carried out according to the rating scale guidelines (1= poor, 2= fair, 3= good, 4= excellent) of the Human Connectome Project (HCP) (https://www.humanconnectome.org/). Subjects with low definition (excessive blurriness) and/or marked ringing, inhomogeneities and motion artefacts were removed from the dataset. The selected scans were then segmented using CAT12 (Computational Anatomy Toolbox - http://www.neuro.uni-jena.de/cat/) implemented in SPM12. The segmentation was performed using the default CAT12 settings, with a 1mm isotropic voxel size. The segmentation was run separately for the three groups with the same pipeline and parameters. Subjects with an image quality score below 70% (no more than 0.6% of the sample) were then discarded according to CAT12 reports of quality assurance rating scale (100-90 = A [Excellent]; 90-80 = B [Good]; 80-70 = C [Satisfactory]; 70-60 = D [Sufficient]; 60-50 = E [Critical]; 50-40 = F [unacceptable/failed]. Only the 6.2% of the selected images were below 80% (B). Subsequently, the processed normalized images Grey Matter (GM) + White Matter (WM) were smoothed with a 2 mm^3 FWHM kernel. Lastly, in order to better account for individual volumetric variability, the Total Intracranial Volume (TIV) was calculated for each subject using CAT12 interface. More details are provided in the supplementary materials.

2.1.2 Region of interest (ROI) masks

All binary ROIs were 1mm3 isotropic voxel size and oriented in the Montreal Neurological Institute (MNI) space as the processed T1 (GM+WM) images. The six ROI masks were obtained by previously published atlases. The technical details and theoretical justifications for the specific ROI definitions are described in the following section for each neuromodulator seed. Further details are provided in the supplementary materials.

Accurate MRI localization of the LC in the human brain is still lacking wide-spread agreement [33]. In the last few years several probabilistic maps of the LC have been released, however, these probabilistic maps are inconsistent in both localization and volume extent within the MNI space. Indeed, different sample sizes have been recruited and this exacerbates the limitations due to different methodologies involved. These differences reflect a large anatomical variability of the samples scanned suggesting that the LC varies across the general population.

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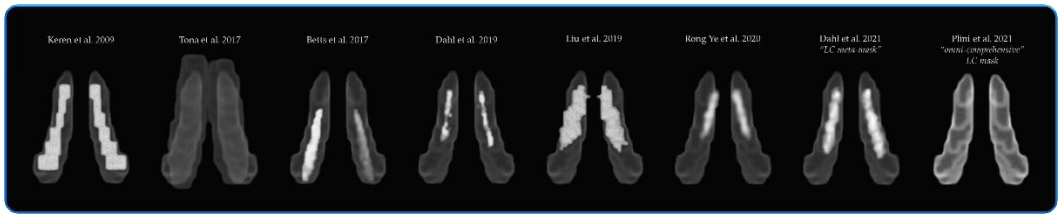
In order to perform volumetric analyses appropriate to the present research, and to attempt to resolve these differences, it was necessary to define a common space that included all the previous maps as to increase the likelihood of inclusion of the entirety of the LC, given the probable increase in between-subject anatomical variability in the present ADNI populations (n=395 HC, n=156 MCI, n=135 AD).

Therefore, a new symmetrical "omni-comprehensive" LC mask in the MNI space was created in order to include the whole LC rostro-caudal extent (see figure 1). Indeed, it was observed that with increasing age the LC signal intensity tends to shift from rostral to caudal portion [33, 81]. This process might be influenced by manifold variables, such as ageing, the degree of biological brain maintenance and even dementia progression, which is likely to exacerbate this "caudal-shifting" process. Moreover, it is acknowledged how the noradrenergic system is susceptible to compensatory changes across the brain involving the caudal portion of the LC and peri-coeruleus/LC-peri-dendritic regions (Epi-coeruleus and Sub-coeruleus) [106, 128, 177, 178, 180, 181, 182, 14]. Therefore, considering a larger area rather than a very specific and concise region would be more informative and appropriate while investigating the LC-NA system on different groups, particularly known the heterogeneity of Alzheimer's Disease. The new "omni-comprehensive" LC mask included the six LC MNI atlases previously published: 1) Keren et al. (2009) [81, 179], 2) Tona et al. (2017) [82], 3) Betts et al. (2017) [83], 4) Dahl et al. (2019) [32], 5) Liu et al. (2019) [183] and 6) Rong Ye et al. (2020) [84] without encroaching the Median Raphe (MR) and the Dorsal Raphe (DR) defined by Beliveau et al. (2015) [85] and the cerebellar white matter. Additionally, the new created LC "omni-comprehensive" mask included the LC meta-mask developed by Dahl et al. (2021) [57], but with a larger and symmetrical rostro-caudal extent as to avoid induced lateralization biases in the analyses. Indeed, as pointed out by Betts et al. [83], the LC asymmetries reported in certain MRI studies could be caused by MRI biases of how radiofrequencies are transmitted and received in the scanner. In fact, post-mortem histological studies consistently revealed symmetrical distribution of LC cells [184, 185, 186, 187, 189, 14].

Figure 1. shows the spatial resolution of the new created symmetrical "omni-comprehensive" LC mask in comparison with the previously published LC MRI atlases and masks.



MR and DR 1mm3 MNI masks were generously provided by Beliveau et al. (2015) [85]. The probabilistic maps and masks were obtained by analysing 232 PET scans matched with high-res 3T structural MRI of healthy subjects between 18 and 45 years old.

The VTA mask was obtained by downloading the VTA MNI probabilistic map from the atlas made by Pauli et al. 2018 [86] from the NeuroVault website (https://neurovault.org/). The atlas was made using the MRI data from the Human Connectome Project (HCP) and was derived from a selected sample size of 168 healthy subjects between 22 and 35 years old. The localisation of the Substantia Innominata (SI) / NBM was more controversial than the previous nuclei, as there are no specific maps available in MNI space. Albeit, probabilistic MNI maps of the Acetylcholine cells of the Forebrain are provided by SPM Anatomy Toolbox 2.2c (https://www.fzjuelich.de/inm/inm1/EN/Forschung/_docs/SPMAnatomyToolbox/SPMAnatomyToolbox_node.html) [87]. However,

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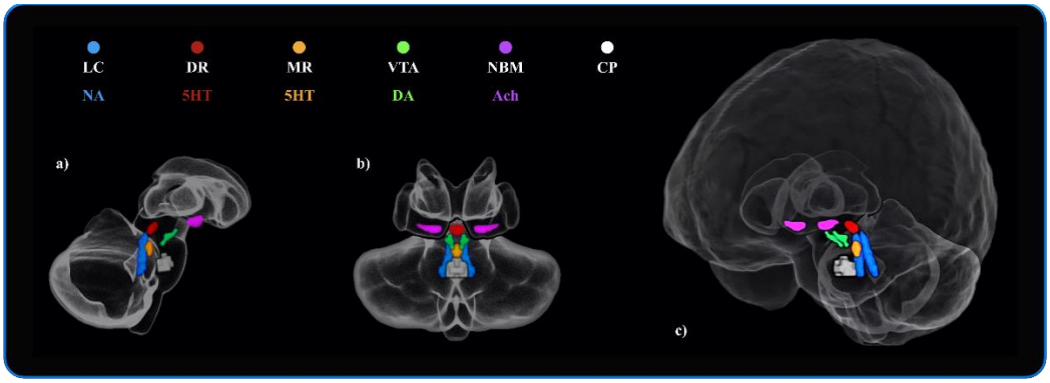
the probabilistic map referring to the SI/NBM (4ch.nii) defined by Zaborszky et al. (2008) [87] is overlapping several subcortical nuclei delineated in other atlases [86, 88, 89, 90, 91, 92, 93, 94]. Therefore, the "4ch.nii" was used as main reference to delineate the SI/NBM, but was adjusted by excluding the subcortical nuclei identified by other atlases while accounting for the probabilistic localisation of the SI/NBM delineated in previous works [95, 96, 68, 97, 69].

In order to control for a "neuromodulator-free" brainstem's region, a squared binary ROI not referring to any anatomical nuclei was drawn in the ventro-rostral portion of the Pons. A greater number of voxels were used in order to obtain a control region similar in voxel-size well-suited for the detection of false positive.

Figure 2. Shows the five neuromodulators' seeds and the neuromodulator-free control region investigated in the VBM analyses. Blue: Locus Coeruleus (LC – "omni-comprehensive") – Noradrenaline (NA) – (714 voxels). Red: Dorsal Raphe Nuclei (DR) – Serotonin (5HT) – (174 voxels). Orange: Median Raphe Nuclei (MR) – Serotonin (5HT) – (108 voxels). Green: Ventral Tegmental Area (VTA) – Dopamine (DA) – (252 voxels). Purple: Nucleus Basalis of Meynert (NBM) – Acethylcholine (Ach) – (492 voxels). White: Control Pontine ROI ("neuromodulator-free" region) – (906 voxels). All the ROI binary masks were symmetrical and 1mm3 isotropic voxel size and there were no overlapping boundaries between the masks. Image a) displays the anatomical localization of the six ROIs in sagittal view of the Cerebellum, Brainstem and Diencephalon. Image b) displays the coronal view. Image c) shows a fronto-lateral view of the whole brain and the anatomical localization of the six ROIs.



2.1.3 BrainPAD measure calculation

Brain Predicted Age Difference (BrainPAD) is a measure of how the brain is ageing, and it is obtained by calculating the discrepancy between the chronological age and the biological age of the brain defined on healthy brain ageing of typical people. Subjects with a younger brain than their chronological age have negative values, whereas if a subject is ageing faster than their chronological age the index is a positive value. BrainPAD is thought to reflect how well Grey Matter (GM) is maintained, hence it is proposed to be an index of brain maintenance. BrainPAD measure by Boyle et al. (2020) [12] was developed using several datasets. In the first instance they defined the normal GM ageing in healthy subjects. They then trained an algorithm to predict successfully the degree of GM deterioration in relation to the chronological age in further 3 populations of healthy subjects. The algorithm used in this study is described in detail in Boyle et al. (2020) [12].

2.1.4. Voxel Based Morphometry (VBM) analyses

VBM analyses were performed using T1 whole brain images (WM+GM), after being pre-processed and smoothed 2 mm^3 FWHM kernel. Each set of analysis aimed to investigate

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five main research interests, based on Robertson's theoretical framework [1, 2]. Each analysis first considered the LC and was then repeated separately for the other brainstem nuclei and the CP ROI as a control procedure testing both positive and negative relations. The statistical thresholds were settled at *P<0.01*, and later increased progressively until the results disappeared (namely: *P<0.001*, *P<0.01 FWE*, *P<0.001 FWE*).

2.1.5. Relationship between LC volume and attention

The first question addressed by this study was to investigate whether the LC volume can be a predictor of attentional performances measured with TMT-A (visuo-motor speed processing). Three multiple regression models were run for each group. In the model, TMT-A was included as a continuous variable and TIV, education and age were insert as covariates. Then, based on previous literature and the main hypothesis, a negative relation between the LC volume and the TMT-A was also investigated, namely, larger LC volume was expected to be related to faster attentional performances (less seconds spent in completing the task). The following contrast was used for negative relation: 0 0 0 0 -1. The contrast: 0 0 0 0 1 was used as well as control analyses testing the positive relation. A further step in the analyses was to indicate the LC mask as "inclusive mask" in order to isolate the LC involvement in the model. Similarly, all the other ROIs were tested in the same way.

2.1.6. Relationship between LC volume and biological brain maintenance

The negative relation between LC volume and BrainPAD was then tested across the three groups, with the hypothesis that greater LC volume would be associated with lower and negative BrainPAD scores, reflecting reduced brain aging relative to chronological age. As the previous analyses BrainPAD was treated as dependent continuous variable and the same covariates and contrasts were used, including chronological age as suggested by Le TT et al. (2018) [98]. The following contrast was used for negative relation: 0 0 0 0 -1. The contrast: 0 0 0 0 1 was used as well as control analyses testing the positive relation. A further step in the analyses was to indicate the LC mask as inclusive in order to isolate the LC involvement in the model. Similarly, all the other ROIs were tested in the same way.

2.2. Mediation Analyses

Mediation analyses with multiple parallel mediators were carried out in order to better clarify the possible role of the LC as key component in mediating Reserve indices and attentional performances. The analyses considered the three groups separately and were performed using the toolbox PROCESS v3.4 and SPSS macro developed by Andrew F.Hayes (http://www.processmacro.org/) implemented in SPSS 25 (https://www.ibm.com/products/spss-statistics). The toolbox PROCESS enables one to perform manifold types of mediation and moderation analyses. In SPSS, from the PROCESS interface it was selected the model number four with 95% confidence intervals and 5000 bootstrap samples. This model number enables to perform mediation analyses with parallel multiple mediators and covariates. TMT- A time in seconds was used as the Y variable and BrainPAD scores as the X variable. The extracted average volume values of the six ROIs were considered as six parallel mediators. TIV and age were treated as covariates.

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2.3. Rational for the neuromodulatory subcortical systems ROIs selection

From Dopamine, Noradrenaline is synthetized subcortically in the brainstem, specifically in the LC, in the dorsal pontine tegmentum and in the lateral tegmental neurons [14]. However, the LC is the most relevant neural basis of NA, it is the main structure responsible for the NA production and also accounts for 90% of its cortical NA innervation. LC's projections are vastly spread throughout the cortex and the Cerebellum [15, 99]. For these reasons, it has been defined as the main core structure of investigation of the noradrenergic theory of cognitive reserve. Given that the analyses were designed to be performed also on clinical samples, control analyses were made to account for the possibility to detect false positive concerning the LC involvement in attention and reserve due the ongoing diffuse neurodegeneration of the samples. Therefore, other main neuromodulators and their main core nuclei were considered as control regions as to better assess the implication the LC-NA system in attention and reserve. The first control neuromodulator defined was the serotoninergic system, because it is believed to broadly modulate markedly different processes than NA. Additionally, Serotonin is synthesised in the Pons very closely to the LC but from a different precursor (Tryptophan) [14], thus this anatomical area is particularly well suited for controlling purposes. The Median and the Dorsal Raphe nuclei are the largest serotoninergic seeds producing and projecting Serotonin to the Cortex and the Cerebellum via the basal forebrain [14, 85]. The dopaminergic system was also examined, and so the Ventral Tegmental Area was taken as a core area for the analyses. VTA is the main brain nucleus together with the Substantia Nigra (SN), where Dopamine is synthesised from the amino acid Tyrosine [14]. The VTA is responsible for the cortical irroration of Dopamine while the SN projects subcortically. For this reason, VTA was defined as control region to control for the dopaminergic system. Regarding Acetylcholine, the Substantia Innominata/Nucleus Basalis of Meynert (NBM) was chosen over the Tegmental Cholinergic Neurons, because it has the largest number of cholinergic neurons and it projects diffusely to the entire cortex. Over 90% of the NBM includes cholinergic magnocellular neurons [14, 95]. Finally, in order to control for a "neuromodulator-free" brainstem region, a ROI not referring to any anatomical nuclei was designed in the ventro-rostral portion of the Pons.

3. Results

Descriptive statistics for key demographic, neural, and neuropsychological variables are presented in table 1.

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Table 1. Sociodemographic, neural indices and neuropsychological characteristics of the HC, MCI and AD groups. Key: TIV, total intracranial volume; BrainPAD, Brain predicted age discrepancy (biological maintenance index); TMT-A. trail making test part A time in seconds. (* $p < .05$; ** $p < .01$; *** $p < .001$ Bonferroni correction)

	Sociodemographic								Neural indices				Neuropsychological	
	Gender		Age***		Education***		Occupation*		TIV		BrainPAD***		TMT-A***	
groups	M	F	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
HC (*n*=395)	168	227	73,45	7,21	16,96	2,21	6,21	1,72	1408,16	146,28	1,59	7,69	30,64	8,85
MCI (*n*=156)	90	66	75,51	8,10	15,98	2,76	5,78	1,85	1426,12	142,78	5,45	9,00	39,07	17,86
AD (*n*=135)	74	61	76,61	8,43	15,64	2,54	5,93	1,84	1385,79	167,47	13,32	9,13	61,61	36,59

3.1. Sociodemographic characteristics and indices of reserve and attention

Age significantly differed across groups, $F(2,683) = 10.13$, $p < .001$. Post hoc comparisons showed that the HC group was significantly younger than the MCI group ($p = 0.014$) and the AD group ($p < 0.001$). The MCI and AD groups did not significantly differ from each other in age ($p = 0.68$). Groups also differed in education, $F(2,683) = 19.41$, $p < .001$. The average years of education was greater for the HC group compared to the MCIs ($p < .001$) and the AD group ($p < .001$). The MCI and AD groups did not differ in mean years of education ($p = 0.68$). There was an effect of occupation, $F(2,683) = 11.71$, $p=.025$. The HC showed a higher occupational rank compared to MCI ($p=.031$). No other group comparisons for occupation were significant (all $p > 0.3$). Chi-squared test showed that gender was not evenly distributed across the three groups ($X^2 = 12.35$; df: 2; $p = 0.002$). As reported in table 1, the HC contains significantly more females (57%) while in MCI and AD males are more highly represented (57.1% and 54.8% respectively). There was no significant difference in TIV by group, $F(2,683)=2.62$, $p=0.07$. However, there was a significant difference in BrainPAD scores, $F(2,683)=101.2$, $p < 0.001$. There was a systematic pattern in which AD patients showed greater BrainPAD scores (indicating an older brain relative to chronological age) compared to MCI patients ($p < 0.0001$), who in turn showed a greater mean BrainPAD score than the HC group ($p < 0.0001$). All groups significantly differed in time taken to complete the TMT- A, $F(2,683) = 127$, $p < 0.001$. AD patients exhibited the longest duration (mean seconds) compared to the MCI ($p < 0.001$), which showed a longer mean time-to-completion than the HC group ($p < 0.001$). More details are provided in the supplementary materials including the average volumetric and gender differences across the three groups for the six ROIs (reported in table 9 and table 10).

3.2. 1st branch of VBM analyses: Multiple Regressions – TMT-A (Attention – visuo-motor speed processing)

Does the LC predict attention performance relative to other neuromodulator seed regions?
As can be observed in table 2, for the statistical threshold of $p<0.001$ only the 3 voxels of the NBM were significant in the HC. For the MCI group, reduced volume of the LC (142 voxels $p<0.01$ and 21 voxels for $p<0.001$) was associated with longer TMT-A completion time. Similarly, in the AD, the strongest predictor of attention performance was the LC with 9 (122 voxels for $p<0.01$) voxels negatively associated with the attentional performance. As shown in figure 3 the average LC results are localised within a region overlapping the LC core defined by previous atlases. Further neuromodulators' seeds also contributing to the variance in TMT-A performance included 14 VTA voxels and 19 NBM

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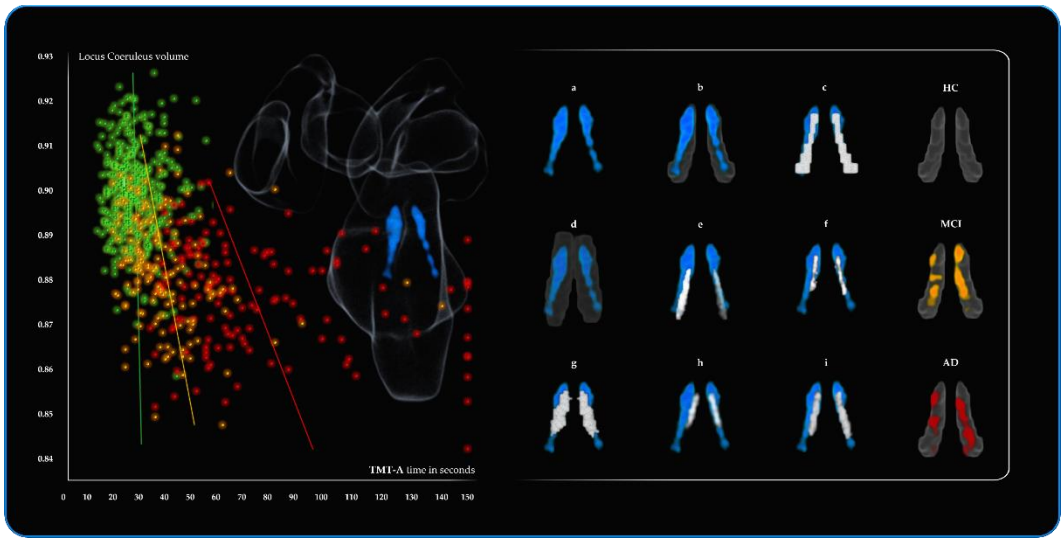
voxels negatively associated with performance. For the three groups these results did not survive when FWE correction was applied. As a control measure, the opposite relationships (positive associations with TMT-A) across the 3 groups for all 6 ROIs were assessed and revealed no significant results. (more details are provided in the supplementary materials section 3.5.)

Figure 3. Results from the VBM multivariate linear regression analyses performed in CAT12 for the three groups (HC, MCI, AD). The results are covaried for total intracranial volume (TIV), age and education. The scatterplot displays the relationship between Locus Coeruleus (LC) volume (y axis) and TMT-A time in seconds (x axis) for the three groups: green (HC, n.395), orange (MCI, n.156), red (AD, n.135). On the x axis (TMT-A) are shown the seconds required to complete TMT-A. More seconds spent in completing TMT-A mirror a slower visuo-spatial cognitive processing related to the LC decline. The systematic decline of the LC volume across the three groups is related to a slower visuo-motor attentional performance. On the left portion of the figure, in blue it is shown the average LC results for the three groups (n=686, P<0.001) on a 3D fronto-lateral view of the Brainstem and the Diencephalon. On the right portion of the figure are shown 3D reconstructions (displayed in the MNI152 space) of the results in comparison with previously published LC atlases and masks. **a**) average LC result; **b**) average LC result is shown in the LC "omni-comprehensive" mask; **c**) Keren et al. (2009) [81, 179]; **d**) Tona et al. (2017) [82]; **e**) Betts et al. (2017) [83]; **f**) Dahl et al. (2019) [32]; **g**) Liu et al. (2019) [183]; **h**) Rong Ye et al. (2020) [84]; **i**) LC meta-mask by Dahl et al. (2021) [57]. The last column on the right shows the regions of the LC mask negatively related with TMT-A performances for the three groups considered separately (p<0.01): HC n=395 (no results), MCI n=156 and AD n=135.



3.3. 2nd branch of VBM analyses: Multiple Regressions - BrainPAD (Reserve – brain maintenance)

Does the LC predict brain maintenance relative to the other neuromodulator seed regions?

Table 3 shows a significant (p<0.001 threshold FWE corrected) cluster of 153 LC voxels predicting BrainPAD score in the HC group, demonstrating that greater LC volume is associated with a lower or negative (i.e. younger) BrainPAD score. Similarly, 71 voxels of the DR were significant as well. MCI showed a similar trend, with statistical threshold of p<0.001, 59 LC voxels and 109 DR voxels predicting BrainPAD score.

As shown in figure 4 the average LC results are localised within a region overlapping the LC core defined by previous atlases. A lesser contribution of 2 VTA voxels and 12 NBM voxels also predicted BrainPAD score. In the AD the most widespread effects were observed. All the ROIs, except the control pontine region, were found to negatively predict BrainPAD scores. At the p<0.001 threshold, the most significant cluster was found in the

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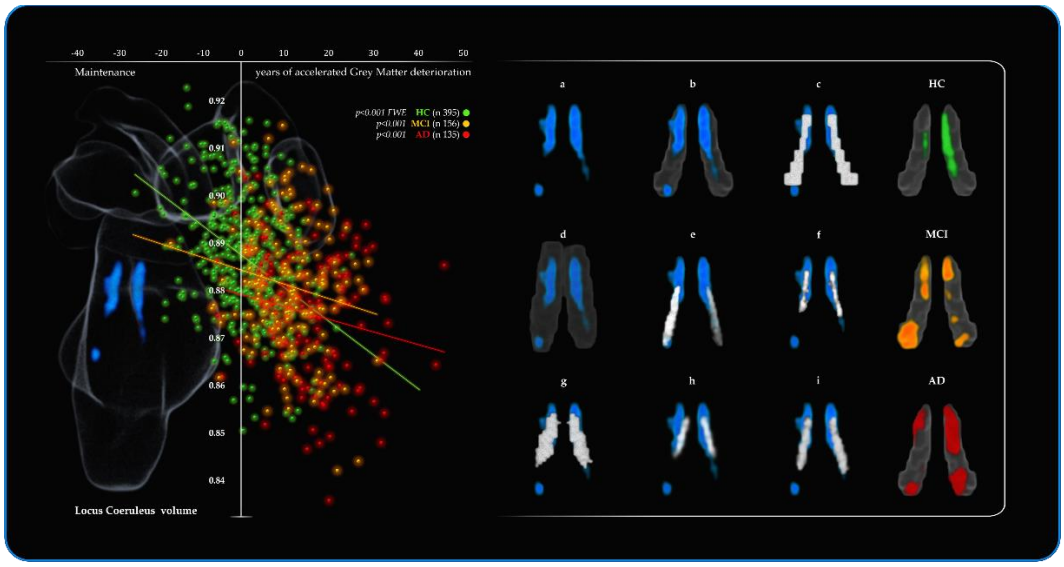
LC (192 voxels). Two clusters of 90 and 20 voxels were observed in the DR and MR respectively.

There were also 2 bilateral clusters in the VTA (9 voxels) and a cluster in the NBM (5 voxels). When FWE correction was applied, no results survived for MCI and AD. When tested, the opposite relationships (positive associations with BrainPAD) across the 3 groups for all the 6 ROIs showed no significant results. (more details are provided in the supplementary materials section 3.6.).

Figure 4. Results from the VBM multivariate linear regression analyses performed in CAT12 for the three groups (HC, MCI, AD). The results are covaried for total intracranial volume (TIV), age and education. The scatterplot displays the relationship between Locus Coeruleus (LC) volume (y axis) and BrainPAD (x axis) for the three groups: green (HC, n.395), orange (MCI, n.156), red (AD, n.135). On the x axis (BrainPAD) are shown the years of discrepancy between chronological age and the actual biological brain age based on the degree of Grey Matter deterioration. Negative values of BrainPAD mirror a better GM brain maintenance corresponding to a "younger brain age" than the chronological age. Positive values of BrainPAD mirror the accelerated brain's GM deterioration. Namely, positive values correspond to a worse biological maintenance, and to an older brain than the chronological age. The systematic decline of the LC volume across the three groups is related to a progressive accelerated GM deterioration. Indeed, HC are more shifted towards the upper-left portion of the graph (negative values of BrainPAD and greater LC volume), whereas MCI and AD are more shifted towards the lower-right portion of the graph (positive values of BrainPAD and lower LC volume). On the left portion of the figure, in blue it is shown the average LC results for the three groups (n=686, P<0.00001 FWE) on a 3D fronto-lateral view of the Brainstem and the Diencephalon. On the right portion of the figure are shown 3D reconstructions (displayed in the MNI152 space) of the results in comparison with previously published LC atlases and masks. **a**) average LC result; **b**) average LC result is shown in the LC "omni-comprehensive" mask; **c**) Keren et al. (2009) [81, 179]; **d**) Tona et al. (2017) [82]; **e**) Betts et al. (2017) [83]; **f**) Dahl et al. (2019) [32]; **g**) Liu et al. (2019) [183]; **h**) Rong Ye et al. (2020) [84]; **i**) LC meta-mask by Dahl et al. (2021) [57]. The last column on the right shows the regions of the LC mask negatively related with BrainPAD values for the three groups considered separately: HC n=395 (P<0.001 FWE), MCI n=156 (P<0.001) and AD n=135 (P<0.001).



3.4. Mediation analyses

Does the LC mediate the relationship between BrainPAD (X) and attention performance (Y)?

A multiple parallel mediation analysis was conducted for each of the three groups. Bootstrap confidence intervals were used to examine the role of the six subcortical nuclei in mediating the relationship between BrainPAD score and attention performance, while controlling for age and TIV (see figure 5 - schematic mediation pathways for MCI group). In HC and AD the total effect of X on Y was significant. The direct effects of X on Y were

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found not significant for the HC and significant for AD groups, indicating that better brain maintenance relative to chronological age was predictive of attention performance (HC total effect of X on Y: 0.1586; se: 0.0552; T:2.874, p= 0.0043; LLCI: 0.0501; ULCI: 0.2672; c_ps: 0.0179; c_cs: 0.1378) (HC direct effect of X on Y: 0.1225; se: 0.0877; T:1.3979, p= 1.630; LLCI: -0.0498; ULCI: 0.2949; c_ps: 0.0138; c_cs: 0.1065). (AD total effect of X on Y: 1.7088; se: 0.3918; T:4.3608, p< 0.0000; LLCI: 0.9336; ULCI: 2.4840; c_ps: 0.0467; c_cs: 0.4262) (AD direct effect of X on Y: 1.2410; se: 0.4658; T:2.6644, p= 0.0088; LLCI: 0.3189; ULCI: 2.1630; c_ps: 0.0339; c_cs: 0.3095). However, no indirect effects of the 6 mediators were apparent. On the other hand, in MCI the LC alone was found to significantly mediate the relationship between BrainPAD (Y) and TMT-A (X) (indirect effect of X on Y: 0.0927; BootSE: 0.0499; BootLLCI: 0.0111; BootULCI: 0.2043). The total effect of X on Y was also significant (effect: 0.4224; se: 0.1583; t: 2.6678; p: 0.0085; LLCI: 0.1096; ULCI: 0.7352; c_ps: 0.0237; c_cs: 0.2130). Controlling for the mediation effect, the direct effect of X on Y is not significant (direct effect: 0.0383; se: 0.2496; t: 0.1535; p: 0.8782, LLCI: -0.4552; ULCI: 0.5318, c'_ps: 0.0021, c'_cs:0.0193), implying that the effect of BrainPAD on attention performance in MCI is mediated indirectly through the LC volume. This finding suggests that the way brain maintenance affects attention performance in MCI patients is disproportionately influenced by the noradrenergic system compared to other neuromodulatory systems.

Figure 5. Statistical diagram of the parallel mediation model (model n.4) testing the relation between BrainPAD (biological measure of brain maintenance) and TMT-A (attentional visuo-motor speed processing) in MCI group (n= 156). The average volumes of the six ROIs were treated as parallel mediators in order to test the noradrenergic theory of cognitive reserve versus the other main neuromodulator's seeds: serotoninergic (Dorsal and Median Raphe), dopaminergic (Ventral Tegmental Area), cholinergic (Nucleus Basalis of Meynert) and additionally with a brainstem control region neuromodulator-free (control pontine ROI). In the MCI group, the only significant mediator of the relation between brain maintenance and cognitive performance was the volume of the LC (Noradrenaline); all the other five ROIs were not significantly mediating the relation. The model was covaried for age and total intracranial volume (TIV).

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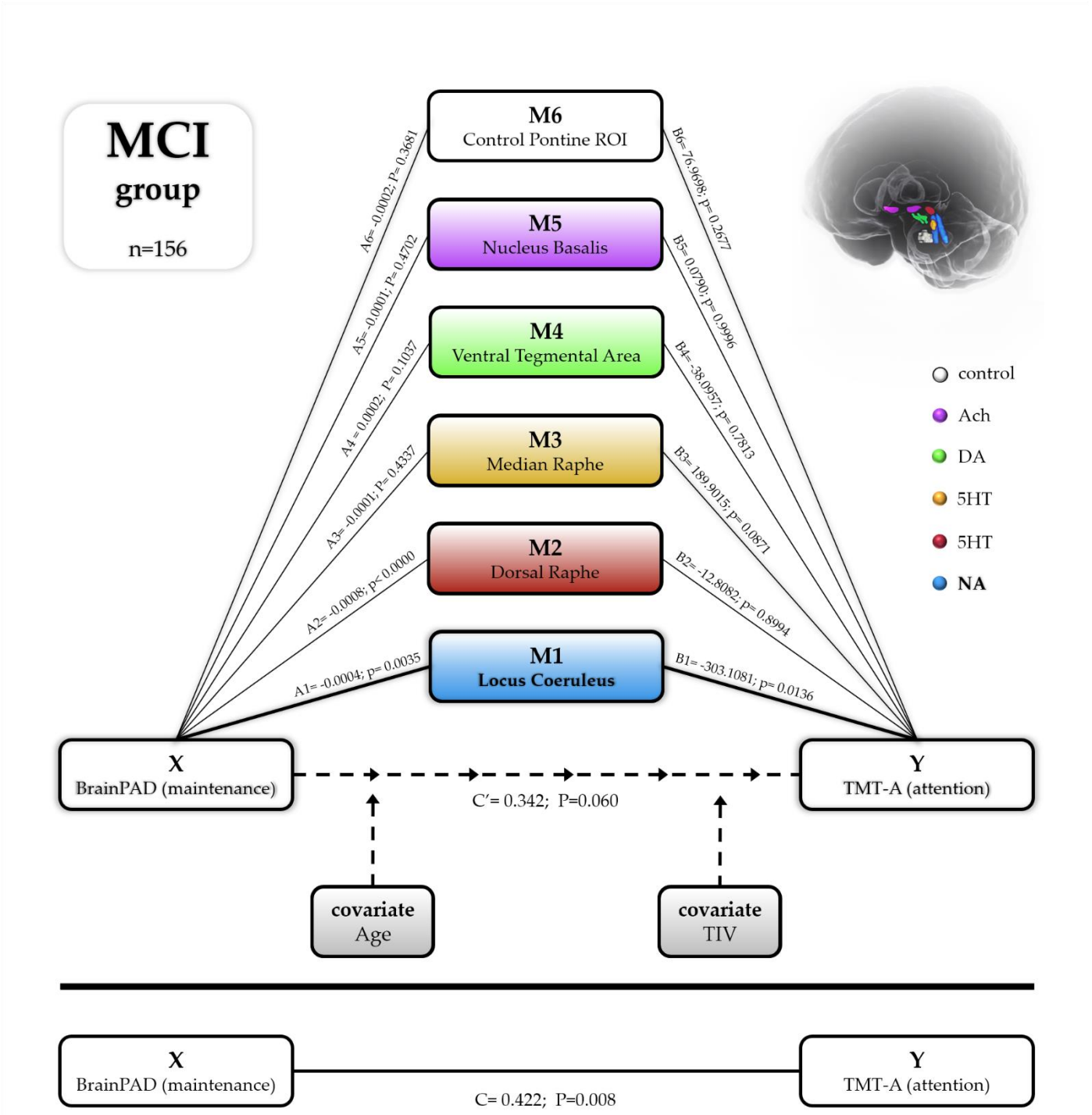

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Table 2. VBM multivariate linear regression analyses for the six ROIs across the 3 groups (HC n=395; MCI n=156; AD n=135). The results were adjusted for total intracranial volume (TIV), age and education were entered as continuous variable. TMT-A time in seconds was treated as continuous dependent variable and the structural scans as the independent variable. For a statistical threshold of p<0.001 the table reports the number of significant voxels negatively related to TMT-A time in seconds.

Brain Regions	**side**	**MNI coordinates** *x*	*y*	*Z*	peak **T** value[a]	peak **Z**-score[b]	peak cluster Ke[c]	p value uncorr[d]	FWE[e]	FDR[f]	total number of voxels *p 0.001* threshold[g]
HC (n. 395)											
Locus Coeruleus	/	/	/	/	/	/	/	/	/	/	/
Dorsal Raphe	/	/	/	/	/	/	/	/	/	/	/
Median Raphe	/	/	/	/	/	/	/	/	/	/	/
Ventral Tegmental Area	/	/	/	/	/	/	/	/	/	/	/
Nucleus Basalis of Meynert	right	14	-4	-12	3.35	3.32	3	0.000	1.000	0.571	3
Control Pontine ROI	/	/	/	/	/	/	/	/	/	/	/
MCI (n. 156)											
Locus Coeruleus	left	-4	-40	-28	3.57	3.49	7	0.000	1.000	0.639	21
Dorsal Raphe	/	/	/	/	/	/	/	/	/	/	/
Median Raphe	/	/	/	/	/	/	/	/	/	/	/
Ventral Tegmental Area	/	/	/	/	/	/	/	/	/	/	/
Nucleus Basalis of Meynert	/	/	/	/	/	/	/	/	/	/	/
Control Pontine ROI	/	/	/	/	/	/	/	/	/	/	/
AD (n. 135)											
Locus Coeruleus	right	6	-36	-20	4.41	4.25	8	0.000	0.992	0.463	9
Dorsal Raphe	/	/	/	/	/	/	/	/	/	/	/
Median Raphe	/	/	/	/	/	/	/	/	/	/	/
Ventral Tegmental Area	left	-4	-22	-16	3.78	3.68	13	0.000	1.000	0.618	14
Nucleus Basalis of Meynert	right	14	-4	-12	3.83	3.72	19	0.000	1.000	0.583	19
Control Pontine ROI	/	/	/	/	/	/	/	/	/	/	/

a) Peak T value: T value of the most significant cluster of contiguous voxels

b) Peak Z-score: Z-score of the most significant cluster of contiguous voxels

c) Peak cluster Ke: number of voxels of the most significant cluster of contiguous voxels

d) FWE = family wise error correction value

e) FDR = false discovery rate correction value (q)

g) Total number of voxels outcoming in the ROI including all clusters of contiguous voxels

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Table 3. VBM multivariate linear regression analyses for the six ROIs across the 3 groups (HC n=395; MCI n=156; AD n=135). The results were adjusted for total intracranial volume (TIV), while age and education were entered as continuous variables. BrainPAD values were treated as continuous dependent variable and the structural scans as independent variable. For a statistical threshold of p<0.001 FWE corrected (HC) and p<0.001 (MCI and AD) the table reports the significant voxels negatively related to BrainPAD.

Brain Regions	**side**	**MNI coordinates** *x*	*y*	*Z*	peak **T** value[a]	peak **Z**score[b]	peak cluster Ke[c]	p value uncorr[d]	FWE[e]	FDR[f]	total number of voxels *p 0.001* ***FWE*** threshold[g]
HC (n. 395)											
Locus Coeruleus	left	-2	-38	-22	9.10	inf	106	0.000	0.000	0.000	153
Dorsal Raphe	right	2	-32	-12	8.14	7.81	71	0.000	0.000	0.000	71
Median Raphe	/	/	/	/	/	/	/	/	/	/	/
Ventral Tegmental Area	/	/	/	/	/	/	/	/	/	/	/
Nucleus Basalis of Meynert	/	/	/	/	/	/	/	/	/	/	/
Control Pontine ROI	/	/	/	/	/	/	/	/	/	/	/
MCI (n. 156)											total number of voxels for *p 0.001* threshold[g]
Locus Coeruleus	left	-2	-34	-14	4.16	4.04	16	0.000	1.000	0.125	59
Dorsal Raphe	right	2	-30	-8	5.78	5.48	109	0.000	0.021	0.563	109
Median Raphe	/	/	/	/	/	/	/	/	/	/	/
Ventral Tegmental Area	left	-2	-16	-14	3.22	3.16	1	0.001	1.000	0.369	2
Nucleus Basalis of Meynert	right	14	-8	-10	4.15	4.03	12	0.000	0.999	0.093	12
Control Pontine ROI	/	/	/	/	/	/	/	/	/	/	/
AD (n. 135)											
Locus Coeruleus	left	-4	-36	-16	5.56	5.25	94	0.000	0.065	0.005	192
Dorsal Raphe	left	-2	-32	-12	4.74	4.54	90	0.000	0.786	0.037	90
Median Raphe	/	0	-34	-22	4.19	4.05	20	0.000	1.000	0.135	20
Ventral Tegmental Area	left	-4	-22	-16	4.49	4.32	9	0.000	0.976	0.067	9
Nucleus Basalis of Meynert	right	14	-6	-12	3.41	3.33	5	0.000	1.000	0.655	5
Control Pontine ROI	/	/	/	/	/	/	/	/	/	/	/

a) Peak T value: T value of the most significant cluster of contiguous voxels

b) Peak Z-score: Z-score of the most significant cluster of contiguous voxels

c) Peak cluster Ke: number of voxels of the most significant cluster of contiguous voxels

d) FWE = family wise error correction value

e) FDR = false discovery rate correction value (q)

g) Total number of voxels outcoming in the ROI including all clusters of contiguous voxels

3.5. Bayes Factors: parameters of evidence strength for the six ROIs involvement in attention and brain maintenance across the three groups

Bayes factors (BF) were calculated in order to better discriminate the differential involvement of the six ROIs in the two main domains investigated (see section 2.2 in the supplementary materials). BF_{10} confirmed the disproportional predictive involvement of the LC-NA system observed in the VBM analyses. Bayesian modelling demonstrated that LC volume exhibited the strongest relationship with BrainPAD and TMT-A (with the one exception of the LC - TMT-A correlation in the HC group). Overall, across the three groups, as indicated by BF_{10}, the LC likelihood to predict brain maintenance is 19321,07 times more than the null hypothesis, whereas it is 779,29 for the other five ROIs when summed together. Similarly, the LC likelihood to predict attention is 4158,30 times more than the null hypothesis, while it is 241,35 for the sum of the other 5 ROIs. However, there are notable differences between the groups. Concerning BrainPAD, the MCI group compared to HC and AD shows the strongest evidence for LC (BF_{10} 19303,214), followed by DR (BF_{10}

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399,634) and NBM (BF_{10} 339,646). Furthermore, it is noteworthy that there is evidence of absent relationships (support for the null hypothesis) for all other ROIs in the MCI group ($BF_{10} < 1$ indicating more evidence for the null hypothesis (i.e., no relationship). Similarly, for TMT-A, the LC shows the strongest evidence (BF_{10} 517,357), followed by the DR (BF_{10} 4,219) and for all the other ROIs there was absent relationships. In the AD group the evidence for the LC is also the most substantial (BF_{10} 46,538), but there is also evidence for more distributed involvement of other nuclei as the DR (BF_{10} 7,031), the MR (BF_{10} 2,541) and the VTA (BF_{10} 4,657) supporting BrainPAD. In the same vein, for TMT-A the strongest evidence is in support of the LC (BF_{10} 3640,710), but strong evidence is also found for the VTA (BF_{10} 124,076) and the NBM (BF_{10} 102,490) and no evidence for the other ROIs. In the HC group the magnitude of the results is less pronounced but follows the same pattern. The LC shows the strongest evidence supporting BrainPAD (BF_{10} 142,324) followed by the DR (BF_{10} 22,466), and no evidence was found for all the other ROIs. In contrast to the clinical groups, no evidence for the ROIs and TMT-A was found in the HC, with the exception of the DR (BF_{10} 9,117). BF_{10} are reported specifically for the three groups in table 4 along with Pearson's correlation coefficients. BF_{10} are covaried for age, education and total intracranial volume.

Table 4. Shows the Bayes factors (BF_{01}) for the three groups showing the strength of relationships between the six ROIs, BrainPAD and TMT-A. ROIs average values are corrected for age, education and total intracranial volume.

HC (n=395)		**Locus Coeruleus**	**Dorsal Raphe**	**Median Raphe**	**Ventral Tegmental Area**	**Nucleus Basalis of Meynert**	**Control Pontine ROI**
BrainPAD	Pearson's r	-0.197***	-0.292***	-0.107	-0.074	-0.107	-0.109
	BF_{10}	142.324	22.466	0.608	0.185	0.599	0.643
TMT-A	Pearson's r	-0.082	-0.158	-0.025	-0.045	0.085	-0.042
	BF_{10}	0.236	9.117	0.071	0.094	0.257	0.089
MCI (n=156)							
BrainPAD	Pearson's r	-0.385***	-0.321***	-0.039	0.147	-0.318***	0.007
	BF_{10}	19303.214	399.634	0.113	0.523	339.646	0.101
TMT-A	Pearson's r	-0.326***	-0.219	0.001	0.019	0.029	0.007
	BF_{10}	517.357	4.219	0.100	0.103	0.107	0.101
AD (n=135)							
BrainPAD	Pearson's r	-0.297**	-0.249	-0.217	-0.305	-0.132	0.100
	BF_{10}	46.538	7.031	2.541	4.657	0.340	0.209
TMT-A	Pearson's r	-0.384***	-0.119	-0.041	-0.319***	-0.315***	-0.5224
	BF_{10}	3640.710	0.272	0.120	124.076	102.490	0.108

* $BF_{10} > 10$, ** $BF_{10} > 30$, *** $BF_{10} > 100$

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3.6. Brief summary of the 3rd,4th,5th and 6th VBM analyses

The other VBM branches of analyses are reported in supplementary materials (extended methods and results sections), a brief summary is provided here.

The third and the fourth branches of VBM analyses examined the extent to which education and the degree of occupational cognitive demand were predicted by the six ROIs. In summary, absent or negligible findings were observed for education (3rd VBM branch) and occupational cognitive demand (4th VBM branch), for further details see sections 2.3.12. and 2.3.13., and section 3.9 with table 5 and table 6 in supplementary materials.

The fifth branch of VBM analyses investigated how the factor group (HC, MCI, AD) affected the volumetric variations within the neuromodulatory subcortical systems. The main areas where the MCI showed decreased volume compared to HC were the DR and VTA. By contrast, there was no LC volume difference in MCI vs. HC group. AD patients showed decreased volume compared to MCI in the LC and in the VTA areas. Consistently with the previous literature [25, 26, 27, 30, 118, 31, 132, 133, 70, 68], the main effect of group on volume reduction was observed in charge of the NBM, the DR, the VTA and the LC (listed in order of statistical power). These areas showed the greater deterioration across the different stages of cognitive decline. For further details see paragraph 2.3.14. (5th VBM branch) and paragraph 3.10 with tables 7 and 8 in supplementary materials along with figure 6 for spatial resolution.

Since the literature concerning LC gender differences is controversial [129, 31, 33, 168, 189], the sixth branch of VBM analyses explored the differential volumetric variation of the neuromodulators due to gender at different stages of cognitive decline. Negligible differences between gender were observed. These differences became weaker or disappeared when covariates (age, TIV and education) were removed from the models. For more details see paragraph 2.3.15 (6th VBM branch) and paragraph 3.11 with table 11 in supplementary materials.

4. Discussion

The present study conducted a volumetric analysis of subcortical nuclei in healthy older controls (HC, n=395), patients with Mild Cognitive Impairment (MCI, n=156) and Alzheimer's Disease (AD, n=135). We hypothesized that structural integrity of the Locus Coeruleus (LC) would be particularly important for brain maintenance and cognitive reserve in the context of age and disease, due to the known neuroprotective effects of the LC-NA system [1, 2]. As anticipated, we observed a systematic reduction in attention performance and biological brain maintenance (BrainPAD) across the HC, MCI and AD groups respectively. We also observed a general reduction in the volume of subcortical nuclei at different stages of the cognitive decline. Compared to the other subcortical nuclei, LC volume was most extensively associated with the degree of brain maintenance across the three groups. However, only in MCI patients was the relationship between brain maintenance and attention performance mediated by LC volume suggesting a unique compensatory role of noradrenergic neuromodulation for MCI patients. Although these findings suggest a significant role for the LC-NA system in brain maintenance, we found negligible or inconsistent associations between the subcortical ROI volumes, BrainPAD scores and indices of cognitive reserve (i.e. education level and occupational status). However, education level did show a positive association with overall brain volume (in the HC and MCI groups), suggesting it might be more closely associated with brain development and expansion rather than later life brain maintenance. Few studies have investigated the relationship between LC volume and attentional performance in older adults [48, 55, 33]. The

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present study utilised the Trail Making Test A (TMT-A) as a putative measure of visual attention speed and found that greater LC volume in MCI and AD patients was associated with faster attention performance. A ceiling effect of TMT-A performance in the HC group gave limited variability for detecting an association with LC volume. However, a pattern of reduced and more heterogeneous TMT-A performance in both MCI and AD group revealed relationships with brainstem nuclei that may counteract progressive cortical decline seen in these patients. Histopathological evidence shows that in the early stages of neurodegeneration, the metencephalic areas appear to be less affected than cortical areas [100, 101, 102, 103, 104, 105, 31, 173]. It is possible that the degree of structural integrity within these metencephalic regions provides an important neuromodulatory and compensatory role in the face of declining cortical function [1, 2, 177, 106, 128, 17, 21]. Indeed, although the LC shows markers of neurodegeneration years before cognitive decline [101, 102], neuronal cell loss in the LC is most appreciable in advanced stages of neurodegeneration rather than in the earlier stages (evidence reported from Braak stage III-IV) [31, 101, 102, 129]. Therefore, throughout the pathological course, the volumetric and functional resilience of the LC (including the maintenance of the surrounding LC-peri dendritic and the epi and sub-coeruleus areas [180, 181, 14]) may provide a supporting and compensating role in the face of the beta-amyloid pathology occurring in the cortex [101, 102, 180, 190, 21, 17, 16]. Interestingly in this regard, a recent work by Bachman et al. [174] found positive relationships between the volume of the LC and surface measures in cortical regions including the rostral medial frontal cortex, which has a high density of noradrenergic varicosities [175].

In MCI patients we found that the structural variation of the LC was unique among the six subcortical ROIs in predicting visual attention performance. Specifically, bayesian analyses demonstrated that there was substantial evidence in support of LC involvement relative to all other ROIs. These analyses strengthened the specificity of the LC-NA system over the other neuromodulators' seeds and outlines its remarkable role in brain health. Widespread transmission of NA from the LC via diverse cortical efferent projections has been shown to significantly affect attention performance [106, 77, 107, 108, 109, 110, 111]. In the context of MCI, these findings suggest that neuromodulation of the LC-NA system, in particular, may help support the diminishing efficiency of cortical attention networks in this group. In AD patients several relationships were observed in which greater volumes of the LC, VTA and NBM were associated with faster visual attention performance. Due to the more severe cortical neurodegeneration in AD, it is conceivable that further compensatory support from both ascending catecholaminergic nuclei, including dopaminergic (VTA) and noradrenergic (LC) regions as well as activation of cholinergic basal forebrain nuclei (NBM), would be necessary to support declining cortical function [112]. Indeed, the basic requirements of the TMT-A are exploratory behaviour and selective attention [76, 169, 170], which are modulated by the catecholaminergic and cholinergic systems respectively [1, 2, 14, 112, 171, 172].

A seminal study by Wilson and colleagues [29] demonstrated that greater LC neural density was associated with reduced cognitive decline and increased reserve from an older adult cohort. In the present study, we found LC volume to be a reliable predictor of brain maintenance in each of the three groups. This pattern of results is consistent with Robertson's noradrenergic theory of reserve [1, 2], hypothesizing that protracted activation of the LC-NA system across the lifespan can enhance brain reserve through neuroplastic change, as well as through the neuroprotective effects of reduced neuroinflammation [23, 39, 40, 41, 113] and increased BDNF production [42, 43, 44, 45, 46, 47].

Given the high sensitivity of predicted age discrepancy measures to brain deterioration [114, 115, 10, 116], the universal relationship between BrainPAD and LC volume could indicate that the LC-NA system is a key driver of brain reserve, which is shaped through a more active and efficient attentional system [1, 2]. Our findings are consistent with the evidence of post-mortem and neuroimaging studies relating greater LC volume to indices of reserve and to reduced neurodegeneration [29, 113, 18, 19, 21, 20]. In addition to the LC

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volume, the observed relationship between DR volume and BrainPAD may also suggest a marked serotoninergic involvement in brain maintenance, particularly in MCI. Serotoninergic deterioration in neurodegenerative diseases has been reported [117, 118, 119, 102, 101, 120] and degeneration of the DR is well documented [31, 119, 104, 105, 121]. However, DR is not only a serotoninergic seed, but a multifunctional nucleus with significant non-serotoninergic pathways [122, 123]. Although 70% of the DR neurons contain Serotonin, the remaining 30% include other neurotransmitters (such as catecholamine [124, 125]) and NA transporters (NET) [126]. Early research [127] has reported that 38% of the amount of the Noradrenaline found in the LC is found in the DR (LC: 1.22 mg/g tissue mean; DR: 0.47 mg/g tissue mean). Therefore, the relationship between BrainPAD and the DR volume must also be considered in the context of the degeneration of the LC-NA system, particularly given the absence of evidence for the MR and BrainPAD. The LC has been shown to exhibit early signs of neurodegeneration before the DR nucleus [31], and patients with dementia exhibit significantly reduced Noradrenaline transporters (NET) in the LC but not in the DR [128]. Together these findings suggest that noradrenergic neurons within the DR might provide compensatory support for the broader LC-NA system [128, 106, 178, 180]. Accordingly, the resilience of the DR as a compensatory nucleus to the LC-NA system decay may, in part, explain the observed relationships between DR volume and BrainPAD in the present study.

In the present study, we also compared the influence of each of the five neuromodulator seed ROIs in mediating the relationship between brain maintenance and attentional efficiency. In keeping with Robertson's noradrenergic theory of cognitive reserve, we hypothesized that greater LC volume would be a key mediator in this relationship. However, only in MCI patients did LC volume account for the association between BrainPAD and attentional performance, suggesting that at prodromal stages of neurodegeneration greater LC integrity in the context of declining cortical systems may provide critical support for attention processes. By contrast, healthy older adults may have sufficient brain maintenance without additional neuromodulatory support from the LC and, in AD patients, pronounced LC degeneration compared to MCI and HC [129, 56, 29, 30, 128] may undermine its compensatory role in later stages of neurodegeneration. Although the DR nucleus has significant noradrenergic expression, we did not find a direct relationship between DR volume and attention performance, nor did DR volume mediate the association between brain maintenance and attention performance. In the current study putative indices of cognitive reserve, education and occupational status were strongly related to each other but not associated with BrainPAD scores, subcortical ROI volumes, or attention performance. Although previous findings [130] have reported an association between higher education and younger brain age, more recent research has not yielded such a relationship [131]. Alternatively, it is plausible that factors such as education and occupation are more directly related to actual reserve built through developmental plasticity in the early stages of life, and indexed by total intracranial volume (TIV), and are therefore more indirectly related to brain maintenance in the later stages of life [8].

5. Limitations

TMT-A is a valuable clinical tool to assess higher cognitive functions and it is widely used for its sensitivity to basic attentive efficiency, but it is a limited measure for assessing overall noradrenergic contributions to cognition. The cortical influence of NA is global and complex, and a single measure lacks the necessary richness to capture this entirely. Still, our findings do suggest a markedly predominant role for the LC in cognitive maintenance,

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particularly given the absence of a relevant effect for other neuromodulatory control nuclei. The sample size of the HC group (n-395) is considerably larger than both MCI (n=156) and AD (n=135), therefore uncorrected results for BrainPAD in MCI and AD might be driven by the reduced size of these groups.

The retrospective broad nature of the measures of sociodemographic indices of Reserve, particularly job complexity, may not offer information precise enough to capture the effects of this variable. The job classification in ranks according to the supposed cognitive demand can only reflect hypothetical contingencies related to the occupation.

Lastly, the methodological limitations of VBM analyses in cross-sectional studies should be taken into account while considering these findings. However, within these limitations, the utmost rigour was employed in defining the subcortical regions, while acknowledging the comprehensive literature on the subject. The processing pipeline was also strict in terms of quality assurance: an attempt was made to account for all possible confounding covariates. Additionally, opposite hypotheses have been tested as well. Despite these limitations, the findings of the current study are consistent both with histopathological and neuroimaging studies on noradrenergic, serotoninergic, cholinergic and dopaminergic systems in the context of neurodegenerative diseases [25, 26, 27, 30, 118, 31, 132, 133, 70, 68].

6. Conclusions and clinical implications

The findings of this study are consistent with the vast literature on the decay of the LC-NA system in neurodegenerative diseases, and with a growing number of studies showing how the LC-NA system is a crucial mediator of reserve both in healthy and pathological ageing, as postulated by Robertson. This work is among the largest MRI studies carried out on the noradrenergic system, counting more than 250 VBM analyses on 686 subjects. And it is the first work investigating the comparative relationships between an objective measure of biological brain health and the integrity of neuromodulatory subcortical systems. This work extends the knowledge of the role of the LC-NA system in the neurobiology of cognitive decline and also as potential in-vivo biomarker of neurodegenerative diseases.

The relationships identified in this study highlight the need to target therapeutic approaches which focus on enhancing the function and the structural integrity of the LC-NA system. As proposed by Robertson, early prevention strategies which focus on upregulation of the noradrenergic system in ageing and dementia may yield important clinical benefits. This is possible through cognitive stimulation via attentional training (involving sustained attention and working memory capacity) [1, 2, 21]. Indeed, visual attention and working memory are domains underpinned by the noradrenergic system [1, 2, 172, 99, 21]. Cognitive interventions involving these domains performing exercises of mental flexibility, problem solving, and visual search might stimulate the LC-NA system enhancing cognition [1, 2]. Short cognitive interventions based on this approach showed cognitive improvements related to frontal areas with predominant presence of noradrenergic receptors [188, 175].

In addition, noradrenergic drugs which increase LC activity and cognitive performances might be beneficial [134, 135, 136, 137]. Studies using noradrenergic drugs showed that interventions ameliorated AD-like pathology and partially re-stored noradrenergic tone in humans [134, 135, 180]. However, the benefit of noradrenergic drugs is controversial and side effects should be considered while evaluating this approach (see Holland et al. (2021) for a review) [172].

Another potential intervention might involve physical exercise, which is among the main preventing factors of dementia [13]. Physical exercise is known to help maintain proper upregulation of the LC-NA system. It has been shown that physical exercise boosts NA

release [38] and activates LC-NA system, which is linked to improved cognition in healthy and MCI populations [138, 139, 21].

Diet may also play a supportive role within the noradrenergic system as a preventing factor of neurodegenerative diseases. Indeed, poor and wrong diet-styles and their related neuroinflammatory consequences [140, 141, 142] are associated with worse prognosis and higher neurodegeneration risks [13, 140, 141, 143, 144]. Interventions on diet may be beneficial to restore potential harmful micro and macro nutrient insufficiencies according to current guidelines for prevention [145, 13]. In particular, as observed in regards of the cholinergic system decay with dementia, a higher level of Choline intake and supplementation has been shown to improve cognitive performances in both healthy people and patients [146, 147, 148]. Likewise, Tyrosine intake and supplementation in healthy elderly and in MCI patients offer another possible conceivable way of ameliorating the LC-NA system degeneration and cognitive decline [149, 150, 151, 103, 152, 153, 128]. It is worth mentioning that several studies in the past linked Tyrosine supplementation to increased cognitive performances in healthy subjects [154, 155, 156, 157, 158]. Furthermore, a recent study by Kühn et al. (2019) [149] found in 1724 healthy individuals that the average dietary Tyrosine intake in grams related to better cognitive performances in working memory, episodic memory and fluid intelligence.

Finally, other potential interventions may involve breathing practices such as meditation, pranayama and breath-control, which are thought to involve the LC-NA system [159, 160]. Some studies on long-term meditators have indeed reported increased brain volume in critical areas affected in dementia, including the brainstem, along with better cognitive efficiency [161, 162, 163, 164, review: 165], after as a little as 5-10 hours of practice [166, 167].

As an ultimate conclusion, it should be considered that the current study did not directly investigate the upregulation of the LC-NA system but explored cross-sectionally the volumetric integrity of the LC-NA system in comparison with the other main neuromodulator seeds. These investigations highlight the relevance of the LC-NA system in attentional domain and in the biological component of Reserve, linking brain health to greater integrity of the LC-NA system. Although greater LC volume may ensure greater availability of NA reported in multiple studies [1, 2, 17, 18, 20, 21, 22, 26, 28, 31, 32, 35, 46, 48, 101, 102, 103, 104, 105, 106, 128, 129, 137, 139, 172, 176, 177], it is important to acknowledge that further integration of the relationship between structure and function of the LC is warranted.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Figure S1: title, Table S1: title, Video S1: title.

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References

1. Robertson IH. A noradrenergic theory of cognitive reserve: implications for Alzheimer's disease. Neurobiol Aging. 2013;34(1):298-308. doi:10.1016/j.neurobiolaging.2012.05.019

2. Robertson IH. Right hemisphere role in cognitive reserve. Neurobiol Aging. 2014 Jun;35(6):1375-85. doi: 10.1016/j.neurobiolaging.2013.11.028. Epub 2013 Dec 4. PMID: 24378088.

3. Tucker AM, Stern Y. Cognitive reserve in aging. Curr Alzheimer Res. 2011;8(4):354-360. doi:10.2174/156720511795745320

4. Valenzuela, M., & Sachdev, P. (2006). Brain reserve and dementia: A systematic review. Psychological Medicine, 36(4), 441-454. doi:10.1017/S0033291705006264

5. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol. 2012;11(11):1006 1012. doi:10.1016/S1474-4422(12)70191-6

6. Stern Y Cognitive reserve. Neuropsychologia 47, 2015–2028, 10.1016/j.neuropsychologia.2009.03.004 (2009)

7. Stern, Y, Arenaza-Urquijo, EM, Bartrés-Faz, D, et al. Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. Alzheimer's Dement. 2020; 16: 1305– 1311. https://doi.org/10.1016/j.jalz.2018.07.219

8. Cabeza R., Albert M., Belleville S., Craik F.I.M., Duarte A., Grady C.L., Lindenberger U., Nyberg L., Park D.C., Reuter-Lorenz P.A., Rugg M.D., Steffener J., Rajah M.N., Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. Nature Reviews Neuroscience volume 19, page772 (2018)

9. Barulli D & Stern Y Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. Trends Cogn. Sci 17, 502–509, doi:10.1016/j.tics.2013.08.012 (2013)

10. Gaser C, Franke K, Klöppel S, Koutsouleris N, Sauer H; Alzheimer's Disease Neuroimaging Initiative. BrainAGE in Mild Cognitive Impaired Patients: Predicting the Conversion to Alzheimer's Disease. PLoS One. 2013 Jun 27;8(6):e67346. doi: 10.1371/journal.pone.0067346. PMID: 23826273; PMCID: PMC3695013.

11. Habeck C, Razlighi Q, Gazes Y, Barulli D, Steffener J, Stern Y. Cognitive Reserve and Brain Maintenance: Orthogonal Concepts in Theory and Practice. Cereb Cortex. 2017 Aug 1;27(8):3962-3969. doi: 10.1093/cercor/bhw208. PMID: 27405332; PMCID: PMC6248534.

12. Boyle, R., Jollans, L., Rueda-Delgado, L. M., Rizzo, R., Yener, G. G., McMorrow, J. P., Knight, S. P., Carey, D., Robertson, I. H., Emek-Savaş, D. D., Stern, Y., Kenny, R. A., & Whelan, R. (2021). Brain-predicted age difference score is related to specific cognitive functions: a multi-site replication analysis. Brain Imaging and Behavior. https://doi.org/10.1007/s11682-020-00260-3

13. Gill Livingston, Andrew Sommerlad, Vasiliki Orgeta, Sergi G Costafreda, Jonathan Huntley, David Ames, Clive Ballard, Sube Banerjee, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Eric B Larson, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam. Dementia prevention, intervention, and care. The Lancet, Volume 390, Issue 10113, 2017, Pages 2673-2734, ISSN 0140-6736, https://doi.org/10.1016/S0140-6736(17)31363-6.

14. Jürgen K. Mai, George Paxinos, The Human Nervous System (Third Edition), Academic Press, 2012, ISBN 9780123742360, https://doi.org/10.1016/B978-0-12-374236-0.10045-8.

15. Chandler, Dan & Jensen, Patricia & McCall, Jordan & Pickering, Anthony & Schwarz, Lindsay & Totah, Nelson. (2019). Redefining Noradrenergic Neuromodulation of Behavior: Impacts of a Modular Locus Coeruleus Architecture. The Journal of Neuroscience. 39. 8239-8249. 10.1523/JNEUROSCI.1164-19.2019.

16. Borodovitsyna O, Flamini M, Chandler D. "Noradrenergic Modulation of Cognition in Health and Disease", Neural Plasticity, vol. 2017, Article ID 6031478, 14 pages, 2017. https://doi.org/10.1155/2017/6031478

17. Sara S.J. The locus coeruleus and noradrenergic modulation of cognition Nat. Rev. Neurosci, 10 (2009), pp. 211-223

18. Brunnström H, Friberg N, Lindberg E, Englund E. Differential degeneration of the locus coeruleus in dementia subtypes. Clin Neuropathol. 2011;30(3):104-110. doi:10.5414/npp30104

19. Benarroch EE. The locus ceruleus norepinephrine system: functional organization and potential clinical significance. Neurology. 2009;73(20):1699-1704. doi:10.1212/WNL.0b013e3181c2937c

20. Kelly SC, He B, Perez SE, Ginsberg SD, Mufson EJ, Counts SE. Locus coeruleus cellular and molecular pathology during the progression of Alzheimer's disease. Acta Neuropathol Commun. 2017;5(1):8. Published 2017 Jan 21. doi:10.1186/s40478-017-0411-2

21. Mather M, Harley CW. The Locus Coeruleus: Essential for Maintaining Cognitive Function and the Aging Brain. Trends Cogn Sci. 2016;20(3):214-226. doi:10.1016/j.tics.2016.01.001

22. Olivieri P, Lagarde J, Lehericy S, et al. Early alteration of the locus coeruleus in phenotypic variants of Alzheimer's disease. Ann Clin Transl Neurol. 2019;6(7):1345-1351. doi:10.1002/acn3.50818

23. Mravec B, Lejavova K, Cubinkova V. Locus (coeruleus) minoris resistentiae in pathogenesis of Alzheimer's disease. Curr Alzheimer Res. 2014;11(10):992-1001. doi:10.2174/1567205011666141107130505

24. Grudzien A, Shaw P, Weintraub S, Bigio E, Mash DC, Mesulam MM. Locus coeruleus neurofibrillary degeneration in aging, mild cognitive impairment and early Alzheimer's disease. Neurobiol Aging. 2007;28(3):327-335. doi:10.1016/j.neurobiolaging.2006.02.007

25. Giorgi FS, Ryskalin L, Ruffoli R, et al. The Neuroanatomy of the Reticular Nucleus Locus Coeruleus in Alzheimer's Disease. Front Neuroanat. 2017;11:80. Published 2017 Sep 19. doi:10.3389/fnana.2017.00080

26. Satoh A, Iijima KM. Roles of tau pathology in the locus coeruleus (LC) in age-associated pathophysiology and Alzheimer's disease pathogenesis: Potential strategies to protect the LC against aging. Brain Res. 2019;1702:17-28. doi:10.1016/j.brainres.2017.12.027

27. Pamphlett R, Kum Jew S. Different Populations of Human Locus Ceruleus Neurons Contain Heavy Metals or Hyperphosphorylated Tau: Implications for Amyloid-β and Tau Pathology in Alzheimer's Disease. J Alzheimers Dis. 2015;45(2):437-447. doi:10.3233/JAD-142445

28. Betts MJ, Kirilina E, Otaduy MCG, Ivanov D, Acosta-Cabronero J, Callaghan MF, Lambert C, Cardenas-Blanco A, Pine K, Passamonti L, Loane C, Keuken MC, Trujillo P, Lüsebrink F, Mattern H, Liu KY, Priovoulos N, Fliessbach K, Dahl MJ, Maaß A, Madelung CF, Meder D, Ehrenberg AJ, Speck O, Weiskopf N, Dolan R, Inglis B, Tosun D, Morawski M, Zucca FA, Siebner HR, Mather M, Uludag K, Heinsen H, Poser BA, Howard R, Zecca L, Rowe JB, Grinberg LT, Jacobs HIL, Düzel E, Hämmerer D. Locus coeruleus imaging as a biomarker for noradrenergic dysfunction in neurodegenerative diseases. Brain. 2019 Sep 1;142(9):2558-2571. doi: 10.1093/brain/awz193. PMID: 31327002; PMCID: PMC6736046.

29. Wilson RS, Nag S, Boyle PA, et al. Neural reserve, neuronal density in the locus ceruleus, and cognitive decline. Neurology. 2013;80:1202–1208

30. Bondareff W, Mountjoy CQ, Roth M (February 1982). "Loss of neurons of origin of the adrenergic projection to cerebral cortex (nucleus locus ceruleus) in senile dementia". Neurology. 32 (2): 164–8. doi:10.1212/wnl.32.2.164. PMID 7198741.

31. Ehrenberg AJ, Nguy AK, Theofilas P, Dunlop S, Suemoto CK, Di Lorenzo Alho AT, Leite RP, Diehl Rodriguez R, Mejia MB, Rüb U, Farfel JM, de Lucena Ferretti-Rebustini RE, Nascimento CF, Nitrini R, Pasquallucci CA, Jacob-Filho W, Miller B, Seeley WW, Heinsen H, Grinberg LT. Quantifying the accretion of hyperphosphorylated tau in the locus coeruleus and dorsal raphe nucleus: the pathological building blocks of early Alzheimer's disease. Neuropathol Appl Neurobiol. 2017 Aug;43(5):393-408. doi: 10.1111/nan.12387. Epub 2017 Mar 31. PMID: 28117917; PMCID: PMC5642282.

32. Dahl, M.J., Mather, M., Düzel, S. et al. Rostral locus coeruleus integrity is associated with better memory performance in older adults. Nat Hum Behav 3, 1203–1214 (2019). https://doi.org/10.1038/s41562-019-0715-2

33. Liu KY, Marijatta F, Hämmerer D, Acosta-Cabronero J, Düzel E, Howard RJ. Magnetic resonance imaging of the human locus coeruleus: A systematic review. Neurosci Biobehav Rev. 2017;83:325-355. doi:10.1016/j.neubiorev.2017.10.023

34. Heneka MT, Nadrigny F, Regen T, Martinez-Hernandez A, Dumitrescu-Ozimek L, Terwel D, Jardanhazi-Kurutz D, Walter J, Kirchhoff F, Hanisch UK, Kummer MP (2010). "Locus ceruleus controls Alzheimer's disease pathology by modulating microglial functions through norepinephrine". Proc Natl Acad Sci U S A. 107 (13): 6058–6063. doi:10.1073/pnas.0909586107. PMC 2851853. PMID 20231476.

35. Chalermpalanupap T, Schroeder JP, Rorabaugh JM, et al. Locus Coeruleus Ablation Exacerbates Cognitive Deficits, Neuropathology, and Lethality in P301S Tau Transgenic Mice. J Neurosci. 2018;38(1):74-92. doi:10.1523/JNEUROSCI.1483-17.2017

36. Duffy KB, Ray B, Lahiri DK, et al. Effects of Reducing Norepinephrine Levels via DSP4 Treatment on Amyloid-β Pathology in Female Rhesus Macaques (Macaca Mulatta). J Alzheimers Dis. 2019;68(1):115-126. doi:10.3233/JAD-180487

37. Heneka MT, Ramanathan M, Jacobs AH, Dumitrescu-Ozimek L, Bilkei-Gorzo A, Debeir T, Sastre M, Galldiks N, Zimmer A, Hoehn M, Heiss WD, Klockgether T, Staufenbiel M (February 2006). "Locus ceruleus degeneration promotes Alzheimer pathogenesis in amyloid precursor protein 23 transgenic mice". J Neurosci. 26 (5): 1343–54. doi:10.1523/jneurosci.4236-05.2006. PMID 16452658

38. Kjaer M, Secher NH, Galbo H. Physical stress and catecholamine release. Baillieres Clin Endocrinol Metab. 1987;1(2):279-298. doi:10.1016/s0950-351x(87)80064-2

39. Heneka, M. T., Carson, M. J., El Khoury, J., Landreth, G. E., Brosseron, F., Feinstein, D. L., Jacobs, A. H., Wyss-Coray, T., Vitorica, J., Ransohoff, R. M., Herrup, K., Frautschy, S. A., Finsen, B., Brown, G. C., Verkhratsky, A., Yamanaka, K., Koistinaho, J., Latz, E., Halle, A., Petzold, G. C., Kummer, M. P. (2015). Neuroinflammation in Alzheimer's disease. The Lancet. Neurology, 14(4), 388–405. https://doi.org/10.1016/S1474-4422(15)70016-5

40. Troadec, M. Marien, F. Darios, A. Hartmann, M. Ruberg, F. Colpaert, P.P. Michel. Noradrenaline provides long-term protection to dopaminergic neurons by reducing oxidative stress. J. Neurochem, 79 (2001), pp. 200-210

41. Feinstein DL, Heneka MT, Gavrilyuk V, Dello Russo C, Weinberg G, GaleaE. Noradrenergic regulation of inflammatory gene expression in brain. Neurochem. Int, 41 (2002), pp. 357-365

42. Giorgi FS, Saccaro LF, Galgani A, et al. The role of Locus Coeruleus in neuroinflammation occurring in Alzheimer's disease. Brain Res Bull. 2019;153:47-58. doi:10.1016/j.brainresbull.2019.08.007

43. Traver S, Salthun-Lassalle B, Marien B, Hirsch EC, Colpaert F, Michel PP. The neurotransmitter noradrenaline rescues septal cholinergic neurons in culture from degeneration caused by low-level oxidative stress. Mol. Pharmacol, 67 (2005), pp. 1882-1891

44. Counts SE, Mufson EJ. Noradrenaline activation of neurotrophic pathways protects against neuronal amyloid toxicity. J. Neurochem, 113 (2010), pp. 649-660

45. Mannari C, Origlia N, Scatena A, Del Debbio A, Catena M, Dell'agnello G, Barraco A, Giovannini L, Dell'osso L, Domenici L, Piccinni A. BDNF level in the rat prefrontal cortex increases following chronic but not acute treatment with duloxetine, a dual acting inhibitor of noradrenaline and serotonin re-uptake. Cell. Mol. Neurobiol, 28 (2008), pp. 457-468

46. Aghajanov M, Chavushyan V, Matinyan S, Danielyan M, Yenkoyan K. Alzheimer's disease-like pathology-triggered oxidative stress, alterations in monoamines levels, and structural damage of locus coeruleus neurons are partially recovered by a mix of proteoglycans of embryonic genesis. Neurochem Int. 2019;131:104531. doi:10.1016/j.neuint.2019.104531

47. Hassani OK, Rymar VV, Nguyen KQ, et al. The noradrenergic system is necessary for survival of vulnerable midbrain dopaminergic neurons: implications for development and Parkinson's disease. Neurobiol Aging. 2020;85:22-37. doi:10.1016/j.neurobiolaging.2019.09.014

48. Clewett, D. V., Lee, T. H., Greening, S., Ponzio, A., Margalit, E., & Mather, M. (2016). Neuromelanin marks the spot: identifying a locus coeruleus biomarker of cognitive reserve in healthy aging. Neurobiology of aging, 37, 117–126. doi:10.1016/j.neurobiolaging.2015.09.019

49. Mueller, S.G., Weiner, M.W., Thal, L.J., Petersen, R.C., Jack, C., Jagust, W., Trojanowski, J.Q., Toga, A.W., Beckett, L., 2005a. The Alzheimer's disease neuroimaging initiative. Neuroimaging Clin. N Am. 15, 869–877, xi–xii.

50. Mueller, S.G., Weiner, M.W., Thal, L.J., Petersen, R.C., Jack, C.R., Jagust, W., Trojanowski, J.Q., Toga, A.W., Beckett, L., 2005b. Ways toward an early diagnosis in Alzheimer's disease: The Alzheimer's Disease Neuroimaging Initiative (ADNI). Alzheimers Dement. 1, 55–66.

51. Ji, X., Wang, H., Zhu, M., He, Y., Zhang, H., Chen, X., et al. (2020). Brainstem atrophy in the early stage of Alzheimer's disease: A voxel-based morphometry study. Brain Imaging and Behavior., 15, 49–59. https://doi.org/10.1007/s11682-019-00231-3.

52. Lee, J. H., Ryan, J., Andreescu, C., Aizenstein, H., & Lim, H. K. (2015). Brainstem morphological changes in Alzheimer's disease. Neuroreport, 26(7), 411–415. https://doi.org/10.1097/WNR.0000000000000362.

53. Chen Z, Chen X, Liu M, Liu S, Ma L, Yu S. Volume gain of periaqueductal gray in medication-overuse headache. J Headache Pain. 2017 Dec;18(1):12. doi: 10.1186/s10194-016-0715-9. Epub 2017 Feb 1. PMID: 28144808; PMCID: PMC5285292.

54. Protopopescu X, Pan H, Tuescher O, Cloitre M, Goldstein M, Engelien A, Yang Y, Gorman J, LeDoux J, Stern E, Silbersweig D. Increased brainstem volume in panic disorder: a voxel-based morphometric study. Neuroreport. 2006 Mar 20;17(4):361-3. doi: 10.1097/01.wnr.0000203354.80438.1. PMID: 16514359.

55. Dutt, S., Li, Y., Mather, M. et al. Brainstem substructures and cognition in prodromal Alzheimer's disease. Brain Imaging and Behavior (2021). https://doi.org/10.1007/s11682-021-00459-y

56. Dutt S, Li Y, Mather M, Nation DA; Alzheimer's Disease Neuroimaging Initiative. Brainstem Volumetric Integrity in Preclinical and Prodromal Alzheimer's Disease. J Alzheimers Dis. 2020;77(4):1579-1594. doi: 10.3233/JAD-200187. PMID: 32925030; PMCID: PMC7868064.

57. Martin J. Dahl, Mara Mather, Markus Werkle-Bergner, Briana L. Kennedy, Samuel Guzman, Kyle Hurth, Carol A. Miller, Yuchuan Qiao, Yonggang Shi, Helena C. Chui, John M. Ringman Locus coeruleus integrity is related to tau burden and memory loss in autosomal-dominant Alzheimer's disease medRxiv 2020.11.16.20232561; doi: https://doi.org/10.1101/2020.11.16.20232561

58. Takahashi J, Shibata T, Sasaki M, Kudo M, Yanezawa H, Obara S, Kudo K, Ito K, Yamashita F, Terayama Y. Detection of changes in the locus coeruleus in patients with mild cognitive impairment and Alzheimer's disease: high-resolution fast spin-echo T1-weighted imaging. Geriatr Gerontol Int. 2015 Mar;15(3):334-40. doi: 10.1111/ggi.12280. Epub 2014 Mar 25. PMID: 24661561; PMCID: PMC4405055.

59. Ayzenberg I, Nastos I, Strassburger-Krogias K, Obermann M, Gold R, Krogias C. Hypoechogenicity of brainstem raphe nuclei is associated with increased attack frequency in episodic migraine. Cephalalgia. 2016;36(8):800-806. doi:10.1177/0333102415617415

60. Li, Z., Zhou, J., Lan, L., Cheng, S., Sun, R., Gong, Q., Wintermark, M., Zeng, F., & Liang, F. (2020). Concurrent brain structural and functional alterations in patients with migraine without aura: an fMRI study. The journal of headache and pain, 21(1), 141. https://doi.org/10.1186/s10194-020-01203-5

61. Supprian T, Reiche W, Schmitz B, Grunwald I, Backens M, Hofmann E, Georg T, Falkai P, Reith W. MRI of the brainstem in patients with major depression, bipolar affective disorder and normal controls. Psychiatry Res. 2004 Sep 15;131(3):269-76. doi: 10.1016/j.pscychresns.2004.02.005. PMID: 15465296.

62. Lee HY, Tae WS, Yoon HK, Lee BT, Paik JW, Son KR, Oh YW, Lee MS, Ham BJ. Demonstration of decreased gray matter concentration in the midbrain encompassing the dorsal raphe nucleus and the limbic subcortical regions in major depressive disorder: an optimized voxel-based morphometry study. J Affect Disord. 2011 Sep;133(1-2):128-36. doi: 10.1016/j.jad.2011.04.006. Epub 2011 May 4. PMID: 21546094.

63. De Marco M, Venneri A. Volume and Connectivity of the Ventral Tegmental Area are Linked to Neurocognitive Signatures of Alzheimer's Disease in Humans. J Alzheimers Dis. 2018;63(1):167-180. doi: 10.3233/JAD-171018. PMID: 29578486.

64. Khan AR, Hiebert NM, Vo A, Wang BT, Owen AM, Seergobin KN, MacDonald PA. Biomarkers of Parkinson's disease: Striatal sub-regional structural morphometry and diffusion MRI. Neuroimage Clin. 2019;21:101597. doi: 10.1016/j.nicl.2018.11.007. Epub 2018 Nov 16. PMID: 30472168; PMCID: PMC6412554.

65. Liu J, Chen L, Chen X, Hu K, Tu Y, Lin M, Huang J, Liu W, Wu J, Qiu Z, Zhu J, Li M, Park J, Wilson G, Lang C, Xie G, Tao J, Kong J. Modulatory effects of different exercise modalities on the functional connectivity of the periaqueductal grey and ventral tegmental area in patients with knee osteoarthritis: a randomised multimodal magnetic resonance imaging study. Br J Anaesth. 2019 Oct;123(4):506-518. doi: 10.1016/j.bja.2019.06.017. Epub 2019 Aug 5. PMID: 31395306.

66. Chen, Z. Y., Chen, X. Y., Liu, M. Q., Ma, L., & Yu, S. Y. (2018). Volume Gain of Brainstem on Medication-Overuse Headache Using Voxel-Based Morphometry. Chinese medical journal, 131(18), 2158–2163. https://doi.org/10.4103/0366-6999.240807

67. Schmitz, T., Nathan Spreng, R., The Alzheimer's Disease Neuroimaging Initiative. et al. Basal forebrain degeneration precedes and predicts the cortical spread of Alzheimer's pathology. Nat Commun 7, 13249 (2016). https://doi.org/10.1038/ncomms13249

68. George S, Mufson EJ, Leurgans S, Shah RC, Ferrari C, de Toledo-Morrell L. MRI-based volumetric measurement of the substantia innominata in amnestic MCI and mild AD. Neurobiol Aging. 2011;32(10):1756-1764. doi:10.1016/j.neurobiolaging.2009.11.006

69. Schulz J, Pagano G, Fernández Bonfante JA, Wilson H, Politis M. Nucleus basalis of Meynert degeneration precedes and predicts cognitive impairment in Parkinson's disease. Brain. 2018;141(5):1501-1516. doi:10.1093/brain/awy072

70. Jethwa KD, Dhillon P, Meng D, Auer DP; Alzheimer's Disease Neuroimaging Initiative. Are Linear Measurements of the Nucleus Basalis of Meynert Suitable as a Diagnostic Biomarker in Mild Cognitive Impairment and Alzheimer Disease? AJNR Am J Neuroradiol. 2019 Dec;40(12):2039-2044. doi: 10.3174/ajnr.A6313. Epub 2019 Nov 14. PMID: 31727757; PMCID: PMC6975347.

71. Colloby, S. J., Elder, G. J., Rabee, R., O'Brien, J. T., & Taylor, J. P. (2017). Structural grey matter changes in the substantia innominata in Alzheimer's disease and dementia with Lewy bodies: a DARTEL-VBM study. International journal of geriatric psychiatry, 32(6), 615–623. https://doi.org/10.1002/gps.4500

72. Ray, N. J., Bradburn, S., Murgatroyd, C., Toseeb, U., Mir, P., Kountouriotis, G. K., Teipel, S. J., & Grothe, M. J. (2018). In vivo cholinergic basal forebrain atrophy predicts cognitive decline in de novo Parkinson's disease. Brain : a journal of neurology, 141(1), 165–176. https://doi.org/10.1093/brain/awx310

73. Jose L. Cantero, Laszlo Zaborszky, Mercedes Atienza, Volume Loss of the Nucleus Basalis of Meynert is Associated with Atrophy of Innervated Regions in Mild Cognitive Impairment, Cerebral Cortex, Volume 27, Issue 8, August 2017, Pages 3881–3889, https://doi.org/10.1093/cercor/bhw195

74. Muth K, Schönmeyer R, Matura S, Haenschel C, Schröder J, Pantel J. Mild cognitive impairment in the elderly is associated with volume loss of the cholinergic basal forebrain region. Biol Psychiatry. 2010 Mar 15;67(6):588-91. doi: 10.1016/j.biopsych.2009.02.026. Epub 2009 Apr 17. PMID: 19375072.

75. Lezak MD, Howieson DB, Loring DW, Hannay HJ, Fischer JS. Neuropsychological Assessment. 4th ed. New York, NY, US: Oxford University Press; 2004.

76. Bowie CR, Harvey PD. Administration and interpretation of the Trail Making Test. Nature Protocols. 2006;1:2277–2281. doi: 10.1038/nprot.2006.390.

77. Gannon M, Wang Q. Complex noradrenergic dysfunction in Alzheimer's disease: Low norepinephrine input is not always to blame. Brain Research. 2019 Jan;1702:12-16. DOI: 10.1016/j.brainres.2018.01.001.

78. Kang, S. S., Liu, X., Ahn, E. H., Xiang, J., Manfredsson, F. P., Yang, X., Luo, H. R., Liles, L. C., Weinshenker, D., & Ye, K. (2020). Norepinephrine metabolite DOPEGAL activates AEP and pathological Tau aggregation in locus coeruleus. The Journal of clinical investigation, 130(1), 422–437. https://doi.org/10.1172/JCI130513

79. van Hooren RWE, Verhey FRJ, Ramakers IHGB, Jansen WJ, Jacobs HIL. Elevated norepinephrine metabolism is linked to cortical thickness in the context of Alzheimer's disease pathology. Neurobiol Aging. 2021 Feb 9;102:17-22. doi: 10.1016/j.neurobiolaging.2021.01.024. Epub ahead of print. PMID: 33667876.

80. Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, Jack CR, Jagust WJ, Shaw LM, Toga AW, Trojanowski JQ, Weiner MW (2010) Alzheimer's Disease Neuroimaging Initiative (ADNI): Clinical characterization. Neurology 74, 201– 209.

81. Keren, N.I., Lozar, C.T., Harris, K.C., Morgan, P.S., Eckert, M.A. (2009). In vivo mapping of the human locus coeruleus. NeuroImage, 47(4), 1261-1267.

82. Tona K-D, Keuken MC, de Rover M, Lakke E, Forstmann BU, Nieuwenhuis S, et al. In vivo visualization of the locus coeruleus in humans: quantifying the test–retest reliability. Brain Structure and Function. 2017. 10.1007/s00429-017-1464-5

83. Betts MJ, Cardenas-Blanco A, Kanowski M, Jessen F, Düzel E. In vivo MRI assessment of the human locus coeruleus along its rostrocaudal extent in young and older adults. Neuroimage. 2017;163:150-159. doi:10.1016/j.neuroimage.2017.09.042

84. Rong Ye, Rua C, O'Callaghan C, Jones PS, Hezemans F, Kaalund SS, Tsvetanov KA, Rodgers CT, Williams G, Passamonti L, Rowe JB. An in vivo Probabilistic Atlas of the Human Locus Coeruleus at Ultra-high Field. bioRxiv 2020.02.03.932087; doi: https://doi.org/10.1101/2020.02.03.932087

85. Beliveau V, Svarer C, Frokjaer VG, Knudsen GM, Greve DN, Fisher PM. Functional connectivity of the dorsal and median raphe nuclei at rest, NeuroImage, Volume 116, 2015, Pages 187-195, ISSN 1053-8119, https://doi.org/10.1016/j.neuroimage.2015.04.065.

86. Pauli, W. M., Nili, A. N., & Tyszka, J. M. (2018). A high-resolution probabilistic in vivo atlas of human subcortical brain nuclei. Scientific data, 5, 180063. doi:10.1038/sdata.2018.63

87. Zaborszky L, Hoemke L, Mohlberg H, Schleicher A, Amunts K, Zilles K. Stereotaxic probabilistic maps of the magnocellular cell groups in human basal forebrain. Neuroimage. 2008;42(3):1127-1141. doi:10.1016/j.neuroimage.2008.05.055

88. Forstmann, B. U., Keuken, M. C., Jahfari, S., Bazin, P.-L., Neumann, J., Schaefer, A., Anwander, A., & Turner, R. (2012). Cortico-subthalamic white matter tract strength predicts interindividual efficacy in stopping a motor response. Neuroimage 60, 370-375.

89. Collins et al. Automatic 3-D model-based neuroanatomical segmentation. Human Brain Mapping 3(3): 190-208. (1995)

90. Mazziotta, J., Toga, A., Evans, A., Fox, P., Lancaster, J., Zilles, K., Woods, R., Paus, T., Simpson, G., Pike, B., Holmes, C., Collins, L., Thompson, P., MacDonald, D., Iacoboni, M., Schormann, T., Amunts, K., Palomero-Gallagher, N., Geyer, S., Parsons, L., Mazoyer, B. (2001). A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). Philosophical transactions of the Royal Society of London. Series B, Biological sciences, 356(1412), 1293–1322. https://doi.org/10.1098/rstb.2001.0915

91. Makris N, Goldstein JM, Kennedy D, Hodge SM, Caviness VS, Faraone SV, Tsuang MT, Seidman LJ. Decreased volume of left and total anterior insular lobule in schizophrenia. Schizophr Res. 2006 Apr;83(2-3):155-71

92. Frazier JA, Chiu S, Breeze JL, Makris N, Lange N, Kennedy DN, Herbert MR, Bent EK, Koneru VK, Dieterich ME, Hodge SM, Rauch SL, Grant PE, Cohen BM, Seidman LJ, Caviness VS, Biederman J. Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. Am J Psychiatry. 2005 Jul;162(7):1256-65

93. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006 Jul 1;31(3):968-80.

94. Goldstein JM, Seidman LJ, Makris N, Ahern T, O'Brien LM, Caviness VS Jr, Kennedy DN, Faraone SV, Tsuang MT. Hypothalamic abnormalities in schizophrenia: sex effects and genetic vulnerability. Biol Psychiatry. 2007 Apr 15;61(8):935-45

95. Liu AK, Chang RC, Pearce RK, Gentleman SM. Nucleus basalis of Meynert revisited: anatomy, history and differential involvement in Alzheimer's and Parkinson's disease. Acta Neuropathol. 2015;129(4):527-540. doi:10.1007/s00401-015-1392-5

96. Kilimann I, Grothe M, Heinsen H, et al. Subregional basal forebrain atrophy in Alzheimer's disease: a multicenter study. J Alzheimers Dis. 2014;40(3):687-700. doi:10.3233/JAD-132345

97. Koulousakis P, Andrade P, Visser-Vandewalle V, Sesia T. The Nucleus Basalis of Meynert and Its Role in Deep Brain Stimulation for Cognitive Disorders: A Historical Perspective. J Alzheimers Dis. 2019;69(4):905-919. doi:10.3233/JAD-180133

98. Le TT, Kuplicki RT, McKinney BA, Yeh HW, Thompson WK, Paulus MP; Tulsa 1000 Investigators. A Nonlinear Simulation Framework Supports Adjusting for Age When Analyzing BrainAGE. Front Aging Neurosci. 2018 Oct 24;10:317. doi: 10.3389/fnagi.2018.00317. PMID: 30405393; PMCID: PMC6208001.

99. Aston-Jones G, Waterhouse B. Locus coeruleus: From global projection system to adaptive regulation of behavior. Brain Res. 2016;1645:75-78. doi:10.1016/j.brainres.2016.03.001

100. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991;82(4):239-259. doi:10.1007/BF00308809

101. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. J Neuropathol Exp Neurol. 2011;70(11):960-969. doi:10.1097/NEN.0b013e318232a379

102. Del Tredici K, Braak H. To stage, or not to stage. Curr Opin Neurobiol. 2020;61:10-22. doi:10.1016/j.conb.2019.11.008

103. Andrés-Benito P, Fernández-Dueñas V, Carmona M, Escobar LA, Torrejón-Escribano B, Aso E, Ciruela F, Ferrer I. Locus coeruleus at asymptomatic early and middle Braak stages of neurofibrillary tangle pathology. Neuropathol Appl Neurobiol. 2017 Aug;43(5):373-392. doi: 10.1111/nan.12386. Epub 2017 Apr 19. PMID: 28117912.

104. Šimić G, Stanic G, Mladinov M, Jovanov-Milosevic N, Kostovic I, Hof PR. Does Alzheimer's disease begin in the brainstem? Neuropathol Appl Neurobiol. 2009 Dec;35(6):532-54. doi: 10.1111/j.1365-2990.2009.01038.x. Epub 2009 Aug 4. PMID: 19682326; PMCID: PMC2787819.

105. Šimić G, Babić Leko M, Wray S, Harrington CR, Delalle I, Jovanov-Milošević N, Bažadona D, Buée L, de Silva R, Di Giovanni G, Wischik CM, Hof PR. Monoaminergic neuropathology in Alzheimer's disease. Prog Neurobiol. 2017 Apr;151:101-138. doi: 10.1016/j.pneurobio.2016.04.001. Epub 2016 Apr 12. PMID: 27084356; PMCID: PMC5061605.

106. Szot P, White SS, Greenup JL, et al. Changes in adrenoreceptors in the prefrontal cortex of subjects with dementia: evidence of compensatory changes. Neuroscience. 2007 Apr;146(1):471-480. DOI: 10.1016/j.neuroscience.2007.01.031.

107. Francis PT, Palmer AM, Sims NR, Bowen DM, Davison AN, Esiri MM, Neary D, Snowden JS, Wilcock GK. Neurochemical studies of early-onset Alzheimer's disease. Possible influence on treatment. N Engl J Med. 1985 Jul 4;313(1):7-11. doi: 10.1056/NEJM198507043130102. PMID: 2582256.

108. Hoogendijk WJ, Sommer IE, Pool CW, Kamphorst W, Hofman MA, Eikelenboom P, Swaab DF. Lack of association between depression and loss of neurons in the locus coeruleus in Alzheimer disease. Arch Gen Psychiatry. 1999 Jan;56(1):45-51. doi: 10.1001/archpsyc.56.1.45. PMID: 9892255.

109. Matthews KL, Chen CP, Esiri MM, Keene J, Minger SL, Francis PT. Noradrenergic changes, aggressive behavior, and cognition in patients with dementia. Biol Psychiatry. 2002;51(5):407-416. doi:10.1016/s0006-3223(01)01235-5

110. Gannon M, Che P, Chen Y, Jiao K, Roberson ED, Wang Q. Noradrenergic dysfunction in Alzheimer's disease. (2015) Frontiers in neuroscience, 9, 220. https://doi.org/10.3389/fnins.2015.00220

111. Aston-Jones G, Rajkowski J, Cohen J. Role of locus coeruleus in attention and behavioral flexibility. Biol Psychiatry. 1999;46(9):1309-1320. doi:10.1016/s0006-3223(99)00140-7

112. Shine JM. Neuromodulatory Influences on Integration and Segregation in the Brain. Trends in Cognitive Sciences. 2019 Jul;23(7):572-583. DOI: 10.1016/j.tics.2019.04.002.

113. Jacobs HIL, Riphagen JM, Ramakers IHGB, Verhey FRJ. Alzheimer's disease pathology: pathways between central norepinephrine activity, memory, and neuropsychiatric symptoms. Mol Psychiatry. 2019 May 28. doi: 10.1038/s41380-019-0437-x. Epub ahead of print. PMID: 31138892.

114. Löwe LC, Gaser C, Franke K; Alzheimer's Disease Neuroimaging Initiative. The Effect of the APOE Genotype on Individual BrainAGE in Normal Aging, Mild Cognitive Impairment, and Alzheimer's Disease. PLoS One. 2016 Jul 13;11(7):e0157514. doi: 10.1371/journal.pone.0157514. PMID: 27410431; PMCID: PMC4943637.

115. Kaufmann T, van der Meer D, Doan NT, Schwarz E, Lund MJ, Agartz I, Alnæs D, Barch DM, Baur-Streubel R, Bertolino A, Bettella F, Beyer MK, Bøen E, Borgwardt S, Brandt CL, Buitelaar J, Celius EG, Cervenka S, Conzelmann A, Córdova-Palomera A, Dale AM, de Quervain DJF, Di Carlo P, Djurovic S, Dørum ES, Eisenacher S, Elvsåshagen T, Espeseth T, Fatouros-Bergman H, Flyckt L, Franke B, Frei O, Haatveit B, Håberg AK, Harbo HF, Hartman CA, Heslenfeld D, Hoekstra PJ, Høgestøl EA, Jernigan TL, Jonassen R, Jönsson EG; Karolinska Schizophrenia Project (KaSP), Kirsch P, Kłoszewska I, Kolskår KK, Landrø NI, Le Hellard S, Lesch KP, Lovestone S, Lundervold A, Lundervold AJ, Maglanoc LA, Malt UF, Mecocci P, Melle I, Meyer-Lindenberg A, Moberget T, Norbom LB, Nordvik JE, Nyberg L, Oosterlaan J, Papalino M, Papassotiropoulos A, Pauli P, Pergola G, Persson K, Richard G, Rokicki J, Sanders AM, Selbæk G, Shadrin AA, Smeland OB, Soininen H, Sowa P, Steen VM, Tsolaki M, Ulrichsen KM, Vellas B, Wang L, Westman E, Ziegler GC, Zink M, Andreassen OA, Westlye LT. Publisher Correction: Common brain disorders are associated with heritable patterns of apparent aging of the brain. Nat Neurosci. 2020 Feb;23(2):295. doi: 10.1038/s41593-019-0553-6. Erratum for: Nat Neurosci. 2019 Oct;22(10):1617-1623. PMID: 31848485.

116. Cole JH. Multimodality neuroimaging brain-age in UK biobank: relationship to biomedical, lifestyle, and cognitive factors. Neurobiol Aging. 2020 Aug;92:34-42. doi: 10.1016/j.neurobiolaging.2020.03.014. Epub 2020 Apr 8. PMID: 32380363; PMCID: PMC7280786.

117. Wilcock GK, Esiri MM, Bowen DM, Hughes AO. The differential involvement of subcortical nuclei in senile dementia of Alzheimer's type. J Neurol Neurosurg Psychiatry. 1988 Jun;51(6):842-9. doi: 10.1136/jnnp.51.6.842. PMID: 3404192; PMCID: PMC1033158.

118. Aletrino MA, Vogels OJ, Van Domburg PH, Ten Donkelaar HJ. Cell loss in the nucleus raphes dorsalis in Alzheimer's disease. Neurobiol Aging. 1992 Jul-Aug;13(4):461-8. doi: 10.1016/0197-4580(92)90073-7. PMID: 1508296.

119. Rüb U, Del Tredici K, Schultz C, Thal DR, Braak E, Braak H. The evolution of Alzheimer's disease-related cytoskeletal pathology in the human raphe nuclei. Neuropathol Appl Neurobiol. 2000 Dec;26(6):553-67. doi: 10.1046/j.0305-1846.2000.00291.x. PMID: 11123722.

120. Rodríguez JJ, Noristani HN, Verkhratsky A. The serotonergic system in ageing and Alzheimer's disease. Prog Neurobiol. 2012 Oct;99(1):15-41. doi: 10.1016/j.pneurobio.2012.06.010. Epub 2012 Jul 2. PMID: 22766041.

121. Grinberg LT, Rüb U, Ferretti RE, Nitrini R, Farfel JM, Polichiso L, Gierga K, Jacob-Filho W, Heinsen H; Brazilian Brain Bank Study Group. The dorsal raphe nucleus shows phospho-tau neurofibrillary changes before the transentorhinal region in Alzheimer's disease. A precocious onset? Neuropathol Appl Neurobiol. 2009 Aug;35(4):406-16. doi: 10.1111/j.1365-2990.2009.00997.x. PMID: 19508444.

122. Michelsen KA, Schmitz C, Steinbusch HW. The dorsal raphe nucleus--from silver stainings to a role in depression. Brain Res Rev. 2007 Oct;55(2):329-42. doi: 10.1016/j.brainresrev.2007.01.002. Epub 2007 Jan 17. PMID: 17316819.

123. Aznar S, Qian ZX, Knudsen GM. Non-serotonergic dorsal and median raphe projection onto parvalbumin- and calbindin-containing neurons in hippocampus and septum. Neuroscience. 2004;124(3):573-81. doi: 10.1016/j.neuroscience.2003.12.020. PMID: 14980728.

124. Baker KG, Halliday GM, Hornung JP, Geffen LB, Cotton RG, Törk I. Distribution, morphology and number of monoamine-synthesizing and substance P-containing neurons in the human dorsal raphe nucleus. Neuroscience. 1991;42(3):757-75. doi: 10.1016/0306-4522(91)90043-n. PMID: 1720227.

125. Kirby LG, Pernar L, Valentino RJ, Beck SG. Distinguishing characteristics of serotonin and non-serotonin-containing cells in the dorsal raphe nucleus: electrophysiological and immunohistochemical studies. Neuroscience. 2003;116(3):669-83. doi: 10.1016/s0306-4522(02)00584-5. PMID: 12573710; PMCID: PMC2832757.

126. Ordway GA, Stockmeier CA, Cason GW, Klimek V. Pharmacology and distribution of norepinephrine transporters in the human locus coeruleus and raphe nuclei. J Neurosci. 1997 Mar 1;17(5):1710-9. doi: 10.1523/JNEUROSCI.17-05-01710.1997. PMID: 9030630; PMCID: PMC6573386.

127. Farley IJ, Hornykiewicz O. Noradrenaline distribution in subcortical areas of the human brain. Brain Res. 1977 Apr 22;126(1):53-62. doi: 10.1016/0006-8993(77)90214-1. PMID: 851895.

128. Szot P, White SS, Greenup JL, et al. Compensatory changes in the noradrenergic nervous system in the locus ceruleus and hippocampus of postmortem subjects with Alzheimer's disease and dementia with Lewy bodies. The Journal of Neuroscience : the Official Journal of the Society for Neuroscience. 2006 Jan;26(2):467-478. DOI: 10.1523/jneurosci.4265-05.2006.

129. Theofilas P, Ehrenberg AJ, Dunlop S, Di Lorenzo Alho AT, Nguy A, Leite REP, Rodriguez RD, Mejia MB, Suemoto CK, Ferretti-Rebustini REL, Polichiso L, Nascimento CF, Seeley WW, Nitrini R, Pasqualucci CA, Jacob Filho W, Rueb U, Neuhaus J, Heinsen H, Grinberg LT. Locus coeruleus volume and cell population changes during Alzheimer's disease progression: A stereological study in human postmortem brains with potential implication for early-stage biomarker discovery. Alzheimers Dement. 2017 Mar;13(3):236-246. doi: 10.1016/j.jalz.2016.06.2362. Epub 2016 Aug 8. PMID: 27513978; PMCID: PMC5298942.

130. Steffener J, Habeck C, O'Shea D, Razlighi Q, Bherer L, Stern Y. Differences between chronological and brain age are related to education and self-reported physical activity. Neurobiol Aging. 2016 Apr;40:138-144. doi: 10.1016/j.neurobiolaging.2016.01.014. Epub 2016 Feb 1. PMID: 26973113; PMCID: PMC4792330.

131. Anatürk, M., Kaufmann, T., Cole, J. H., Suri, S., Griffanti, L., Zsoldos, E., … de Lange, A. G. (2020, June 12). Prediction of brain age and cognitive age: quantifying brain and cognitive maintenance in aging. https://doi.org/10.31234/osf.io/gwqnt

132. Krashia P, Nobili A, D'Amelio M. Unifying Hypothesis of Dopamine Neuron Loss in Neurodegenerative Diseases: Focusing on Alzheimer's Disease. Front Mol Neurosci. 2019 May 17;12:123. doi: 10.3389/fnmol.2019.00123. PMID: 31156387; PMCID: PMC6534044.

133. Bozzali, M., D'Amelio, M., & Serra, L. (2019). Ventral tegmental area disruption in Alzheimer's disease. Aging, 11(5), 1325–1326. https://doi.org/10.18632/aging.101852

134. Chalermpalanupap T, Kinkead B, Hu WT, Kummer MP, Hammerschmidt T, Heneka MT, Weinshenker D, Levey AI. Targeting norepinephrine in mild cognitive impairment and Alzheimer's disease. Alzheimers Res Ther. 2013 Apr 29;5(2):21. doi: 10.1186/alzrt175. PMID: 23634965; PMCID: PMC3706916.

135. Phillips C, Fahimi A, Das D, Mojabi FS, Ponnusamy R, Salehi A. Noradrenergic System in Down Syndrome and Alzheimer's Disease A Target for Therapy. Curr Alzheimer Res. 2016;13(1):68-83. doi: 10.2174/1567205012666150921095924. PMID: 26391048.

136. Dockree PM, Barnes JJ, Matthews N, Dean A, Abe R, Nandam LS, et al. (2017): The Effects of Methylphenidate on the Neural Signatures of Sustained Attention. Biological Psychiatry.Volume 82, Issue 9, 1 November 2017, Pages 687-694

137. Minzenberg MJ, Watrous AJ, Yoon JH, Ursu S, Carter CS. Modafinil shifts human locus coeruleus to low-tonic, high-phasic activity during functional MRI. Science. 2008;322:1700–1702

138. Segal SK, Cotman CW, Cahill LF. Exercise-induced noradrenergic activation enhances memory consolidation in both normal aging and patients with amnestic mild cognitive impairment. J Alzheimers Dis. 2012;32(4):1011-8. doi: 10.3233/JAD-2012-121078. PMID: 22914593; PMCID: PMC3951984.

139. Mather M, Huang R, Clewett D, Nielsen SE, Velasco R, Tu K, Han S, Kennedy BL. Isometric exercise facilitates attention to salient events in women via the noradrenergic system. Neuroimage. 2020 Apr 15;210:116560. doi: 10.1016/j.neuroimage.2020.116560. Epub 2020 Jan 21. PMID: 31978545; PMCID: PMC7061882.

140. Choudhary P, Pacholko AG, Palaschuk J, Bekar LK. The locus coeruleus neurotoxin, DSP4, and/or a high sugar diet induce behavioral and biochemical alterations in wild-type mice consistent with Alzheimers related pathology. Metab Brain Dis. 2018 Oct;33(5):1563-1571. doi: 10.1007/s11011-018-0263-x. Epub 2018 Jun 3. PMID: 29862455.

141. Pacholko AG, Wotton CA, Bekar LK. Poor Diet, Stress, and Inactivity Converge to Form a "Perfect Storm" That Drives Alzheimer's Disease Pathogenesis. Neurodegener Dis. 2019;19(2):60-77. doi: 10.1159/000503451. Epub 2019 Oct 10. PMID: 31600762.

142. Engelborghs S, Gilles C, Ivanoiu A, Vandewoude M. Rationale and clinical data supporting nutritional intervention in Alzheimer's disease. Acta Clin Belg. 2014 Jan-Feb;69(1):17-24. doi: 10.1179/0001551213Z.0000000006. PMID: 24635394.

143. Seidl SE, Santiago JA, Bilyk H, Potashkin JA. The emerging role of nutrition in Parkinson's disease. (2014). Frontiers in aging neuroscience, 6, 36. https://doi.org/10.3389/fnagi.2014.00036

144. Scarmeas, N., Luchsinger, J. A., Mayeux, R., & Stern, Y. (2007). Mediterranean diet and Alzheimer disease mortality. Neurology, 69(11), 1084–1093. https://doi.org/10.1212/01.wnl.0000277320.50685.7c

145. Barnard ND, Bush AI, Ceccarelli A, Cooper J, de Jager CA, Erickson KI, Fraser G, Kesler S, Levin SM, Lucey B, Morris MC, Squitti R. Dietary and lifestyle guidelines for the prevention of Alzheimer's disease. Neurobiol Aging. 2014 Sep;35 Suppl 2:S74-8. doi: 10.1016/j.neurobiolaging.2014.03.033. Epub 2014 May 14. PMID: 24913896.

146. Poly C, Massaro JM, Seshadri S, Wolf PA, Cho E, Krall E, Jacques PF, Au R. The relation of dietary choline to cognitive performance and white-matter hyperintensity in the Framingham Offspring Cohort. (2011) The American journal of clinical nutrition, 94(6), 1584–1591. https://doi.org/10.3945/ajcn.110.008938

147. Ylilauri MPT, Voutilainen S, Lönnroos E, Virtanen HEK, Tuomainen TP, Salonen JT, Virtanen JK. Associations of dietary choline intake with risk of incident dementia and with cognitive performance: the Kuopio Ischaemic Heart Disease Risk Factor Study. Am J Clin Nutr. 2019 Dec 1;110(6):1416-1423. doi: 10.1093/ajcn/nqz148. PMID: 31360988.

148. Spiers PA, Myers D, Hochanadel GS, Lieberman HR, Wurtman RJ. Citicoline improves verbal memory in aging. Arch Neurol. 1996 May;53(5):441-8. doi: 10.1001/archneur.1996.00550050071026. Erratum in: Arch Neurol 1996 Oct;53(10):964. PMID: 8624220.

149. Kühn S, Düzel S, Colzato L, Norman K, Gallinat J, Brandmaier AM, Lindenberger U, Widaman KF. Food for thought: association between dietary tyrosine and cognitive performance in younger and older adults. Psychol Res. 2019 Sep;83(6):1097-1106. doi: 10.1007/s00426-017-0957-4. Epub 2017 Dec 18. PMID: 29255945; PMCID: PMC6647184.

150. Aliev G, Shahida K, Gan SH, Firoz C, Khan A, Abuzenadah AM, Kamal W, Kamal MA, Tan Y, Qu X, Reale M. Alzheimer disease and type 2 diabetes mellitus: the link to tyrosine hydroxylase and probable nutritional strategies. CNS Neurol Disord Drug Targets. 2014 Apr;13(3):467-77. doi: 10.2174/18715273113126660153. PMID: 24059309.

151. Forssell LG, Eklöf R, Winblad B, Forssell L. Early Stages of Late Onset Alzheimer's Disease. (1989) Acta Neurologica Scandinavica, 79: 27-42. doi:10.1111/j.1600-0404.1989.tb04875.x

152. Rasmussen DD, Ishizuka B, Quigley ME, Yen SS. Effects of tyrosine and tryptophan ingestion on plasma catecholamine and 3,4-dihydroxyphenylacetic acid concentrations. J Clin Endocrinol Metab. 1983 Oct;57(4):760-3. doi: 10.1210/jcem-57-4-760. PMID: 6885965.

153. Agharanya JC, Alonso R, Wurtman RJ. Changes in catecholamine excretion after short-term tyrosine ingestion in normally fed human subjects. Am J Clin Nutr. 1981 Jan;34(1):82-7. doi: 10.1093/ajcn/34.1.82. PMID: 7192489.

154. Mahoney CR, Castellani J, Kramer FM, Young A, Lieberman HR. Tyrosine supplementation mitigates working memory decrements during cold exposure. Physiol Behav. 2007 Nov 23;92(4):575-82. doi: 10.1016/j.physbeh.2007.05.003. Epub 2007 May 22. PMID: 17585971.

155. Thomas JR, Lockwood PA, Singh A, Deuster PA. Tyrosine improves working memory in a multitasking environment. Pharmacol Biochem Behav. 1999 Nov;64(3):495-500. doi: 10.1016/s0091-3057(99)00094-5. PMID: 10548261.

156. Deijen JB, Orlebeke JF. Effect of tyrosine on cognitive function and blood pressure under stress. Brain Res Bull. 1994;33(3):319-23. doi: 10.1016/0361-9230(94)90200-3. PMID: 8293316.

157. Deijen JB, Wientjes CJ, Vullinghs HF, Cloin PA, Langefeld JJ. Tyrosine improves cognitive performance and reduces blood pressure in cadets after one week of a combat training course. Brain Res Bull. 1999 Jan 15;48(2):203-9. doi: 10.1016/s0361-9230(98)00163-4. PMID: 10230711.

158. Lieberman HR, Corkin S, Spring BJ, Wurtman RJ, Growdon JH. The effects of dietary neurotransmitter precursors on human behavior. Am J Clin Nutr. 1985 Aug;42(2):366-70. doi: 10.1093/ajcn/42.2.366. PMID: 4025206.

159. Melnychuk MC, Dockree PM, O'Connell RG, Murphy PR, Balsters JH, Robertson IH. Coupling of respiration and attention via the locus coeruleus: Effects of meditation and pranayama. Psychophysiology. 2018 Sep;55(9):e13091. doi: 10.1111/psyp.13091. Epub 2018 Apr 22. PMID: 29682753.

160. Craigmyle NA. The beneficial effects of meditation: contribution of the anterior cingulate and locus coeruleus. Front Psychol. 2013 Oct 16;4:731. doi: 10.3389/fpsyg.2013.00731. PMID: 24137145; PMCID: PMC3797386.

161. Luders E, Toga AW, Lepore N, Gaser C. The underlying anatomical correlates of long-term meditation: larger hippocampal and frontal volumes of gray matter. 2009 NeuroImage, 45(3), 672–678. https://doi.org/10.1016/j.neuroimage.2008.12.061

162. Vestergaard-Poulsen P, van Beek M, Skewes J, Bjarkam CR, Stubberup M, Bertelsen J, Roepstorff A. Long-term meditation is associated with increased gray matter density in the brain stem. Neuroreport. 2009 Jan 28;20(2):170-4. doi: 10.1097/WNR.0b013e328320012a. PMID: 19104459.

163. Singleton O, Hölzel BK, Vangel M, Brach N, Carmody J, Lazar SW. Change in Brainstem Gray Matter Concentration Following a Mindfulness-Based Intervention is Correlated with Improvement in Psychological Well-Being. Front Hum Neurosci. 2014 Feb 18;8:33. doi: 10.3389/fnhum.2014.00033. PMID: 24600370; PMCID: PMC3927233.

164. Holzel, B. K., Carmody, J., Vangel, M., Congleton, C., Yerramsetti, S. M., Gard, T., & Lazar, S. W. (2011). Mindfulness practice leads to increases in regional brain gray matter density. Psychiatry Research: Neuroimaging, 191(1), 36–43. https://doi.org/10.1016/j.pscychresns.2010.08.006

165. Fox, K. C., Nijeboer, S., Dixon, M. L., Floman, J. L., Ellamil, M., Rumak, S. P., ... & Christoff, K. (2014). Is meditation associated with altered brain structure? A systematic review and meta-analysis of morphometric neuroimaging in meditation practitioners. Neuroscience & Biobehavioral Reviews, 43, 48-73.

166. Tang, Y. Y., Lu, Q., Geng, X., Stein, E. A., Yang, Y., & Posner, M. I. (2010). Short-term meditation induces white matter changes in the anterior cingulate. Proceedings of the National Academy of Sciences, 107(35), 15649-15652.

167. Tang, R., Friston, K. J., & Tang, Y. Y. (2020). Brief Mindfulness Meditation Induces Gray Matter Changes in the Brain Hub. Neural Plasticity, 2020.

168. Ycaza Herrera A, Wang J, Mather M. The gist and details of sex differences in cognition and the brain: How parallels in sex differences across domains are shaped by the locus coeruleus and catecholamine systems. Prog Neurobiol. 2019 May;176:120-133. doi: 10.1016/j.pneurobio.2018.05.005. Epub 2018 May 19. PMID: 29772255; PMCID: PMC6485927.

169. Tom N. Tombaugh, Trail Making Test A and B: Normative data stratified by age and education, *Archives of Clinical Neuropsychology*, Volume 19, Issue 2, March 2004, Pages 203–214, https://doi.org/10.1016/S0887-6177(03)00039-8

170. Elizabeth A. Gaudino, Mark W. Geisler & Nancy K. Squires (1995) Construct validity in the trail making test: What makes part B harder?, Journal of Clinical and Experimental Neuropsychology, 17:4, 529-535, DOI: 10.1080/01688639508405143

171. O'Callaghan C, Walpola IC, Shine JM. Neuromodulation of the mind-wandering brain state: the interaction between neuromodulatory tone, sharp wave-ripples and spontaneous thought. Philos Trans R Soc Lond B Biol Sci. 2021 Feb;376(1817):20190699. doi: 10.1098/rstb.2019.0699. Epub 2020 Dec 14. PMID: 33308063; PMCID: PMC7741077.

172. Holland N, Robbins TW, Rowe JB. The role of noradrenaline in cognition and cognitive disorders. Brain. 2021 Mar 16:awab111. doi: 10.1093/brain/awab111. Epub ahead of print. PMID: 33725122.

173. Koychev I, Hofer M, Friedman N. Correlation of Alzheimer Disease Neuropathologic Staging with Amyloid and Tau Scintigraphic Imaging Biomarkers. J Nucl Med. 2020 Oct;61(10):1413-1418. doi: 10.2967/jnumed.119.230458. Epub 2020 Aug 6. PMID: 32764121.

174. Bachman, S.L., Dahl, M.J., Werkle-Bergner, M., Duzel, S., Forlim, C.G., Lindenberger, U., Kuhn, S., Mather, M., Locus coeruleus MRI contrast is associated with cortical thickness in older adults, Neurobiology of Aging (2021), doi: https://doi.org/10.1016/j.neurobiolaging.2020.12.019

175. N. Palomero-Gallagher, K. Amunts, K. Zilles,Transmitter Receptor Distribution in the Human Brain,Editor(s): Arthur W. Toga,Brain Mapping, Academic Press,2015,Pages 261-275,ISBN 9780123973160, https://doi.org/10.1016/B978-0-12-397025-1.00221-9.

176. Klimek V, Stockmeier C, Overholser J, Meltzer HY, Kalka S, Dilley G, Ordway GA. Reduced levels of norepinephrine transporters in the locus coeruleus in major depression. J Neurosci. 1997 Nov 1;17(21):8451-8. doi: 10.1523/JNEUROSCI.17-21-08451.1997. PMID: 9334417; PMCID: PMC6573768.

177. Hoogendijk WJ, Feenstra MG, Botterblom MH, Gilhuis J, Sommer IE, Kamphorst W, Eikelenboom P, Swaab DF. Increased activity of surviving locus ceruleus neurons in Alzheimer's disease. Ann Neurol. 1999 Jan;45(1):82-91. doi: 10.1002/1531-8249(199901)45:1<82::aid-art14>3.0.co;2-t. PMID: 9894881.

178. Szot, P., Leverenz, J. B., Peskind, E. R., Kiyasu, E., Rohde, K., Miller, M. A., & Raskind, M. A. (2000). Tyrosine hydroxylase and norepinephrine transporter mRNA expression in the locus coeruleus in Alzheimer's disease. Molecular Brain Research, 84(1-2), 135–140. doi:10.1016/s0169-328x(00)00168-6

179. Keren, N. I., Taheri, S., Vazey, E. M., Morgan, P. S., Granholm, A.-C. E., Aston-Jones, G. S., & Eckert, M. A. (2015). Histologic validation of locus coeruleus MRI contrast in post-mortem tissue. NeuroImage, 113, 235–245. doi:10.1016/j.neuroimage.2015.03.020

180. Matchett, B.J., Grinberg, L.T., Theofilas, P. et al. The mechanistic link between selective vulnerability of the locus coeruleus and neurodegeneration in Alzheimer's disease. Acta Neuropathol 141, 631–650 (2021). https://doi.org/10.1007/s00401-020-02248-1

181. Ishimatsu M, Williams JT. Synchronous activity in locus coeruleus results from dendritic interactions in pericoerulear regions. J Neurosci. 1996 Aug 15;16(16):5196-204. doi: 10.1523/JNEUROSCI.16-16-05196.1996. PMID: 8756448; PMCID: PMC6579296.

182. Janitzky K. Impaired Phasic Discharge of Locus Coeruleus Neurons Based on Persistent High Tonic Discharge-A New Hypothesis With Potential Implications for Neurodegenerative Diseases. Front Neurol. 2020 May 12;11:371. doi: 10.3389/fneur.2020.00371. PMID: 32477246; PMCID: PMC7235306.

183. Liu KY, Acosta-Cabronero J, Cardenas-Blanco A, Loane C, Berry AJ, Betts MJ, Kievit RA, Henson RN, Düzel E; Cam-CAN, Howard R, Hämmerer D. In vivo visualization of age-related differences in the locus coeruleus. Neurobiol Aging. 2019 Feb; 74:101-111. doi: 10.1016/j.neurobiolaging.2018.10.014. Epub 2018 Oct 20. Erratum in: Neurobiol Aging. 2020 Jul;91:172-174. PMID: 30447418; PMCID: PMC6338679.

184. K.G. Baker, I. Törk, J.-P. Hornung, P. Halasz. The human locus coeruleus complex: an immunohistochemical and three dimensional reconstruction study. Exp. Brain Res., 77 (1989), pp. 257-270

185. D.C. German, B.S. Walker, K. Manaye, W.K. Smith, D.J. Woodward, A.J. North. The human locus coeruleus: computer reconstruction of cellular distribution. J. Neurosci., 8 (1988), pp. 1776-1788

186. T.G. Ohm, C. Busch, J. Bohl. Unbiased estimation of neuronal numbers in the human nucleus coeruleus during aging. Neurobiol. Aging, 18 (1997), pp. 393-399

187. Chan-Palay, E. Asan. Quantitation of catecholamine neurons in the locus coeruleus in human brains of normal young and older adults and in depression. J. Comp. Neurol., 287 (1989), pp. 357-372

188. Chapman SB, Aslan S, Spence JS, Keebler MW, DeFina LF, Didehbani N, Perez AM, Lu H, D'Esposito M. Distinct Brain and Behavioral Benefits from Cognitive vs. Physical Training: A Randomized Trial in Aging Adults. Front Hum Neurosci. 2016 Jul 18;10:338. doi: 10.3389/fnhum.2016.00338. PMID: 27462210; PMCID: PMC4939293.

189. Fernandes, P., Regala, J., Correia, F. *et al.* The human locus coeruleus 3-D stereotactic anatomy. *Surg Radiol Anat* **34,** 879–885 (2012). https://doi.org/10.1007/s00276-012-0979-y

190. Ivan Koychev, Monika Hofer and Nicholas Friedman. Correlation of Alzheimer Disease Neuropathologic Staging with Amyloid and Tau Scintigraphic Imaging Biomarkers. Journal of Nuclear Medicine October 2020, 61 (10) 1413-1418; DOI: https://doi.org/10.2967/jnumed.119.230458