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Original Research

Dietary Tyrosine Intake (FFQ) Is Associated with Locus Coeruleus, Attention and Grey Matter Maintenance: An MRI Structural Study on 398 Healthy Individuals of the Berlin Aging Study-II

E.R.G. Plini[1], M.C. Melnychuk[1], A. Harkin[1,2], M.J. Dahl[3,4], M. McAuslan[2], S. Kühn[6], R.T. Boyle[5], R. Whelan[1], R. Andrews[1], S. Düzel[3,13], J. Drewelies[6], G.G. Wagner[3], U. Lindenberger[3,7], K. Norman[8-11], I.H. Robertson[1,12], P.M. Dockree[1]

1. Department of Psychology, Trinity College Institute of Neuroscience, Trinity College Dublin, Lloyd Building, 42A Pearse St, 8PVX+GJ Dublin, Ireland; 2. School of Pharmacy and Pharmaceutical Sciences, Trinity College Institute of Neuroscience, Trinity College Dublin, Lloyd Building, 42A Pearse St, 8PVX+GJ Dublin, Ireland; 3. Center for Lifespan Psychology, Max Planck Institute for Human Development, 14195 Berlin, Germany; 4. Leonard Davis School of Gerontology, University of Southern California, 90089 Los Angeles, CA, USA; 5. Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Building 149, Charlestown MA, USA; 6. Lise Meitner Group for Enviromental Neuroscience, Max Planck Institute for Human Development, 14195 Berlin, Germany; 7. Max Planck UCL Centre for Computational Psychiatry and Ageing Research, Berlin and London; 8. Department of Nutrition and Gerontology, German Institute of Human Nutrition Potsdam-Rehbruecke, 14558 Nuthetal, Germany; 9. Institute of Nutritional Science, University of Potsdam, 14558 Nuthetal, Germany; 10. 10. Department of Geriatrics and Medical Gerontology, Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, 13347 Berlin, Germany; 11. German Centre for Cardiovascular Research (DZHK), Partner Site Berlin, 10785 Berlin, Germany; 12. Department of Psychology, Global Brain Health Institute, Trinity College Dublin, Lloyd Building, 42A Pearse St, 8PVX+GJ Dublin, Ireland; 13. Friede Springer Cardiovascular Prevention Center at Charité, Berlin, Germany

Corresponding Author: Emanuele RG Plini, Department of Psychology, Trinity College Institute of Neuroscience, Trinity College Dublin, Lloyd Building, 42A Pearse St, 8PVX+GJ Dublin, Ireland, plinie@tcd.ie

Abstract

BACKGROUND AND OBJECTIVE: It is documented that low protein and amino-acid dietary intake is related to poorer cognitive health and increased risk of dementia. Degradation of the neuromodulatory pathways, (comprising the cholinergic, dopaminergic, serotoninergic and noradrenergic systems) is observed in neurodegenerative diseases and impairs the proper biosynthesis of key neuromodulators from micro-nutrients and amino acids. How these micro-nutrients are linked to neuromodulatory pathways in healthy adults is less studied. The Locus Coeruleus–Noradrenergic System (LC-NA) is the earliest subcortical structure affected in Alzheimer's disease, showing marked neurodegeneration, but is also sensitive for age-related changes. The LC-NA system is critical for supporting attention and cognitive control, functions that are enhanced both by tyrosine administration and chronic tyrosine intake. The purpose of this study was to 1) investigate whether the dietary intake of tyrosine, the key precursor for noradrenaline (NA), is related to LC signal intensity 2) whether LC mediates the reported association between tyrosine intake and higher cognitive performance (measured with Trail Making Test – TMT), and 3) whether LC signal intensity relates to an objective measure of brain maintenance (BrainPAD).

METHODS: The analyses included 398 3T MRIs of healthy participants from the Berlin Aging Study II to investigate the relationship between LC signal intensity and habitual dietary tyrosine intake-daily average (HD-Tyr-IDA - measured with Food Frequency Questionnaire - FFQ). As a control procedure, the same analyses were repeated on other main seeds of the neuromodulators' subcortical system (Dorsal and Medial Raphe, Ventral Tegmental Area and Nucleus Basalis of Meynert). In the same way, the relationships between the five nuclei and BrainPAD were tested.

RESULTS: Results show that HD-Tyr-IDA is positively associated with LC signal intensity. Similarly, LC disproportionally relates to better brain maintenance (BrainPAD). Mediation analyses reveal that only LC, relative to the other nuclei tested, mediates the relationship between HD-Tyr-IDA I and performance in the TMT and between HD-Tyr-IDA and BrainPAD.

CONCLUSIONS: These findings provide the first evidence linking tyrosine intake with LC-NA system signal intensity and its correlation with neuropsychological performance. This study strengthens the role of diet for maintaining brain and cognitive health and supports the noradrenergic theory of cognitive reserve. Within this framework, adequate tyrosine intake might increase the resilience of LC-NA system functioning, by preventing degeneration and supporting noradrenergic metabolism required for LC function and neuropsychological performance.

Key words: Tyrosine, protein, Locus Coeruleus, grey Matter maintenance, healthy aging, healthy nutrition.

Introduction

Dementia is an ever growing disease estimated to affect a total of 78 million people worldwide by 2030, and potentially reaching 139 million by 2050 (https://www.alzint.org/). Dementia's etiopathogenesis is not completely understood and there currently is no remedy available to treat the disease nor slow it down (1). Prevention remains the only possible strategy to tackle this global upward trend. It is estimated that 40% of known dementia causes are modifiable by simply addressing people's lifestyle. Of this 40%, dietary behaviour plays a crucial role lowering the risk of developing dementia (1). For instance, adherence to a Mediterranean diet was observed to be protective against dementia supporting brain health and cognitive functions (2-6). Healthy diet is crucial in providing the necessary nutrients for adequate physiological functioning. Indeed, it is documented how a poor dietary lifestyle can worsen cognitive functioning while negatively affecting brain health (reduced cognitive performances and exacerbated inflammation and neurodegeneration) (7-10). Specifically, low protein and amino-acid dietary intake has been related to poor cognitive health and increased risk of dementia (7, 8, 11-14). This is possibly due

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to the lack of proper micro-nutrients and amino-acid supply needed for the appropriate biosynthesis of key neuromodulators which affect brain metabolism and cognitive functioning (15-18).

The degradation of the neuromodulatory pathways, comprising the cholinergic (ACh), dopaminergic (DA), serotoninergic (5-HT) and noradrenergic (NA) systems, is widely observed in neurodegenerative diseases (19). Since the well documented cholinergic decline in dementia, studies have investigated whether choline intake (precursor of Acethylcoline) would be related to better cognitive functioning and reduced neurodegeneration (20). Consequently, choline intake was associated with reduced dementia risk observed through biomarkers of neurodegeneration, along with more preserved cognitive functioning in several studies both on healthy and demented populations (21, 22). Mechanistically these findings proposed the role of choline in diet as a potential modifiable factor to help prevent neurodegeneration and reduce the incidence of dementia (21-23).

However, a growing body of literature identifies the noradrenergic system, originating in the Locus Coeruleus (LC) as the main driver of neurodegenerative dynamics (24-26). Indeed, the LC is the earliest brain structure affected in Alzheimer's disease showing early signs of neurodegeneration (24-26) and characterising disease progression and staging (26, 27). The LC-NA system is critical for supporting broad integrative function across large scale brain networks to support attention and exploratory behaviour, and stands in contrast to cholinergic-mediated segregation of specific cognitive networks (28-30). In the last decade, the integrity of the LC-NA system has been associated with greater brain and cognitive health (31-36), including better attentive and mnemonic functions both in healthy and clinical populations (32, 35, 37-40). These findings are in line with consideration of the LC-NA system MRI signal intensity (parameter of tissue density - integrity) serving as a potential in-vivo biomarker for neurodegenerative diseases (41), while being crucial for maintaining brain and cognitive health (28, 42, 43), as was previously postulated by the "noradrenergic theory of cognitive reserve" proposed by Robertson (42) (for details, see box1 in the supplementary materials).

Despite these relevant implications, and the central role of diet in dementia prevention, no studies to date have investigated a potential relationship between dietary behaviour and LC-NA system and functioning in healthy adults. In light of the pre-existing literature on choline intake, we aimed to investigate in this study whether the intake of tyrosine (the precursors of NA synthesised in the LC) (44), could be related to greater LC MRI signal intensity, and therefore better brain maintenance supporting higher-order cognitive functioning in healthy adults without cognitive impairment (35, 45-47). Our main hypothesis was also based on the literature reporting how malnutrition can negatively impact on overall brain mass (including subcortical structure) and cognition (48, 49), and how low amino-acids and protein intake was associated to increased neuro-inflammation and brain atrophy (9, 10) suggesting that amino-acidic profile intake as an important factor to assess dementia risk (11-14, 48).

Tyrosine (TYR) is an amino acid present in animal protein and serves as a principal precursor of catecholamine biosynthesis - http://www.ncc.umn.edu/ndsr-database-page/ - (44). In fact, throughout the ascending reticular arousal system (ARAS) (44), tyrosine is converted to L-dopa, then, to Dopamine. Dopamine is subsequently converted to NA within the LC neurons. Finally, within the adrenergic neurons of the Medulla oblongata NA Adrenaline (ADR) within the adrenergic neurons of the Medulla oblongata (44).

Catecholamines concentrations varies depending on the availability of amino acid precursor and diet can affect concentrations in the central nervous system (15-17, 47, 50). Protein intake stimulates biosynthesis because of the availability of precursors crossing the blood-brain barrier (51). Acute intake of amino acids like tyrosine is associated with increased concentrations of plasma catecholamines in humans and rodents (52, 53). Since administration of amino acid precursors have been associated with changes in behaviour and cognition (54), several studies investigating acute administration of tyrosine reported that tyrosine enhanced or restored higher order cognitive functions relative to controls (55-57). By administering between 2 and 12gr within 20–60 minutes before a variety of cognitive tests with or without cold exposure or military exercises, tyrosine supported attentive cognitive functioning in domains typically associated with the LC-NA system (28, 30, 42, 43). Remarkably, these effects were mostly appreciable under stressful conditions (i.e. cold exposure [58], extended wakefulness (59) and working memory load and task-switching (60, 61) – a comprehensive revision of this topic is beyond the scope of this work, for reviews please refer to (55-57).

This evidence inspired the concept that chronic dietary tyrosine intake might be associated with cognitive performances. The only study examining this hypothesis was carried out by Kühn and colleagues (45). The authors assessed tyrosine intake with a self-report measure of habitual food intake (the "food frequency questionnaire" - https://dapa-toolkit.mrc.ac.uk/diet/subjective-methods/food-frequency-questionnaire - (62), and reported that greater dietary tyrosine intake was associated with better fluid intelligence, greater working memory scores and more accurate episodic memory, in a sample of 1724 healthy participants (old and young) from the Berlin Aging Study II – BASE-II (63). This study also revealed that the association between habitual dietary tyrosine intake-daily average (HD-Tyr-IDA) and higher order cognitive performances was independent of age differences, and that cross-sectionally, both in young and old populations, the results were generalisable over the greater variation of cognitive performances between groups.

These findings informed the design of the current study, which utilises 398 high-resolution MRI scans available from a total of 1724 participants aiming at 1) investigating whether greater HD-Tyr-IDA is related to LC MRI signal intensity and 2) whether LC mediates the reported association between tyrosine and better cognitive performance (45, 55-57). In addition, since higher order cognitive functions have been associated with better brain maintenance (35, 64) we hypothesised that greater HD-Tyr-IDA could be associated with

better brain maintenance, measured using BrainPAD developed by Boyle et al. 2021 (64) (Brain Predicted Age Difference – BrainPAD – for details, see box2 in the supplementary materials). Therefore, a third aim 3) is to test whether greater HD-Tyr-IDA relates to better BrainPAD scores and if this relationship is mediated by LC integrity. Lastly, a fourth aim 4) is to replicate the association between LC signal intensity and BrainPAD observed by Plini et al. 2021 (35).

Methods

This study employs comprehensive control analyses aimed to strengthen the reliability of the key findings reported herein. For the sake of clarity and brevity, additional control procedures and other subsidiary analyses are reported in the extended methods and result sections of the supplementary materials. We refer to these in the main text.

Pre-registration

Before accessing the data, the study hypotheses, the rationale, and the detailed analyses methodology were registered at Max Plank Institute for Human Development via online documentation on March 9th 2021.

Data

Cognitive and neuro-imaging data of younger and older participants were collected at the Max Planck Institute for Human Development (Berlin, Germany) at two time points (T1 and T2) between 2013 and 2016. The study is part of the Berlin Aging Study II (BASE-II) [63 - https://www.mpib-berlin.mpg.de/research/research-centers/lip/projects/aging/base-ii). All participants (white Caucasian) were screened as medically and cognitively healthy (no major pathologies and generally healthier than average German population see cohort profile in Bertram et al. 2020 - 63). On average, data acquisitions were 2.21 years apart (standard deviation (SD) = 0.52, range = 0.9–3.2). Neuro-imaging data were collected on separate occasions at each time point (mean interval = 9.16 days, SD = 6.32, range = –2–44; for T2). Data for this study is based on the previous work of Kühn and colleagues (45) and included anonymised MRI images of 398 healthy participants at time point 1 (T1) (249 males – 149 females; age range 24 – 38 [n. 81] and 61 – 81 [n. 317]) and 291 subjects at time point 2 (T2) approximately three years later, between 1 and 4 years (in average 4.09 years for the old group and 3.79 for the young group. For T2 in total were considered 190 males – 101 females; age range 25 – 40 (n. 54) and 62 – 83 (n. 237).

MRI, Neuropsychological, cognitive and Nutritional Assessments

At T1 participants of BASE-II underwent a neuropsychological assessment examining a variety of domains, in the current study we focused on the following measures: Mini-Mental Sate Examination (MMSE) to account for broad cognitive functioning, Trail Making Test A; B and B minus A (TMT-A; TMT-B; TMT-B-A) to consider visuospatial attention and cognitive control. We also included measures of spatial working memory (Spatial Update – SU - 65), fluid intelligence (practical problem solving - PP - 66) and finally episodic memory assessed by the Rey Auditory Verbal Learning Test (RAVLT) at immediate and delayed (20min later) recall. All these measures were selected since they are typically associated with LC-NA function. For further details please refer to Kühn and colleagues (45) and Duzel and colleagues (67).

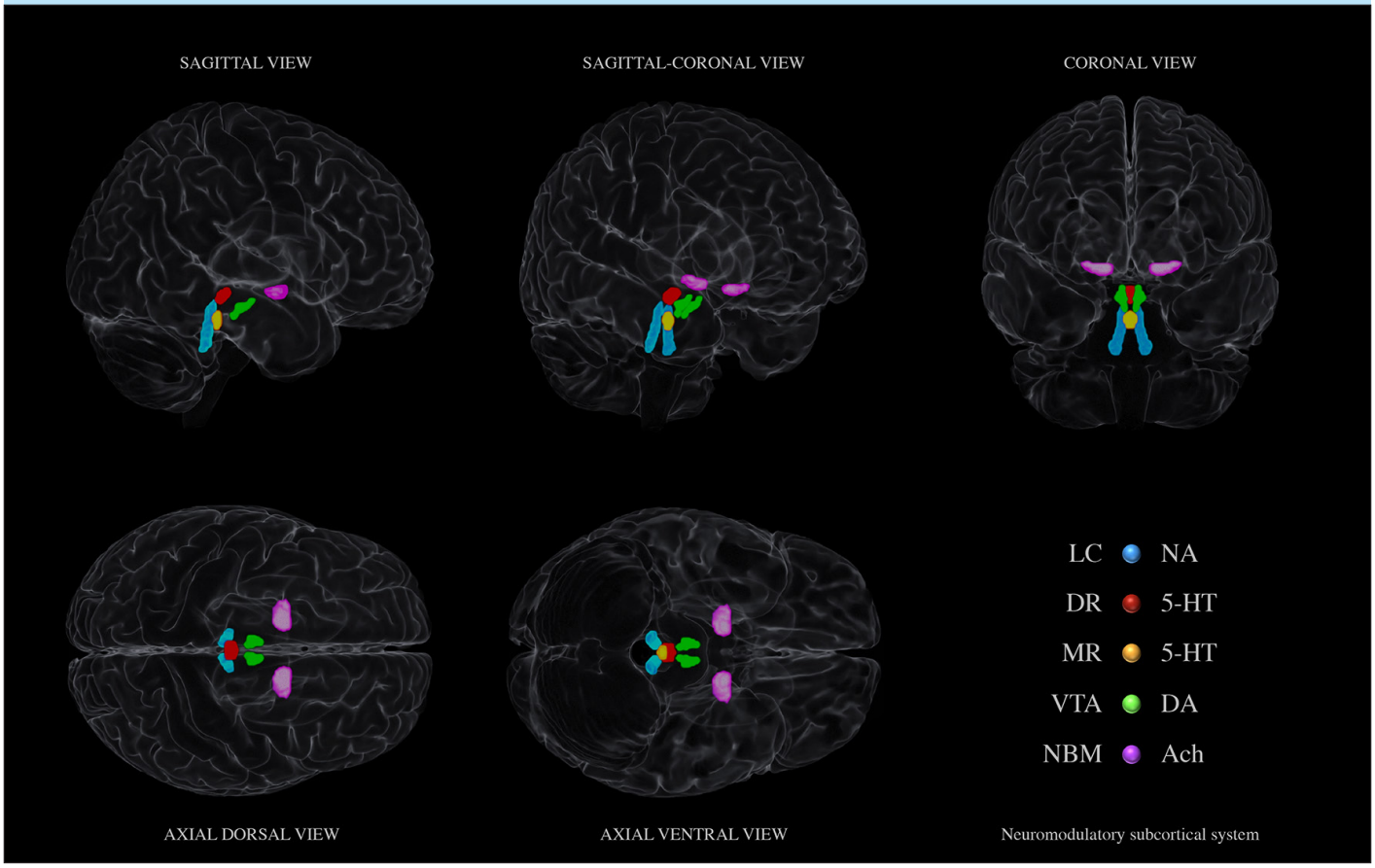
The nutritional assessment was carried out at T1 using the "food frequency questionnaire" FFQ - https://dietassessmentprimer.cancer.gov/profiles/questionnaire/ - (62). This questionnaire developed by the European Prospective Investigation into Cancer and Nutrition (EPIC - https://epic.iarc.fr/) assesses the habitual daily intake of 148 different kinds of food covering a period of 12 months before the questionnaire administration. From this measure Kühn and colleagues (45), referring to the values provided by a federal coding system, extracted the habitual dietary intake-daily average (HD-Tyr-IDA) from regular diets and each food-item of the FFQ (for further details please refer to Kühn and colleagues – (45). Kühn and colleagues also calculated the habitual dietary total food intake-daily average (HD-TF-IDA), and more specifically the habitual dietary carbohydrates intake-daily average (HD-Car-IDA), the habitual dietary fat intake-daily average (HD-Fat-IDA), the habitual of protein intake-daily average (HD-Pro-IDA) and the habitual dietary water intake-daily average (HD-Wat-IDA). In addition, they also provided body mass index (BMI), body weight, height and waist circumference of 330 participants (24 females and 45 males were missing, 50 within the old group and 18 within the young group). In the current study we used the above-mentioned nutritional scores without any additional interference.

MRI protocols of T1 included a variety of structural MRI sequences. In the current study we only used 3T structural MPRAGE scans of 398 subjects and 291 subjects of T2. For further information, please refer to (63) - https://www.mpib-berlin.mpg.de/research/research-centers/lip/projects/aging/base-ii). T2 assessment was carried out roughly 3 years after T1 and did not include FFQ and TMT. Images from T2 are used only for exploratory analyses described in the following sections and reported in supplementary materials.

Neuromodulatory subcortical system ROI definition

To strengthen the sensitivity of this study, control analyses were implemented for each of the aims described. Analyses investigating the noradrenergic hypothesis, were repeated testing the other main neuromodulatory subcortical nuclei projecting to the cortex. Namely the Dorsal Raphe (DR) and the Median Raphe (MR) for the serotoninergic system (5-HT), the Ventral Tegmental Area (VTA) for the dopaminergic system (DA) and the Nucleus Basalis of Meynert (NBM) for the cholinergic system (ACh). The 5 nuclei were isolated using the same methodology described in Plini et al. 2021. Namely, the LC region was identified using the "Plini omni-

Figure 1. Displaying a 3D reconstruction of the neuromodulatory subcortical system



In blue the Locus Coeruleus -LC- (Noradraenaline - NA), in red the Dorsal Raphe -DR- (Serotonin – 5-HT), in orange the Median Raphe -MR- (Serotonin -5-HT), in green the Ventral Tegmental Area -VTA- (Dopamine – DA), in purple the Nucleus Basalis of Meynert -NBM- (Acetylcholine – ACh).

comprehensive LC MRI mask" (35) - https://www.youtube.com/watch?v=90bsA6Jqxs4], while the MR and DR were isolated using the work of Beliveau et al. 2015 (68)), and VTA and the NBM referencing Pauli et al. 2018 (69) and Zaborszky et al. 2008 (70) respectively. For further information see the methods section in the supplementary materials and refer to Plini et al. 2021 (35).

Summary of MRI pre-processing for structural analyses and BrainPAD

De-faced 3T high-resolution T1-weighted MRIs in Nifti format were processed using CAT12 (http://www.neuro.uni-jena.de/cat/) implemented in SPM12. The segmentation was run following the default CAT12 settings, except for the voxel size that was settled at 1mm isotropic voxel size. All the 398 images of T1 and the 291 images of T2 were classified above 80% by CAT12 quality rating (grade B on a scale of: A – Excellent; B- Good; C- Satisfactory; D- Sufficient; E- Critical; F- Unacceptable/Failed). Lastly, to better account for individual volumetric variability in the Voxel Based Morphometry (VBM) analyses, the Total Intracranial Volume (TIV) was calculated for each participant using CAT12 interface. At competition of these processes, in SPM12, with the code pipeline provided by Boyle and colleagues (64), Brain Predicted Age Discrepancy (BrainPAD) was calculated for all the participants. BrainPAD is an objective measure reflecting how grey matter (GM) is ageing and is obtained by calculating the discrepancy between the chronological age and the degree of GM deterioration defined on a healthy brain ageing trajectory. BrainPAD was considered in this study with the aim of replicating and extending the findings reported in Plini et al. 2021 (35), where LC signal intensity was related to better brain maintenance (lower BrainPAD scores) across 686 participants, both healthy controls, mild cognitive impairments, and demented subjects. Greater details about BrainPAD are provided in the supplementary materials and in Boyle et al. 2021 (64).

Voxel-Based Morphometry Analyses (VBM) – (voxel-wise approach)

VBM analyses were performed using processed and unsmoothed whole brain images, Grey Matter (GM) + white matter (WM) considered together. In CAT12, VBM multiple regression models were built in order to assess the main relationship between LC-NA system signal intensity and HD-Tyr-IDA and BrainPAD.

The first model treating TIV, age, gender, education and HD-TF-IDA as covariates, examined the relationship between LC signal intensity and HD-Tyr-IDA in keeping with the main

hypothesis. As control procedure, the same model was repeated considering the DR, MR, VTA and NMB, testing the same relationship with HD-Tyr-IDA to contrast the noradrenergic hypothesis against the other main neuromodulatory systems. Additionally, the opposite (negative) relationships were tested to account for directionality other than hypothesized. In total the first model was contrasted against 9 alternative hypotheses. The same procedure was repeated at T2 on 291 participants by using all the covariates of T2 with the only exception of HD-Tyr-IDA which was taken 3 years before. This was the only analysis performed at T2.

To further increase control procedures, additional VBM multiple regression models were built to test the relationship between LC signal intensity and average macronutrients and water intake (control analyses on macro-nutrients). Namely, controlling for TIV, age, gender, education and HD-TF-IDA, 4 different models examined LC in relationship with HD-Fat-IDA, HD-Car-IDA, HD-Pro-IDA, HD-Wat-IDA. This additional practice aimed to strengthen the reliability of findings enabling a broader understanding of the data. By doing so, the first model was contrasted with 4 alternative hypotheses for a total of 21 antithetic VBM analyses. (several other control analyses were performed, for the sake of brevity we remand to the supplementary materials for the full details).

Another branch of analyses investigated the relationship between LC signal intensity and BrainPAD in order to replicate and extend the findings reported in Plini et al. 2021 (35). The same multiple regression model was built, and controlling for TIV, age, gender and education, the negative relationship between LC and BrainPAD was tested. Namely, greater LC signal intensity related to lower BrainPAD scores reflecting better maintained brain – less brain deterioration. As already performed in Plini et al. 2021 (35), the analyses were repeated for the other ROIs (DR, MR, VTA and NBM) and opposite relationships were investigated as well. In total, also this model was contrasted against 9 alternative antithetic hypotheses.

Statistical analyses in JASP and Bayesian Modelling – (ROI approach)

In order to perform ROI analyses and calculate Bayesian Factors (BF), the average signal intensity of the regions of interest (ROIs) was extracted in FMRIB Software Library (FSL - https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) by using the binary masks on the unsmoothed whole brain images. In FSL terminal, the flags of "fslstats" "-k" (mask) and "-m" (output mean) were used to gather the average voxel intensities for each ROI participant by participant.

The same models performed for voxel-wise analyses were re-built in JASP for BF calculation and to examine the 5 ROIs simultaneously within the same model. This had the aim to check the stability of the result with different methodologies. Several other secondary analyses and control analyses were performed, for the sake of brevity we remand to the supplementary materials for the full details).

Tyrosine and Protein intake in level: ANCOVAs

To better contextualise within the ESPEN guidelines the participants' dietary behaviour in matter of tyrosine and protein intake, HD-Tyr-IDA and HD-Pro-IDA were divided in levels and treated as a factor in ANCOVA models. HD-Tyr-IDA was divided in 4 levels: low intake (below 2gr, medium intake between 2 and 3gr, medium high between 3 and 4gr, and high intake above 4gr) and HD-Pro-IDA was divided in 3 levels: (low: 0 to 60gr daily; medium: 61 to 90gr daily; and high: 91 to 210gr daily). In these models LC signal intensity was treated as dependent variable while controlling for age, gender, education, TIV and HD-TF-IDA. In a second instance, BMI and body weight were added as covariates were added for more rigorous analyses. Further details are provided in the supplementary materials along with several other analyses.

Mediation Models with parallel multiple mediators

Mediation analyses were performed to test whether the relationships between HD-Tyr-IDA neuropsychological tests and BrainPAD were mediated by the LC-NA system. HD-Tyr-IDA was treated as a predictor (Y) and the following variables as outcome (X): TMT-A, TMT-B, TMT-B-A, RVALT immediate, RVALT delayed, MMSE, Spatial WM (SU), fluid intelligence (PP), BrainPAD. The 5 ROIs were treated in parallel as mediators while covaring for TIV, age, gender, education and HD-TF-IDA. All models followed the standard settings with 95% confidence intervals and 10000 bootstrap samples.

Results

Descriptive data

Key variables of the current sample are reported in table 1a,b,c. Table 1a reports the socio-demographic variables the key brain parameters and body metrics. Table1b, reports the average values recorded at the selected neuropsychological tests. Table 1c reports the daily average intake of tyrosine and macro-nutrients including also total food, water intake and average caloric intake. Table 1d in the supplementary materials reports the same nutritional values comparing the young group with the old group.

Voxel-Based Morphometry Analyses (VBM)

VBM – Tyrosine and Bayesian modelling

In accordance with our hypothesis, voxel-wise VBM analyses revealed a positive relationship between LC signal intensity and greater tyrosine intake in grams while controlling for age, gender, education, TIV and total food intake. As reported in table 2, for $P<0.01$, 129 voxels within the bilateral LC regions were associated with greater dietary tyrosine intake (maximal BF10 14050.14). As shown in figure 2, we note that

Table 1A. Socio-demographic and body metrics descriptive statistics

	Age		Education		TIV		Cortical Thickness		BRAINPAD		BMI		weight	
	F	M	F	M	F	M	F	M	F	M	F	M	F	M
Valid	150	248	150	248	150	248	150	248	150	248	149	248	127	203
Missing	0	0	0	0	0	0	0	0	0	0	1	0	23	45
Mean	59.623	60.404	13.863	14.351	1352.446	1550.066	2.555	2.510	5.978	5.239	25.647	26.364	68.924	81.628
Median	66.378	67.172	13.000	14.000	1360.965	1548.745	2.550	2.510	5.326	4.684	24.977	26.136	67.200	81.400
Std. Deviation	16.420	16.396	2.828	2.581	106.884	114.315	0.114	0.131	7.405	7.644	4.428	3.314	12.052	10.430
Minimum	23.023	22.001	7.000	9.000	1091.550	1222.940	2.260	2.220	-11.373	-20.088	17.158	17.904	45.100	54.000
Maximum	75.954	80.646	18.000	18.000	1608.510	2134.020	2.930	2.840	31.366	29.083	37.923	40.163	112.900	123.200

Table 1B. Neuropsychological descriptive statistics

	MMSE		TMT-A		TMT-B		TMT B-A		PP		SU		VLMT – recall 1		VLMT –recall 2	
	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M
Valid	113	187	110	186	110	183	110	183	149	248	148	241	149	248	148	240
Missing	37	61	40	62	40	65	40	65	1	0	2	7	1	0	2	8
Mean	28.814	28.390	38.636	43.054	80.673	95.967	2.189	2.310	10.537	10.601	21.642	23.610	11.235	10.270	7.020	5.692
Median	29.000	29.000	36.000	41.000	76.500	88.000	2.038	2.088	11.000	11.000	22.000	23.000	12.000	10.000	7.000	5.000
Std. Deviation	1.065	1.388	12.387	13.025	24.902	37.242	0.705	0.876	2.798	2.935	9.274	9.759	3.010	3.313	3.845	3.753
Minimum	26.000	22.000	19.000	20.000	41.000	42.000	1.088	0.922	1.000	1.000	0.000	0.000	1.000	0.000	0.000	0.000
Maximum	30.000	30.000	90.000	96.000	203.000	244.000	5.061	7.560	15.000	16.000	40.000	40.000	15.000	15.000	15.000	15.000

Table 1C. Dietary descriptive statistics

	HD-Tyr-IDA		HD-Pro-IDA		HD-Fat-IDA		HD-Car-IDA		HD-Wat-IDA		HD-TF-IDA		average Cal/Kg intake	
	F	M	F	M	F	M	F	M	F	M	F	M	F	M
Valid	150	248	150	248	150	248	150	248	150	248	150	248	150	248
Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean	2.369	3.252	69.084	94.367	87.767	117.469	209.580	252.877	3049.456	3096.498	3473.643	3635.221	8342.311	10899.342
Median	2.277	3.178	65.485	92.320	81.845	111.450	202.155	241.195	2935.750	3034.700	3378.065	3584.020	7947.050	10582.100
Std. Deviation	0.699	1.051	21.103	29.916	29.780	38.262	65.751	83.583	1058.177	1044.132	1118.820	1139.174	2407.178	3093.949
Minimum	1.245	1.238	35.790	37.450	31.870	39.410	97.910	82.200	895.500	1155.600	1184.200	1483.830	4612.800	3685.200
Maximum	5.966	7.483	160.550	213.140	197.090	249.290	543.320	585.510	6923.600	8114.500	7403.880	8937.640	18730.590	20073.390

Table 1a – abbreviations: TIV – total intracranial volume; BrainPAD – brain predicted age difference; BMI – body mass index. Table1b - abbreviations for neuropsychological tests: MMSE – Mini Mental Examination State; Trail-A – Trail Making Test Part A; Trail-B – Trail Making Test part B; Trail B-A- Trail Making Test part B minus part A; SU – Spatial Update (working memory); PP – Practical Problem solving (fluid intelligence); RAVLT recall 1 and 2 - Rey Auditory Verbal Learning Test. Table 1c - abbreviations: HD-Tyr-IDA– habitual dietary tyrosine intake on daily average; HD-TF-IDA - habitual total food intake on daily average; HD-Pro-IDA - habitual dietary protein intake on daily average HD-Fat-IDA - habitual dietary fat intake on daily average; HD-Car-IDA - habitual dietary carbohydrates intake on daily average; HD-Wat-IDA - habitual dietary water intake on daily average.

Table 2. VBM analyses table: Multiple Regression models relating HD-Tyr-IDA to signal intensity of neuromodulatory subcortical system

Neuromodulatory system	side	MNI coordinates			peak T value[a]	peak Z score[b]	peak cluster Ke[c]	p value uncorr[d]	FWE[e]	FDR[f]	total number of voxels for p<0.01 with max BF_{10}[g]
		x	y	Z							
Tyrosine intake											
Locus Coeruleus*	left	-2	-36	-22	5.02	4.93	45	0.000	0.663	0.593	129 (BF10 14050.14)
Dorsal Raphe	right	2	-30	-12	3.02	3.00	5	0.001	1.000	0.999	9 (BF10 0.735)
Median Raphe	/	/	/	/	/	/	/	/	/	/	/
Ventral Tegmental Area	left	-2	-22	-16	2.65	2.64	5	0.004	1.000	0.999	5 (BF10 0.848)
Nucleus Basalis of Meynert	left	-10	-4	-10	2.45	2.44	3	0.007	1.000	0.999	2 (BF10 0.150)

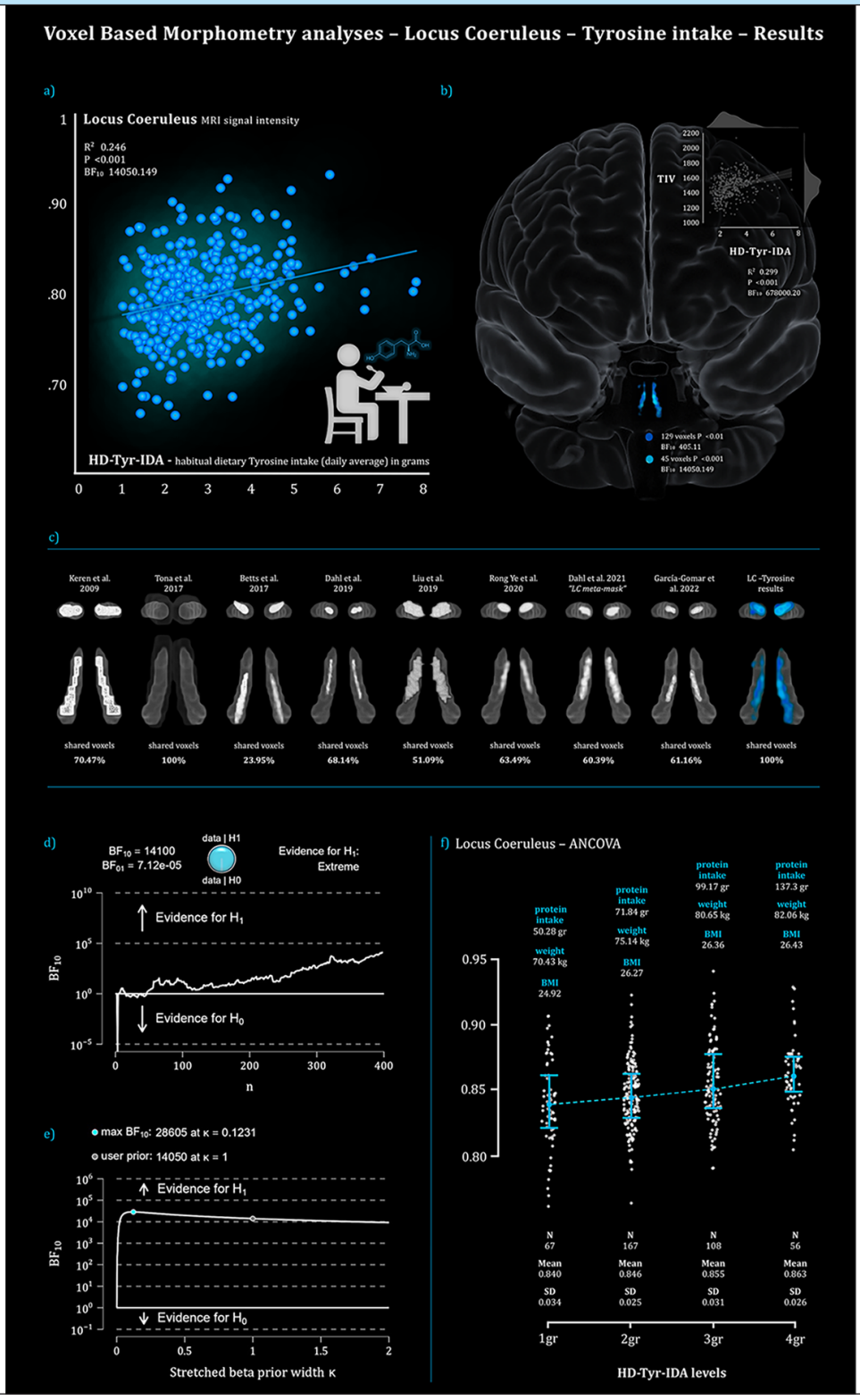
Table 2 shows the results for the VBM multivariate linear regression analyses testing the positive relationship between the five ROIs and HD-Tyr-IDA. The results across the n.398 healthy subjects are covaried for age, gender, total intracranial volume, education and total food intake. The table reports the significant clusters of voxels predicting habitual dietary tyrosine daily average intake for the statistical threshold of p<0.01. Bayesian Factors (BF10) are reported as parameter of strength in brackets. Cluster of voxels surviving p<0.001 are marked with*. No clusters survived multiple comparison corrections (FWE); 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. P value uncorrected; e. FWE = family wise error correction value; f. FDR = false discovery rate correction value (q); g. Total number of voxels outcoming in the ROI including all clusters of contiguous voxels (in brackets are reported Bayes Factors)

a significant portion of these LC findings overlap with the core of previously published LC atlases and masks ((32, 36, 71-77) – the significant LC cluster is available for download in Nifti format – download button).

By testing the other neuromodulator seeds, negligible or no results arose. In the same way, no results emerged when the opposite relationships for the five ROIs were tested.

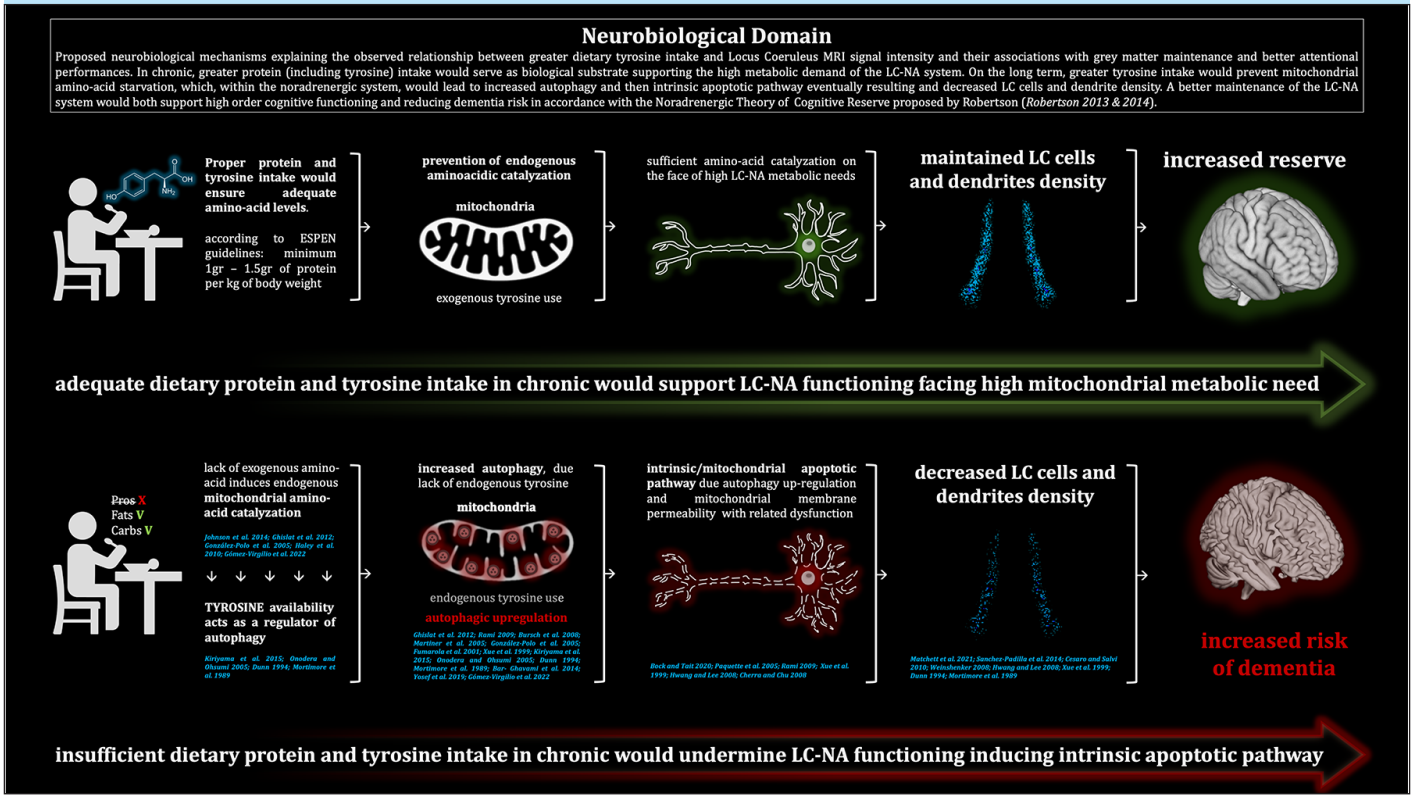
When examining the five ROIs simultaneously in the same Bayesian multiple regression model (ROI analyses based on ROI's average signal intensity), the combined effect of LC + VTA (BF10 231041.046) resulted in the strongest model related to tyrosine intake, and the relationship between tyrosine and VTA emerged (BFinclusion 4.710), but the disproportionate involvement of LC-NA system was predominant (BFinclusion 792.331 - for details refer to table 4 in the supplementary materials). Furthermore, when in the model was additionally controlled for participants' BMI, body weight, height, waist circumference and the 4th ventricle, the same pattern of findings was obtained. Noticeably, the LC+VTA effect increased to BF10 to 349682.325 and the LC BFinclusion

Figure 2. the structural MRI results



a) scatterplot showcasing the relationship between daily average of dietary tyrosine intake in grams and Locus Coeruleus MRI signal intensity across n.398 healthy participants (age range 25-81) for P<0.001 threshold. Greater LC signal intensity is related with greater Tyrosine intake, these results are corrected for age, gender, education, total intracranial volume and daily average of total food intake. b) The significant LC cluster of voxels (in blue) is shown on a coronal 3D reconstruction of the brain)on the right the smaller scatterplot reports the association between total intracranial volume and Tyrosine intake. c) The LC findings are shown in comparison with the spatial resolution of the previously published LC MRI masks and atlases. From an axial and coronal point of views, the LC-Tyrosine cluster is displayed on a 3D LC reconstruction of the "omni-comprehensive" LC mask by Plini et al. 2021. Below the LC atlases comparisons are reported the percentage of overlaps (shared voxels) between the LC-Tyrosine cluster and the specific atlas. d) showcases the Bayesian sequential analyses for the LC-Tyrosine relationship while e) reports the Bayesian Factor rouboustness check for such association. f) shows the LC average signal intensity across the 4 different levels of daily habitual tyrosine intake in grams. There is a significant main effect of tyrosine level **P<0.001 Bonf.** Cohen's d 0.98; 10000 replicates). In upper portion of the figure the average daily protein intake (HD-Pro-IDA), the average body weight and average BMI are reported. In the lower portion of the figure, sample numerosity is reported together with average Locus Coeruleus signal intensity for each level of tyrosine intake.

Figure 3. Proposed neurobiological mechanisms explaining the observed relationship between greater dietary tyrosine intake and Locus Coeruleus MRI signal intensity and their associations with grey matter maintenance and better attentional performances



In chronic, greater protein (including tyrosine) intake would serve as biological substrate supporting the high metabolic demand of the LC-NA system. On the long term, greater tyrosine intake would prevent mitochondrial amino-acid starvation, which, within the noradrenergic system, would lead to increased autophagy and then intrinsic apoptotic pathway eventually resulting and decreased LC cells and dendrite density. A better maintenance of the LC-NA system would both support high order cognitive functioning and reducing dementia risk in accordance with the Noradrenergic Theory of Cognitive Reserve proposed by Robertson (42). While the nature of the observed relationship between LC and Tyrosine intake is correlational, it should be considered that the other experiments reported causational effects between amino-acid depletion and related mitochondrial (autophagic) dysfunction, which ultimately lead to intrinsic apoptosis, studied also within the noradrenergic neurons (99). However, it should be taken into account that the proposed underlining mechanisms may be explained by other variables and potentially reside also within other neurobiological dynamics.

doubled to 1412.285 while the VTA raised to 40.732. For further details refer to table 4b in the supplementary materials.

Lastly, the young and older group did not significantly differ in HD-Tyr-IDA, neither in LC signal intensity. At visual inspection and with formal analyses, the LC-tyrosine relationship showed the same trajectory and the same pattern in both young and old populations (for further details please refer to table 4c and 4d and figure 2b in the supplementary materials). This result is consistent with the findings by Kühn and colleagues (45), where no differences in the relationship between Tyrosine and cognitive functions were found in young and older participants.

Levels of Tyrosine intake and Locus Coeruleus average signal intensity: ANCOVA

Further investigation on Tyrosine intake revealed that also at factorial level, different intakes of tyrosine were significantly associated with greater LC signal intensity (ROI analyses based on ROI's average signal intensity). The most significant difference between tyrosine intake levels was observed between individuals eating more than 4gr per day with individual eating less than 2gr per day. These differences were Bonferroni corrected ($P<0.001$ for 10.000 successful bootstrapping repetitions) and controlled for age, gender, education, TIV and HD-TF-IDA. For greater details refer to figure 2 and table 4 and 5, and to figure 2c and figure 2d in the supplementary materials for differences between young and old groups.

Brief result summary on BrainPAD, Mediation models, control and T2 analyses

The relationship between brain maintenance and the five neuromodulators' seeds revealed a disproportionate relationship between LC signal intensity and lower BrainPAD scores in comparison with the other nuclei (details are reported in table 8 and 8b in the supplementary materials, see also figure 5). These results replicated the same pattern of findings in Plini et al. 2021 (35).

Mediation models with parallel multiple mediators shown that LC signal intensity only significantly mediated the relationship between HD-Tyr-IDA and TMTB-A, and HD-Tyr-IDA and BrainPAD, in comparison with other neuromodulator nuclei while controlling for age, gender, education, TIV and HD-TF-IDA (details are provided in the supplementary materials table 6 and 7).

Control analyses on macro-nutrients revealed no associations between LC signal intensity HD-Car-IDA and HD-Wat-IDA (table 5f supplementary materials). In contrast, significant associations between LC signal intensity and HD-Pro-IDA and HD-Fat-IDA emerged. However, the associations between LC and Protein and Fat intake were weaker than the association between LC and Tyrosine (LC-Tyrosine [BF10 14050.14], LC-HD-Pro-IDA [BF10 6926.05], LC-HD-Fat-IDA [BF10 483.20] - for further detail see table 5g in the supplementary materials).

Lastly, the analyses investigating the possible relationship between HD-Tyr-IDA at T1 and LC integrity taken at T2 3 years later, revealed that HD-Tyr-IDA reported 3 years earlier related to the T2 LC signal intensity (BF10 1.96 – anecdotal evidence). However, the magnitude and the cluster extent were reduced (further details are provided in the supplementary table 3c and figure 2d).

Discussion

The present study provides evidence that dietary tyrosine intake relates to LC MRI signal intensity in a sample of 398 healthy adults (age range 25-83). Negligible associations were found for the other ROIs indicating a predominant sensitivity of the LC to tyrosine intake in contrast to the other main neuromodulatory nuclei. In addition, LC signal intensity was disproportionately related to brain maintenance (BrainPAD) and, by comparison with the other subcortical nuclei, only the LC significantly mediated the relationship between tyrosine intake and BrainPAD, and tyrosine intake and one measure of high order cognitive functions (TMT B-A). This novel evidence indicates how associations between diet and brain health may be underpinned by the LC-NA system and provides further neurobiological insight into the relationship between diet, cognition and overall brain health across the life-span. Moreover, tyrosine intake measured at T1 relates with LC signal intensity 3 years later (T2 n. 291). Lastly, protein and fat intake related to LC-NA system signal intensity although the relationship between tyrosine and LC-NA was statistically stronger, which lead to the inference that LC signal intensity might be more specifically affected by tyrosine as opposed to protein and fat intake. Together these findings present the first evidence linking habitual dietary tyrosine intake to MRI in-vivo signal intensity of the LC-NA system, and suggest that diet (protein and related tyrosine intake) might significantly affect brain maintenance and cognitive functioning through LC-NA system integrity in healthy individuals.

Tyrosine intake, Locus Coeruleus and Trail Making Test (attentive cognitive control)

Evidence indicating a beneficial role of tyrosine on cognitive functions might be explained by the relationship observed in this sample. Our results propose that greater tyrosine intake, by supporting LC structural integrity, would ensure adequate/greater NA metabolism when needed, while laying the ground for better cognitive performance. This view is consistent with pharmacological studies reporting enhanced cognitive performances when noradrenergic drugs are administered (78-80). Specifically, cognition is enhanced in attentional tasks, visuo-spatial functions and cognitive control, aspects which are underpinned by the LC-NA system (28, 30, 42, 43, 78) evaluated by TMT, more precisely by TMTB-A (81). Indeed, associations between TMT and LC-NA system were already recorded in literature (35, 37, 39, 40). Accordingly, the mediation of the relationship between tyrosine and TMT-B-A by LC, is in line both with earlier empirical observations and our working hypothesis, offering plausible insight into the LC-NA system in relation to diet and higher order cognitive functioning.

Tyrosine intake, Locus Coeruleus and BrainPAD (brain maintenance)

These results provide some explanation for the widely documented role of diet in neurodegenerative disease prevention, and for the previously reported associations between tyrosine intake and greater attentional performances, which, might be mechanistically mediated by the LC-NA system over the other main neuromodulatory systems.

Consistent with Robertson's model (42), LC signal intensity was disproportionally associated with better brain maintenance compared to other ROIs (see also Plini et al. 2021) (35). In addition, the relationship between tyrosine intake and BrainPAD was mediated exclusively by LC-NA system. We interpret this interdependence as a way to account for how diet may affect brain health via the LC-NA system. Greater dietary tyrosine intake could preserve brain health by supporting the LC-NA system consistent with literature reporting greater protein and amino-acid intake relating to brain health and preserved cognition (7, 8, 12-14). Dietary tyrosine intake would ensure adequate NA biosynthesis which would affect brain and cognitive health arising from the neurotrophic and neuroprotective protective actions of NA in the brain (82-85) as postulated by Robertson (42).

Control analyses on macro-nutrients

The results of the control analyses underline the difficulty in differentiating between micro and macro nutrient intake in this sample while suggesting they reflect actual meat intake. Indeed, as pointed out by Kühn and colleagues (45), tyrosine intake was highly related to meat intake (r 0.85 P<0.001). Therefore, the associations observed between the LC-NA system and HD-Pro-IDA and HD-Fat-IDA might even be read within the reported beneficial role of meat intake both for the health aspects of fatty-acid and amino acid content (including amino-acid tyrosine) (2, 4, 86-88). However, we believe that these analyses do not diminish the relevance of tyrosine findings since the LC-tyrosine relationship remains the strongest accordingly to Bayes Factors, namely LC-tyrosine (BF10 14050.14), LC-HD-Pro-IDA (BF10 6926.05), LC-HD-Fat-IDA (BF10 483.20). According to Bayesian modelling, tyrosine findings appear to be more specific in relationship to LC in comparison with the main macro-nutrients.

Summary

Potential neuro-chemical mechanistic framework behind LC-Tyrosine relationship

The bio-chemical mechanism behind the LC-tyrosine relationship potentially resides in the neurochemistry of neuromodulator biosynthesis and apoptosis. Since it is documented that: 1) amino-acid depletion induces autophagy and then apoptosis (89, 90), that 2) the lack of exogenous amino-acids induces endogenous (mitochondrial) amino-acid catalysation (91-94) and that 3) tyrosine availability acts as a regulator of autophagy (95, 96), within the same continuum, the lack of tyrosine supply, or insufficient tyrosine levels, might negatively affect LC functionality, increasing its cellular vulnerability to neurodegeneration (89, 96-99). Even though autophagy can have a protective role (100-102), autophagy induced by amino-acid deficiency (the most influential factor) (93, 96, 95, 103) can lead to cell death, particularly in large projecting neurons such as sympathetic neurons (90; 94; 99, 103). It is further documented that LC neurons are more susceptible than other nuclei to oxidative stress, heavy metal accumulation and chronic inflammation (97, 98). This drives LC vulnerability towards accelerated neurodegeneration in comparison with other nuclei (24-26, 98). Thus, insufficient tyrosine levels may negatively impact on the metabolic burden made on the LC ultimately affecting its integrity (loss of cells and white matter innervations) and functionality (89, 96-99). The lack of amino-acids may also paradoxically contribute to a metabolic shift via the breakdown of endogenous peptides and amino-acids within mitochondria (91-93, 95-97, 104) burdening the metabolic capacity of LC cells inducing an apoptotic state – intrinsic/mitochondrial apoptotic pathway (90, 94, 97, 99, 104-106). On the other hand, sufficient tyrosine availability supports LC functions. Noticeably, as pointed out by Matchett and colleagues (98), because the high and unique bioenergetic needs of the LC, tyrosine levels might play a relevant role in compensating for mitochondrial associated oxidative stress (and related LC vulnerability) (95, 96, 98, 99, 106). Given LC vulnerability, and the neuroprotective role of NA in the brain (42, 83) what is described by Matchett and colleagues (98) also provides an explanation for the negligible findings observed between HD-Tyr-IDA and VTA and other nuclei compared to the LC. The greater LC vulnerability (and related neuroprotective role of NA in the brain) (42, 83, 84), might be responsible for the emergence of the Tyrosine-LC relationship in comparison with the other neuromodulatory nuclei, which are biologically more resilient and characterised by greater number of neurons (44, 98). Regarding the VTA, a potential reason for the weaker Tyrosine VTA-DA system associations is suggested by Smith et al. (107). They proposed that most DA turnover happens within pre-synaptic terminals, specifically in areas like the Striatum and cortex, rather than the Substantia Nigra and VTA, unlike NA's turnover in Pons-LC regions. This could explain the almost absent association between HD-Try-IDA and VTA-DA, which might be due to diffuse dopamine synthesis throughout the brain, therefore not detectable with our methodology.

In conclusion, as discussed above and consistent with our findings, the role of tyrosine might be read as supporting the biosynthesis of NA in the LC. Accordingly, greater levels of tyrosine, by supporting the high bioenergetic demand of the LC-NA system, would prevent LC degeneration while providing for brain maintenance arising from the neurotrophic and neuroprotective actions of NA throughout the neuroaxis. Greater NA synthesis (arising from tyrosine availability) would preserve brain functioning via neurodynamics including enhanced expression of brain-derived neurotrophic factors (BDNF) and the anti-inflammatory and anti-oxidative effects of NA across the brain (42, 82-85, 98) – see figure 3 for summary.

Limitations

As pointed out by Kühn and colleagues (45), the main limitation encountered analysing these data concerns tyrosine assessment. Given the self-report nature of the EPIC questionnaire, HD-Tyr-IDA cannot be precisely evaluated, and the observed effect might be attributable to other macro- and micro-nutrients and potentially even to other unknown variables. Given the strong link between meat intake and tyrosine, the effects observed might rely on overall protein and fat intake reflecting meat consumption. The observed positive effects in terms of brain and cognitive health may not solely stem from tyrosine but also from other meat-based amino acids and beneficial nutrients like omega-3s, iron, zinc, vitamin D, and B-group vitamins (2-4, 86-88, 108, 109). However, control analyses proved LC-Tyrosine statistically stronger than LC-Protein and LC-Fat associations, suggesting a more specific and probable interplay between tyrosine and the LC-NA system.

Another constraint involves the methodological limitations of in-vivo MRI analyses in retrospective and longitudinal studies. Ex-vivo histological study could yield to more precise brain-diet related quantifications, particularly if dietary behavior is directly recorded. Nevertheless, within these bounds, our findings align with our pre-registered hypothesis and earlier research on tyrosine and protein intake (1, 7, 8, 11-14, 48, 60, 110-113), along with similar in-vivo studies (22, 35, 39, 114). Moreover, our design's solidity improved with comprehensive control analyses. The LC-tyrosine hypothesis was tested against 37 anti-thetic hypotheses while systematically controlling for relevant confounders. The LC-Tyrosine association was confirmed across diverse methods and even replicated "anecdotally" in a 3-year follow-up. Further corroboration by Bayesian modelling, further strengthens the reliability of observations

As noted by a reviewer, this study couldn't control for individual medication and micro-nutrients interfering with tyrosine assimilation (e.g., Thyroid hormones, hepatic medication, detailed micro-nutrient profile). Since tyrosine shares absorption pathways with other amino acids, like phenylalanine, high phenylalanine intake, from sources like sweeteners or certain proteins, might compete for tyrosine absorption, impacting various aspects.

Finally, a key consideration pertains to the neuroimaging methods: voxel-wise versus ROI analyses (ROI's average signal

intensity). Voxel-wise LC-tyrosine association didn't withstand stringent FWE correction, lacking solid statistical power. Yet, at ROI level, results consistently survived Bonferroni correction. This suggests constraints in investigating LC signal intensity variation voxel-wise across diverse individuals, likely due to acknowledged LC differences by age (32, 36, 71-77). Age-related LC rostro-caudal shifting impacts LC MRI localization (71, 75, 115), compounded by inter-individual disparities. Therefore, voxel-wise FWE comparison struggles to consistently identify LC voxels shared among individuals relative to tyrosine intake (sample size and association strength may also play a role). In contrast, ROI analysis would offer a broader picture of LC signal intensity whilst being less reliant on voxel-wise inter-individual discrepancies. This approach sidesteps computational problems, replicating LC-tyrosine association in several models surviving Bonferroni after 10000 bootstraps. Despite needing future confirmation, this preliminary study's observed LC-tyrosine association, supported by control analyses, is representative and clinically relevant.

Conclusions, clinical implications and future directions

This study provides the first evidence linking dietary tyrosine intake with in-vivo LC-NA system and its intercorrelation both with brain maintenance and neuropsychological performances in healthy adults. These results strengthen the role of dietary style in supporting brain health and reducing risk of neurodegeneration and imply that diet can influence LC-NA system MRI signal intensity (tissue density / integrity). The evidence provides support for the most recent European nutritional guidelines (ESPEN - https://www.espen.org/guidelines-home/espen-guidelines) which considers adequate protein intake in general population to set the minimal protein intake to 1–1.5 gr per kg of body weight specifically in older adults (116, 117). The evidence may also open new approaches to prevention and treatment or ameliorating brain and cognitive function in healthy and clinical populations (1, 46).

Chronic tyrosine supplementation might be clinically feasible and useful to maintain brain health, particularly when the minimal dietary requirements are not met or potentially when catecholaminergic drugs are administered and in other catecholaminergic up-regulation (i.e. cold exposure, prolonged exercise). However, the right amount of tyrosine as supplement has to be evaluated within the whole dietary lifestyle at individual level. Additionally, too low or excessive acute dosages, without a preliminary progressive administration, may not being beneficial for certain individuals depending on their clinical conditions (118). Indeed, while some studies did not report a significant positive effect of tyrosine administration (119-121), other interventions based on protein supplementation and amino acid intake (including tyrosine alone) reported beneficial effects on cognitive health (55-61, 110-113). Accordingly, adjusting dietary behaviour might efficiently extend cognitive longevity while protecting against neurodegenerative diseases (1, 7, 8, 12-14, 110-112).

Future research should replicate and expand these findings through observational and experimental longitudinal studies. These should encompass diverse dietary nutrients, blood markers, lifestyle factors, physical measures, multimodal MRI, and neuropsychological assessments. Further investigation should clarify diet's impact on the LC-NA and subcortical systems, enhancing neurodegenerative disease neurobiology understanding.

Ethicals standard: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflicts of interet: The authors declare no conflict of interest.

Authors contributions: ERGP: Conceptualization, study design, statistical analyses, results interpretation and visualization, manuscript writing. MCM: manuscript editing and statistical analyses support, AH: interpretation support and manuscript editing; MM: interpretation support and manuscript editing; RA: statistical analyses support. RB: BrainPAD methodology. RW: BrainPAD supervision; IHR: conceptualization, supervision and manuscript editing. PMD: supervision; SK: provided the data and calculated nutritional factors SD: provided MRI and neuropsychological data, manuscript editing; MJD: assisted with statistical design, calculated data for time point 2, manuscript editing; KN: provided the data, manuscript edits, JD: provided the data, manuscript edits; GGW: provided the data; UL: provided the data. All authors approved the final version of the manuscript. Thanks are extended to Francesca Fabbricatore for the thoughtful comments and for proofreading the manuscript.

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Informed consent: Informed consent was obtained from all individual participants included in the study.

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