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PII: S0195-6663(22)00184-2

DOI: https://doi.org/10.1016/j.appet.2022.106093

Reference: APPET 106093

To appear in: *Appetite*

Received Date: 1 December 2021

Revised Date: 16 March 2022

Accepted Date: 19 May 2022

Please cite this article as: Brecht A.-K., Medawar E., Thieleking R., Sacher J., Beyer F., Villringer A. & Witte A.V., Dietary and serum tyrosine, white matter microstructure and inter-individual variability in executive functions in overweight adults: Relation to sex/gender and age, *Appetite* (2022), doi: https://doi.org/10.1016/j.appet.2022.106093.

Dietary and serum tyrosine, white matter microstructure and inter-individual variability in executive functions in overweight adults: relation to sex/gender and age

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Abstract

Tyrosine (tyr), the precursor of the neurotransmitter dopamine, is known to modulate cognitive functions including executive attention. Tyr supplementation is suggested to influence dopamine-modulated cognitive performance. However, results are inconclusive regarding the presence or strength and also the direction of the association between tyr and cognitive function. This pre-registered cross-sectional analysis investigates whether diet-associated serum tyr relates to executive attention performance, and whether this relationship is moderated by differences in white matter microstructure.

59 healthy, overweight, young to middle-aged adults (20 female, 28.3 ± 6.6 years, BMI: 27.3 ± 1.5 kg/m^2) drawn from a longitudinal study reported dietary habits, donated blood and completed diffusion-weighted brain magnetic resonance imaging and the attention network test. Main analyses were performed using linear regressions and non-parametric voxel-wise inference testing.

Confirmatory analyses did neither support an association between dietary and serum tyr nor a relationship between relative serum tyr/large neutral amino acids (LNAA) levels or white matter microstructure and executive attention performance. However, exploratory analyses revealed higher tyr intake, higher serum tyr and better executive attention performance in the male sex/gender group. In addition, older age was associated with higher dietary tyr intake and lower fractional anisotropy in a widespread cluster across the brain. Finally, a positive association between relative serum tyr/LNAA and executive attention performance was found in the male sex/gender group when accounting for age effects.

Our analysis advances the field of dopamine-modulated cognitive functions by revealing sex/gender and age differences which might be diet-related. Longitudinal or intervention studies and larger sample sizes are needed to provide more reliable evidence for links between tyr and executive attention.

Introduction

Dietary intake of the amino acid tyrosine (tyr), a precursor of the neurotransmitter dopamine, has been claimed to modulate brain functions and cognitive performance, such as executive functions (Aquili, 2020). In rodents, protein-rich diets (single meals or habitual intake) or direct tyr injection increased serum and brain tyr concentrations and dopamine (DA) synthesis in the brain (reviewed in (John D. Fernstrom & Fernstrom, 2007)). Human studies also showed that dietary tyr/protein intake changes serum levels of tyr (J D Fernstrom et al., 1979; Strang et al., 2017; van de Rest et al., 2017; Wurtman et al., 2003), and acute depletion of tyr decreased brain DA measured indirectly using positron emission tomography (PET) (Leyton et al., 2004). Considering cognitive effects, some studies showed that tyr intake correlated with differences in inhibitory control (Colzato et al., 2014), task switching (Steenbergen et al., 2015) as well as working memory performance (Colzato et al., 2013; Hensel et al., 2019; Kühn et al., 2019; Thomas et al., 1999; van de Rest et al., 2017) and reward processing (Aquili, 2020), resulting in either improved (habitual dietary tyr or protein shakes) or both improved and weakened (high-dose oral supplementary tyr) test performance. In parallel, other studies could not demonstrate significant effects of tyr intake on executive function such as conflict monitoring and resolution measured with the attention network task (ANT) (Frings et al., 2020) or with a related task combining subliminal priming and flanker interference (Stock et al., 2018).

These at first glance contradictory findings might be insightful considering several important aspects of the tyr-DA and DA-cognition relationship: Firstly, the direction and strength of DA-enhancing drug effects on task performance has been found to depend on differences in baseline DA levels. This baseline dependence may be modeled by an inverted U-shaped dose-response curve leading to either improvement, maintenance, or impairment of task performance by increasing DA availability (Cools & D'Esposito, 2011). The inverted U-shaped curve presumably relates to complex autoregulatory mechanisms of the dopaminergic system which controls DA synthesis and release (Cools, 2019), including tyr concentration-dependent activity differences of brain tyr hydroxylase (Reed et al., 2010). Secondly, the amount of serum tyr reaching the brain depends on blood concentrations of other large neutral amino acids (LNAA; i.e. tryptophan, phenylalanine, leucine, isoleucine, valine, methionine) (Wurtman et al., 2003). This dependance is based on a competitive transport system at the carrier site (J. D. Fernstrom, 1983). Therefore, it is crucial (1) to consider baseline DA levels and (2) to measure

tyr/LNAAs ratios in blood to estimate tyr levels in the brain (John D. Fernstrom & Fernstrom, 2007). Notably, blood LNAAs also change in response to insulin secretion and related uptake of amino acids into peripheral tissues (John D. Fernstrom, 2013). Therefore, overall macronutrient composition, intake and diurnal changes in the metabolism need to be considered when evaluating how dietary tyr affects DA-related cognitive function (J D Fernstrom et al., 1979; Strang et al., 2017; Wurtman et al., 2003). In addition, dopaminergic drug effects have been suggested to also depend on inter-individual differences in microstructural properties of white matter tracts that are associated with targeted cognitive function (van der Schaaf et al., 2013; Martine R. Van Schouwenburg et al., 2013). The relevance of white matter connectivity is also supported by numerous studies indicating structure-function associations (Chaddock-Heyman et al., 2013; Cremers et al., 2016; Niogi et al., 2010; M. R. Van Schouwenburg et al., 2014; Vinçon-Leite et al., 2020; Yin et al., 2013). Therefore, differences in regional white matter microstructure should be considered when examining the effects of tyr on cognitive performance.

Taken together, the relationship between dietary tyr intake and cognitive performance is rather complex and requires a careful consideration of numerous interacting mechanisms and conditions which have not been fully addressed in studies on executive function. We therefore aimed (1) to examine how inter-individual differences in self-reported dietary tyr intake relate to individual differences in serum tyr levels and (2) to determine whether differences in serum tyr (and tyr/LNAA ratio) could explain variation in executive attention performance measured with the ANT. The study sample was young to middle-aged adults with omnivorous, naive eating habits resembling a typical Western European diet. Moreover, we examined possible structure-function relationships to address whether the strength and direction of potential associations between serum tyr and executive attention performance might depend on differences in white matter microstructure of the executive attention network. To investigate possible structure-function relationships, we calculated tract-based fractional anisotropy (FA) based on diffusion weighted magnetic resonance imaging (dwMRI). We pre-registered all hypotheses and analyses at https://osf.io/hbjyr to increase transparency and reproducibility. A visualisation of our hypotheses is presented in Figure 1.

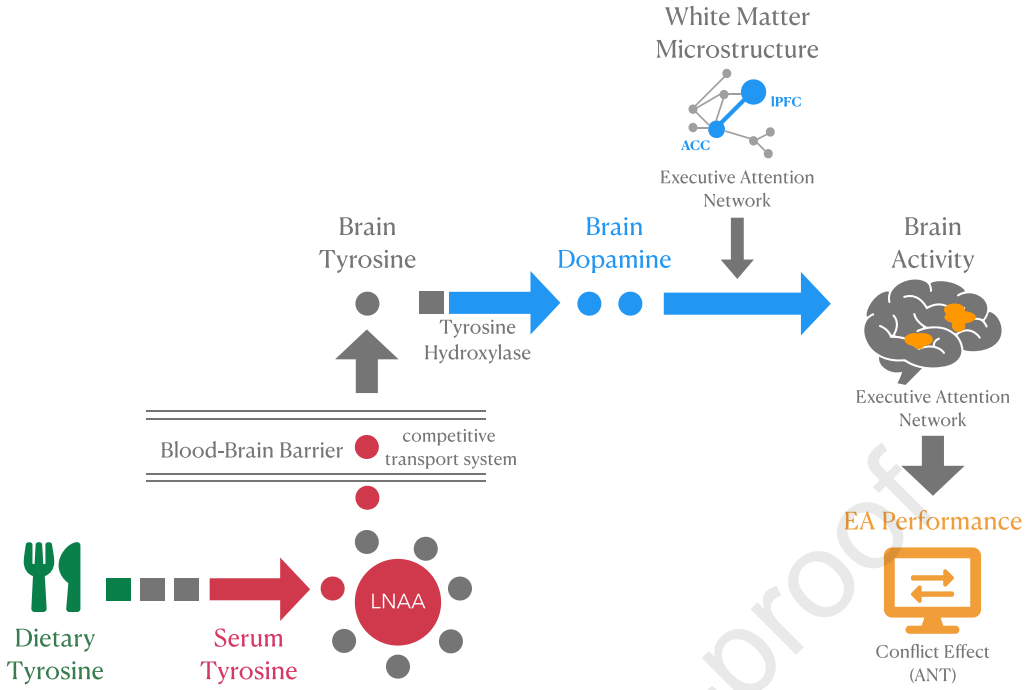


Figure 1: Hypothesized mechanism underlying a link between tyrosine intake and executive attention performance. Abbreviations: LNAA, large neutral amino acids; ACC, anterior cingulate cortex; lPFC, lateral prefrontal cortex; EA, executive attention; ANT, attention network test.

Methods

Study design and participants

Data was drawn from baseline assessments of a two-arm cross-over within-subject randomized controlled dietary intervention study with four time points (https://clinicaltrials.gov/ct2/show/NCT03829189). Participants were randomly assigned to fiber-placebo or placebo-fiber arm (30g inulin vs. equicaloric maltodextrin powder) with a 14-day supplementation each, divided by a 14-day wash-out period. In total, 60 young to middle-aged adults were recruited from the participant database of the Max Planck Institute for Human Cognitive and Brain Sciences (Leipzig, Germany) or via advertisements. The institutional ethics board of the Medical Faculty of the University of Leipzig, Germany, raised no concerns regarding the study protocol (228/18-ek) and all participants provided written informed consent. They received reimbursement for participation. For the current analysis, baseline assessments are drawn from the longitudinal data set. This cross-sectional analysis used the overall data from the first time point regardless of the participants' assignment to the two different intervention groups.

Participants were included based on body mass index (BMI; range 25-30kg/m²) and eating behaviour (i.e., they reported to not follow restrictive dietary patterns such as vegetarian or vegan, and no food allergies etc., as well as no eating behaviour disorders). The latter was monitored based on self-report on clinical questionnaires as well as additional questions such as "Do you follow a certain dietary habit such as vegetarian or vegan? Did you follow a diet to lose weight in the last three month?". In a 14-day food frequency questionnaire (FFQ) (for details see "Self-reported dietary tyrosine intake"), participants reported omnivorous diets with a mean total energy intake of 1615.9 (SD = 509.51) kcal per day (see Table 5). Male participants showed a higher mean energy intake (M = 1723.66, SD = 518.34) than female participants (M = 1405.78, SD = 429.88). Note that subjects differed greatly in their energy intake, ranging from 501 kcal to 2727 kcal per day (Figure 2E). Daily energy expenditure in this sample was estimated to 1592 (SD = 104) kcal for females and to 2063 (SD = 161) kcal for males according to Harris and Benedit (1919). Pertaining to our inclusion criteria, no participant consumed > 50 g of alcohol, > 10 cigarettes, or > 6 cups of coffee per day. Hormonal contraceptive use (pill, intrauterine device or vaginal ring) was another inclusion criterion for female participants.

Exclusion criteria were neurological or psychiatric disorders, severe metabolic or internal disease or any medications acting on the central nervous system. Participants were

excluded if they were pregnant or breastfeeding females. Due to high depressive symptoms at testing day, one subject was excluded from data analysis. Testing sessions were scheduled at either 07.15, 08.00, 09.15, 10.30 or 11.15 a.m. and began with blood drawing followed by physiological measurements, MRI scanning, computer tasks and the filling in of questionnaires. The cognitive assessment was conducted post-MRI 3 to 3.5 hours after the blood drawing.

Attention Network Test

To measure individual differences in the efficiency of the executive attention network, we used a computerized version of the *Attention Network Test* (ANT) developed by Fan, Posner and colleagues (Fan et al., 2002). ANT data of n=58 was available; one data set was faulty due to technical problems. The participants' task was to identify the direction of a centrally presented arrow flanked by neutral (lines), congruent (arrows in the same direction), or incongruent (arrows of opposite direction) stimuli (see Figure). In addition, the task included four cue conditions (no cue, center cue, double cue, spatial cue) that preceded the presentation of the stimuli and could indicate the location of the upcoming target stimuli (only spatial cue). A 30-minute test session consisted of a practice block of 24 trials in which subjects received feedback, and 3 experimental blocks consisting of 96 randomly ordered trials without feedback. The efficiency of each network is quantified by error rates (ER) and reaction times (RT). ER represent an accuracy score. RT of only correct trials are used to compute so-called alerting, orienting and conflict effects that quantify respective performance in one of the three attentional components. Conflict effects measure the processing of conflicting visual information (i.e., the influence of incongruent flankers on the processing of a target stimulus). The smaller the difference between the RT in processing incongruent and congruent visual information, the better the EA performance.

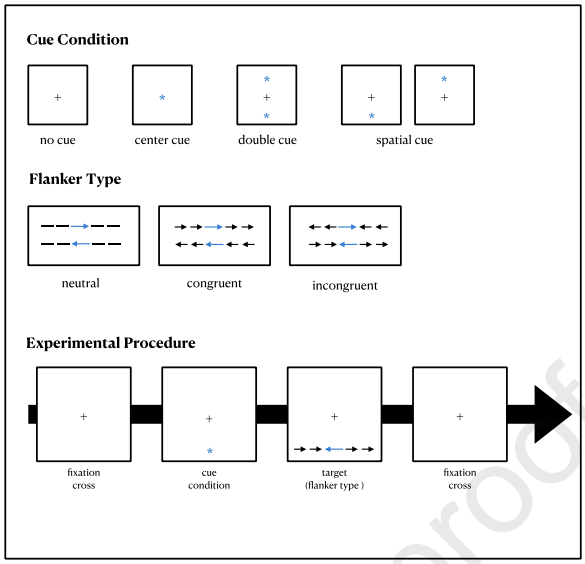
Conflict effects – as a measure for the efficiency of the EA network – were calculated by subtracting mean RT of all congruent from mean RT of all incongruent trials. In addition, *alerting effects* were calculated by subtracting the mean RT of all double cue trails from the mean RT of all no cue trails and *orienting effects* were calculated by subtracting the mean RT of all spatial cue trails from the mean RT of all center cue trails.

Formulas for calculating ANT Effects:

$$\text{Conflict Effect} = RT_{\text{incongruent}} - RT_{\text{congruent}}$$

$$\text{Alerting Effect} = RT_{\text{no cue}} - RT_{\text{double cue}}$$

Orienting Effect = $RT_{center\ cue}$ - $RT_{spatial\ cue}$



Experimental procedure of the Attention Network Test reproduced according *to Fan et al. (2002).*

Self-reported dietary tyrosine intake

Habitual dietary tyr intake over the last 7 days was assessed with the validated German Food Frequency Questionnaire (FFQ) DEGS1 by the Robert Koch Institute (Berlin, Germany); a tool to measure the intake of 53 single food items consumed based on self-reported frequency and quantity (Haftenberger et al., 2010). In this sample FFQ data from two baseline assessments for all macronutrients for a recall period of 7 days was fair to good ($kappa_{all} \geq 0.40$, $kappa_{max} = 0.73$, all $p < 0.001$), with highest agreement for protein and lowest for fat intake. To get a measure of dietary tyr intake, we calculated the mean tyr intake per day using reference food items from the German Nutrient Database (Bundeslebensmittelschlüssel (BLS), Version 3.02) or - in rare cases - individual sources directly from food suppliers (e.g., for plant-based milk). Further details on nutrient scoring: https://osf.io/h73wj/. First, we controlled tyr intake for total kcal to put very high or low tyr intake into perspective. Second, we accounted for the intake of other dietary LNAAs to provide a more meaningful measure of dietary tyr intake and its potential effect in the brain (cf. competing transport system at the blood-brain barrier).

Blood markers

Blood sampling was performed after overnight fasting (12.5 ± 2.2 h fasted) and about 2.5 hours before the ANT. The following amino acids were of interest: tyr, tryptophan,

phenylalanine, leucine/isoleucine, valine, methionine. Blood samples were centrifuged and stored at -80 °C. Analyses were conducted at the Institute for Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics (ILM) Leipzig University, Leipzig, Germany. Missing values due to limit of detection (LLOD) or limit of quantification (LLOQ) were substituted with values just below the limits (LLOD - 0.1 and LLOQ - 0.1). To relate dietary intake of tyr with serum tyr levels, absolute tyr levels were used. To get a proxy for acute brain DA levels, relative serum tyr/LNAAs ratios were calculated. Serum tyr/LNAAs ratios were calculated by dividing the tyr concentration by the summed concentration of all remaining LNAAs, i.e., tryptophan, phenylalanine, leucine, isoleucine, valine, methionine.

Sex/Gender

Sex/gender variable was collected by asking participants in German about their "Geschlecht" with three response options: "*weiblich*", "*männlich*" and "*keine Antwort"*. The third option was not chosen by anyone. The German word "Geschlecht" was used ambiguously, since the German term carries both the meaning of biological sex and social gender without further specification. This conceptual indeterminacy affects the two response options "weiblich" (female/feminine) and "männlich" (male/masculine). Unfortunately, no other option such as "diverse" or "third gender" was provided. Since we cannot be certain which concept (i.e., biological sex or social gender) has been captured, we use the composite term *sex/gender* throughout the paper to highlight the underdetermination. Since a dichotomous question was asked, we will maintain this distinction between two groups by using the terms "*male sex/gender group"* and "*female sex/gender group"*. The reluctance to clearly assign the measured variable to biological sex or social gender will be particularly important when interpreting the results.

Socio-economic status

Socio-economic status (SES) was included as a control variable because differences in both cognitive performance and tyr intake may be due to differences in SES (Cinelli et al., 2020; Kühn et al., 2019). SES was assessed using a questionnaire on SES and subjective social status (Lampert et al., 2013). The SES index was calculated as a sum value based on three sub-dimensions: education, occupation and income (theoretical range: 3 to 21 points). The SES index was considered as a continuous variable. The SES index was available for n=51 participants, eight participants did not provide information.

Image acquisition and processing

Anatomical MRI. Anatomical MRI was acquired with a T1-weighted Magnetization Prepared - RApid Gradient Echo (MP-RAGE) sequence using the Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol http://adni.loni.usc.edu/methods/documents/mri-protocols/ with the following parameters: repetition time (TR) = 2300 ms; echo time (TE) = 2.98 ms; flip angle = 9°; Field-of-view (FOV): $(256\ mm)^2$; voxel size: $(1.0\ mm)^3$; 176 slices. Preprocessing included skull stripping and realignment to anterior and posterior commissure and tissue segmentation with the default settings using SPM12.

Diffusion-weighted MRI (dwMRI). dwMRI was acquired using the following parameters: TR = 5200 ms; TE = 75 ms; flip angle = 90°; FOV: $(220\ mm)^2$; voxel size: $(1.7mm)^3$; 88 slices; max. b = 1000 s/mm^2 in 60 diffusion directions; partial Fourier = 7/8; GeneRalized Autocalibrating Partially Parallel Acquisitions (GRAPPA) factor = 2 (Griswold et al., 2002); interpolation = OFF. Ap/pa-encoded b0-images were acquired for distortion correction. We acquired n=58 dwMRI data sets; one participant aborted the MRI session due to nausea before dwMRI acquisition.

Preprocessing was performed with standard pipelines, including denoising (MRtrix v3.0) of the raw data, removal of Gibbs-ringing artifact from all b0 images using the local subvoxel-shift method (Kellner et al., 2016) and outlier replacement using the eddy tool in FMRIB Software Library (FSL) (Andersson & Sotiropoulos, 2016). Subsequently, data was corrected for head motion and linearly co-registered to the T1 image with *Lipsia tools* (Lohmann et al., 2001). Finally, we applied tensor model fitting and generated fractional anisotropy (FA) images as an index of white matter coherence.

Through tract-based spatial statistics (TBSS) (Smith et al., 2006), we obtained FA maps of the individual white matter skeletons and extracted the mean FA value for each participant. All FA maps were co-registered using affine and non-linear transformations to FMRIB58_FA standard space and the individual local maximal FA values were projected onto the standard FA skeleton to match individual's anatomy. The threshold for these standardized white matter fiber tract maps was set at 0.2. The FA skeleton maps were fed into voxel-wise analysis of FA for statistical comparison using the randomise tool by FSL version 5.0.11. We used 10,000 permutations (Winkler et al., 2014) in the confirmatory analyses and 5,000 permutations in the exploratory analyses concerning age

correlations. Threshold-free cluster enhancement (TFCE) was applied as test statistic (Smith & Nichols, 2009) and significance level was set at α(FWE)=0.05. Voxel-wise analysis was conducted on a whole-brain level and in the exploratory age correlation analysis we controlled for frame-wise displacement as a measure of head motion (Beyer et al., 2017).

Statistical analyses

Based on the OSF-preregistration, we distinguished between *pre-registered confirmator*y (systematically testing four hypotheses) and pre-registered *sensitivity* or *exploratory* analyses (including additional control variables). In addition, we performed additional *non-pre-registered exploratory* analyses to further elucidate possible relationships or underlying mechanisms. The selection and definition of the non-registered analyses builds on the results of the pre-registered analyses. All statistical analyses (except for brain data) were performed in *R* (version 4.0.3). Regression models and prerequisite testing were computed with *R base* functions, plots were created using *R base* functions or the R package *ggplot2*. The level of significance was set at $\alpha = 0.05$.

(1) Dietary - Serum Tyrosine Relationship (pre-registered)

To investigate the relationship of dietary tyr intake and absolute serum tyr levels, we performed a multiple linear regression analysis controlling for sex/gender.

Regression model:

$$\text{Absolute Serum tyr Level} = \beta_0 + \beta_1 \text{ Dietary tyr Intake} + \beta_2 \text{ sex/gender} + \varepsilon$$

(2) Serum Tyrosine and Executive Attention (pre-registered)

To examine the relationship between serum tyr/LNAAs ratio and executive attention performance (i.e., conflict effects), we performed multiple linear regression analyses controlling for sex/gender. Executive attention performance was quantified by calculating conflict effects based on reaction times (RT). The serum tyr/LNAAs ratio was calculated by dividing the serum tyr level by the sum of the remaining LNAA.

Regression model:

$$\text{Conflict Effect} = \beta_0 + \beta_1 \text{ serum tyr/LNAAs ratio} + \beta_2 \text{ sex/gender} + \varepsilon$$

(3) Executive Attention and White Matter Microstructure (pre-registered)

To examine the neural basis of inter-individual variability in executive attention performance, we performed voxel-wise cross-subject whole-brain analyses on the FA skeletons to correlate *fractional anisotropy* (FA) values with conflict effects.

General Linear Model:

$$\text{4D skeletonized FA image} = \beta_0 + \beta_1 \text{ Conflict Effect} + \varepsilon$$

(4) Moderation Analysis (pre-registered)

Because of the lack of significant correlations between executive attention performance and FA values during the aforementioned voxel-wise whole-brain correlation analysis, this moderation analysis was not conducted.

Sensitivity and Exploratory Analyses (pre-registered)

In subsequent sensitivity analyses, additional control variables (BMI, SES, age) were added (Table 1 & Table 2**Error! Reference source not found.**). We applied a *hierarchical regression analysis approach* (Lewis, 2007), adding each variable one after the other to examine the contribution of each predictor to the model. The level of significance was set at $\alpha = 0.05$ for all sensitivity analyses.

Table 1: Sensitivity Analyses Models: Executive Attention and Serum tyr/LNAAs ratio

Models: Executive Attention and Serum tyr
$\text{Conflict Effect} = \beta_0 + \beta_1 \text{ serum tyr/LNAAs ratio} + \beta_2 \text{ sex/gender} + \beta_3 \text{ age} + \varepsilon$
$\text{Conflict Effect} = \beta_0 + \beta_1 \text{ serum tyr/LNAAs ratio} + \beta_2 \text{ sex/gender} + \beta_3 \text{ age} + \beta_4 \text{ BMI} + \varepsilon$
$\text{Conflict Effect} = \beta_0 + \beta_1 \text{ serum tyr/LNAAs ratio} + \beta_2 \text{ sex/gender} + \beta_3 \text{ age} + \beta_4 \text{ BMI} + \beta_5 \text{ SES} + \varepsilon$

Table 2: Sensitivity Analyses Models: Dietary and Serum tyr

Models: Dietary - Serum tyr Relationship
$\text{Serum tyr Level} = \beta_0 + \beta_1 \text{ Dietary tyr Intake} + \beta_2 \text{ sex/gender} + \beta_3 \text{ age} + \varepsilon$
$\text{Serum tyr Level} = \beta_0 + \beta_1 \text{ Dietary tyr Intake} + \beta_2 \text{ sex/gender} + \beta_3 \text{ age} + \beta_4 \text{ BMI} + \varepsilon$
$\text{Serum tyr Level} = \beta_0 + \beta_1 \text{ Dietary Tyrosine Intake} + \beta_2 \text{ sex/gender} + \beta_3 \text{ age} + \beta_4 \text{ BMI} + \beta_5 \text{ SES} + \varepsilon$

In addition, the multiple regression analysis was repeated for absolute dietary tyr intake as predictor variables to examine which tyr measures (self-reported dietary tyr intake vs.

tyr serum level) better predicted differences in executive attention performance. Following Hensel et al. and Kühn et al., we adjusted dietary tyr intake to body weight. In addition, total energy intake was included as control variable.

Regression Model:

$$\text{Conflict Effect} = \beta_0 + \beta_1 \text{ Dietary tyr Intake/Body weight} + \beta_2 \text{ Energy Intake} + \varepsilon$$

In addition, for the ANT, a two-way Analysis of Variance (ANOVA) was calculated to examine the influence of the two factors (1) flanker type (3 factor levels: neutral, congruent, incongruent) and (2) cue condition (4 factor levels: no cue, central cue, double cue, spatial cue) on the measured continuous dependent variable reaction times (RT) and error rates (ER), respectively. ANOVAs, post-hoc analyses for multiple pairwise comparisons (i.e., Tukey's test), and Shapiro-Wilk normality test were calculated using R base functions. Homoscedasticity was tested with Levene's test using the R package car.

Non-Pre-registered Exploratory Analyses

1. Correlation Analyses of Tyrosine Markers

First, we explored associations between dietary tyr and serum tyr markers using Pearson's correlation coefficients for the following relationships:

- Dietary tyr intake – serum tyr levels
- Dietary tyr intake – serum tyr/LNAAs ratios
- Dietary tyr intake (adjusted for energy intake) – serum tyr levels
- Dietary tyr intake (adjusted for body weight) – serum tyr levels
- Absolute serum tyr levels - relative serum tyr/LNAAs ratios

Correlational models (*Pearson's product-moment correlation*) and prerequisite testing were computed with R base functions.

2. Analyses of Sex/Gender Differences

Next, we examined sex/gender differences in variables of interest using non-parametric Mann-Whitney U test (i.e., Wilcoxon rank sum test), i.e.: dietary tyr intake, dietary tyr intake adjusted for energy intake, absolute serum tyr levels, relative tyr tyr ratios, ANT conflict effects RT, age, BMI, SES. Analyses were performed using the R package stats. The level of significance was set at $\alpha = 0.05$.

In addition, we performed the regression analyses outlined above with serum tyr/LNAAs ratio as predictor variable and executive attention performance (measured by conflict effects) as criterion variable for the male and female sex/gender group separately. In both models, we controlled for age because previous literature indicates detrimental age effects on executive functions (Ferguson et al., 2021).

Regression model per sex/gender group:

$$\text{Male participants : Conflict Effect} = \beta_0 + \beta_1 \text{ serum tyr/LNAAs ratio} + \beta_2 \text{ age} + \varepsilon$$

$$\text{Female participants: Conflict Effect} = \beta_0 + \beta_1 \text{ serum tyr/LNAAs ratio} + \beta_2 \text{ age} + \varepsilon$$

3. Age Relationships

Further, a simple linear regression approach was applied to examine possible associations between age and dietary tyr intake, serum tyr levels or executive attention performance (Table 3). Regression analyses were performed including all participants. To test whether the effect of the variable age depended on the variable sex/gender, we extended the simple regression models by the interaction term age*sex/gender and repeated the analysis (Table 4).

Table 3: Simple Linear Regression Models: Age Relationship

Models: Age Relationships
Dietary tyr Intake = $\beta_0 + \beta_1$ age + ε
Serum tyr Level = $\beta_0 + \beta_1$ age + ε
executive attention Performance/Conflict Effect = $\beta_0 + \beta_1$ age + ε

Table 4: Multiple Regression Models: Age Relationships

Models: Age Relationships (Interaction)
Dietary tyr Intake = $\beta_0 + \beta_1$ age + β_2 sex/gender + β_3 age*sex/gender+ ε
Serum tyr Level = $\beta_0 + \beta_1$ age + β_2 sex/gender + β_3 age*sex/gender + ε
executive attention Performance/Conflict Effect = $\beta_0 + \beta_1$ age + β_2 sex/gender + β_3 age*sex/gender + ε

To further elucidate the neural basis of age effects, we performed voxel-wise whole-brain analyses to correlate FA values with age.

General Linear Model:

$$\text{4D skeletonized FA image} = \beta_0 + \beta_1 \text{ Age} + \varepsilon$$

Results

Descriptives

In total, 59 individuals were included in the analyses (female sex/gender group = 20, male sex/gender group = 39) with a mean age of 28 years (SD = 6.6), a mean BMI of 27.3 kg/m^2 (SD = 1.5) and a mean SES score of 14.5 (SD = 3.11; n=51), reflecting medium to high socio-economic status (for details, see Table 5 & Figure 2).

Table 5: Descriptive Statistics of the sample. Abbreviations: n, number of subjects; BMI, Body Mass Index; SD, standard deviation; SE, standard error; SES, socio-economic status; RT, reaction time; FA, fractional anisotropy.

Variable	**N**	**min**	**max**	**median**	**mean**	**sd**	**se**
Age (years)	59	19	45	28	28.3	6.57	0.86
BMI (kg/m^2)	59	24.95	30.07	26.98	27.25	1.48	0.19
SES score	51	5.1	19.2	14.8	14.54	3.11	0.44
Dietary tyr intake (g)	59	0.23	5.96	2.24	2.3	1.07	0.14
Energy intake (kcal)	59	500.87	2727.3	1694.9	1615.9	509.51	66.33
tyr/body weight (g/kg)	59	0	0.07	0.03	0.03	0.01	<0.01
Serum tyr level (µmol/l)	58	25.5	88.5	53.7	53.37	11.99	1.57
Serum tyr ratio	58	0.04	0.13	0.07	0.08	0.02	<0.01
Conflict Effect RT (ms)	58	50.16	249.61	107.96	120.09	45.49	5.97
Whole-brain mean FA (skeleton)	58	0.44	0.5	0.48	0.48	0.01	<0.01

Briefly, participants consumed on average 2.3 g of tyr per day (SD = 1.07) or 0.03 g tyr per kg of body weight per day (SD = 0.01). They differed greatly in self-reported total energy intake (min = 501 kcal/d; max = 2727 kcal/d). Serum tyr levels ranged from 25.5 to 88.5 µmol/l and serum tyr/LNAAs ratios from 0.04 to 0.13.

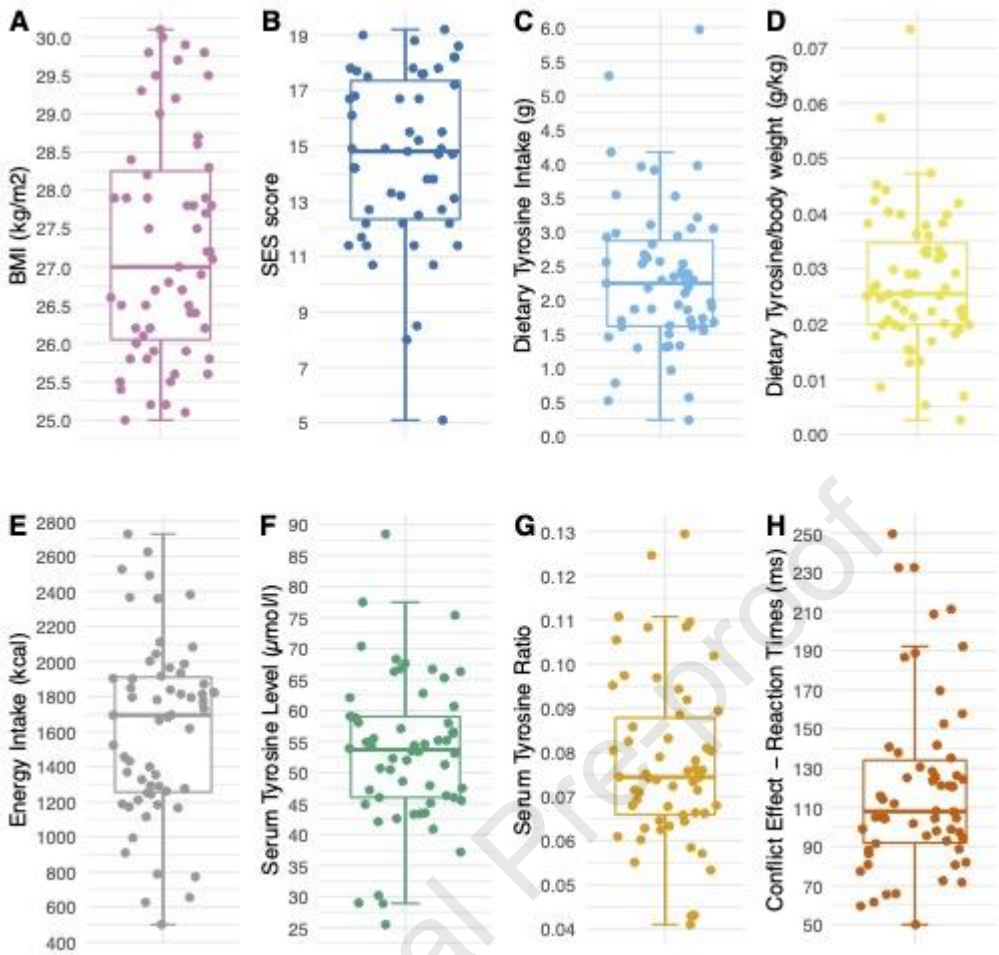


Figure 2: Descriptive statistics of variables of interest. Boxplots visualize maximum, minimum, median, first and third quartiles. The length of the whisker is 1.5 times the interquartile range (IQR); outliers are depicted above or below. Abbreviations: BMI, Body Mass Index; SES, Socio-Economic Status.

ANT performance

Regarding executive attention performance quantified by conflict effects based on reaction times (RT), the sample showed a mean conflict effect of 120.09 ms (SD = 45.49). The medium error rate was consistently 0% across all flanker and cue conditions with the exception of the incongruent flanker type (Figure 3 A & C). Both mean RT and mean error rate were highest in the incongruent flanker condition across all cue types (main effect of flanker type, error rate: $F(2, 696) = 101$, $p < 2e\text{-}16$, RT: $F(2, 684) = 171$, $p < 2e\text{-}16$; Figure 3 C & D) (see **SI** SI Table **&**

SI Table for details). In addition, the spatial cue condition resulted in the lowest mean RT and the no-cue condition resulted in the highest mean RT across all flanker conditions

($F(3, 684) = 26.241$, $p = 4.49e^{-16}$, Figure 3 D). Overall, these results reflected the pattern reported by the original study by Fan and colleagues (Fan et al., 2002).

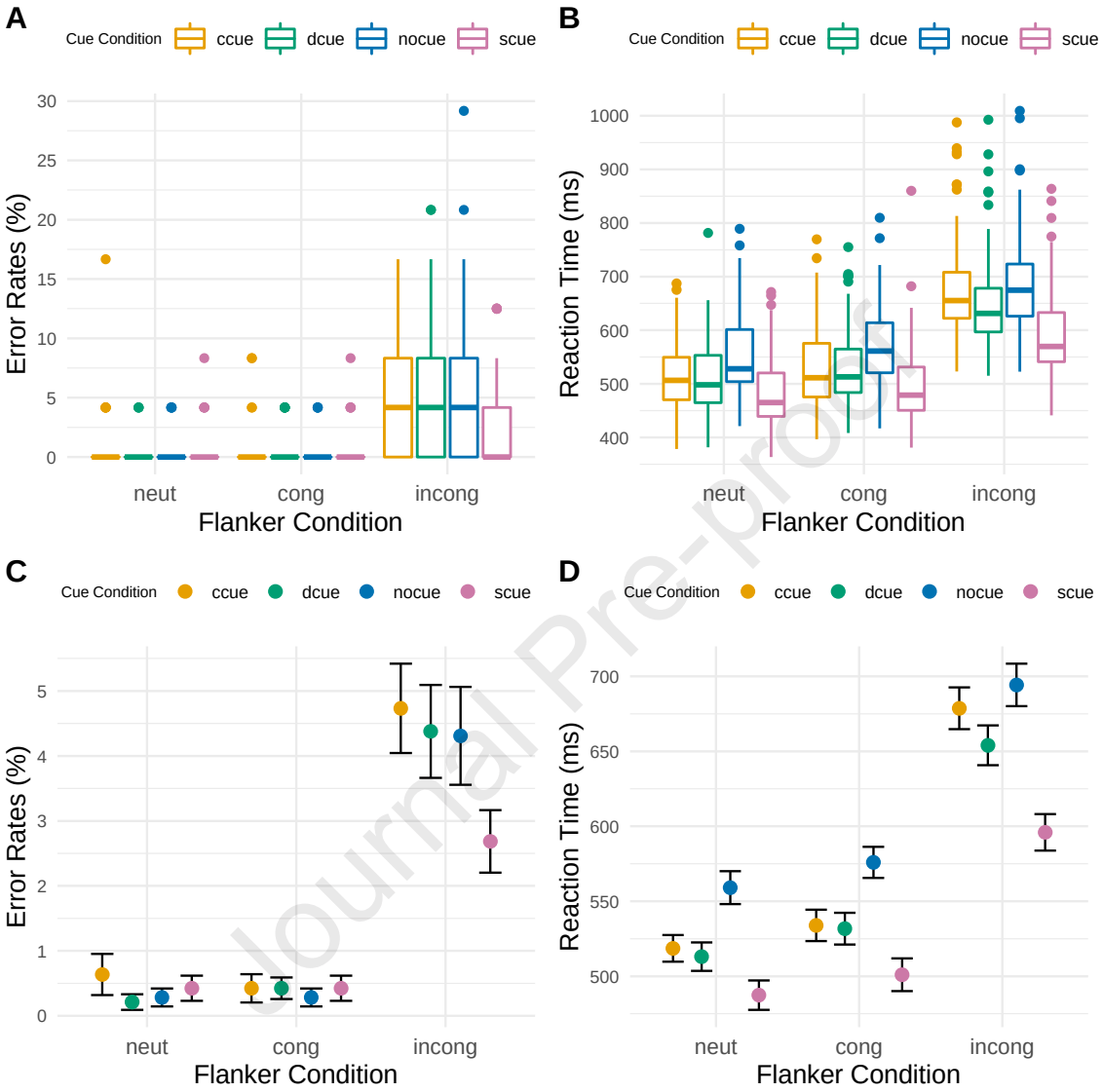


Figure 3: Error rates and reaction times as a function of cue condition and flanker type. Figure A & B visualize minimum, maximum, median, first and third quartiles. The length of the whiskers is 1.5 times the interquartile range (IQR); outliers are depicted above or below. Figure C & D show means and standard errors. Abbreviations: ccue, center cue; dcue, double cue; nocue, no cue; scue, spatial cue; neut, neutral; cong, congruent; incong, incongruent.

Post-hoc Tukey tests for RT showed that the difference in means is highly significant for the incongruent vs. neutral and incongruent vs. congruent flanker type pairs and for all cue-type pairs ($p_{adj} < 0.003$), except for the congruent vs. neutral flanker type pair ($p = 0.11$) and the double cue vs. center cue pair ($p_{adj} = 0.65$).

Summary statistics considering alerting, orienting and conflict (executive attention) effect of the ANT are summarized in Table 6 and visualized in Figure 4. Note that the mean

conflict (executive attention) effect of 120 ms (SD = 46) was larger than that measured by Fan et al. (84 ms, SD = 25).

Table 6: Summary Statistics ANT Effects. Abbreviations: n, number of subjects; sd, standard deviation; se, standard error.

	n	Min [ms]	Max [ms]	Median [ms]	Mean [ms]	Sd [ms]	Se [ms]
Alerting Effect	58	-59.982	131.981	40.46	43.508	29.196	3.834
Orienting Effect	58	1.792	106.503	48.004	48.92	23.057	3.028
Conflict Effect	58	50.156	249.607	107.96	120.092	45.486	5.973

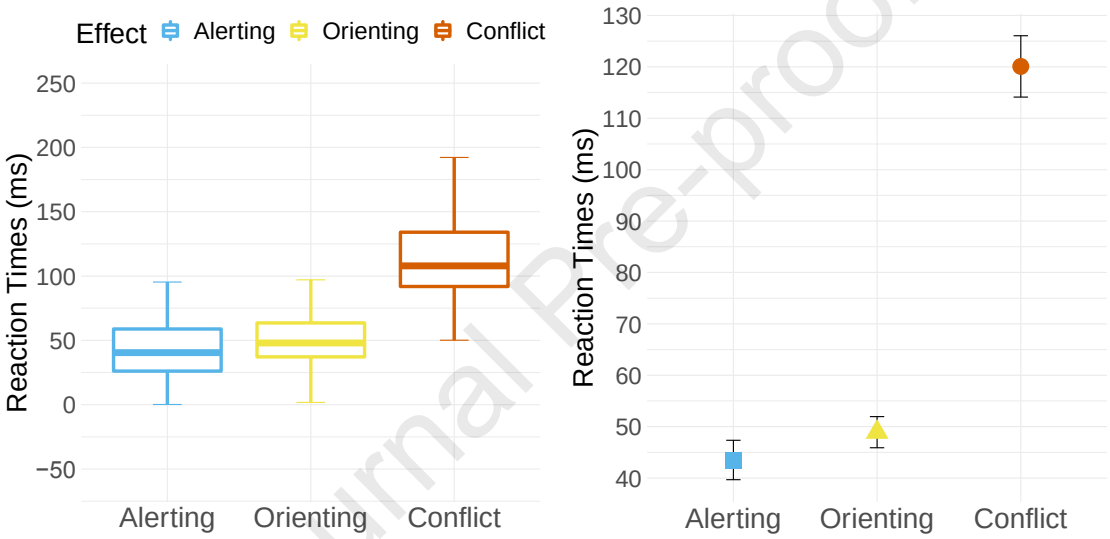


Figure 4: Summary statistics of ANT effects (i.e.; alerting effect, orienting effect, conflict effect) based on reaction times. First figure visualizes minimum, maximum, median, first and third quartiles. The length of the whiskers is 1.5 times the interquartile range (IQR); outliers are depicted above or below. Second figure shows means and standard errors. Abbreviations: ANT, attention network test.

Dietary - serum tyr relationship

In contrast to our hypothesis, dietary tyr intake was not significantly related to serum tyr levels according to linear regression ($\beta = 0.2$, $p = 0.89$). However, the model revealed sex/gender as a significant predictor ($\beta = 13.07$, $p = 9.6e\text{-}05$; $R_{adj}^2 = 0.25$, $F(2, 55) = 10.31$, $p < 2e\text{-}4$).

Serum tyr ratio and executive attention performance

Against our expectation, serum tyr ratios were not significantly related to executive attention performance ($\beta = 0.42$, $p > 0.99$). However, the non-significant model ($R_{adj}^2 =$

0.05, F(2, 54) = 2.42, p < 0.098) pointed towards sex/gender as significant predictor of executive attention performance (β = -27.50, p < 0.04).

Executive attention and white matter microstructure

Two individuals were excluded due to missing ANT or dwMRI data. With respect to executive attention performance operationalized as conflict effects, results showed neither a positive (TFCE, $p_{FWE} > 0.16$) nor a negative (TFCE, $p_{FWE} > 0.95$) relationship between differences in white matter integrity and executive attention performance.

Sensitivity and exploratory analyses

To determine the specific contributions of additional variables to the model predicting executive attention performance as a function of serum tyrosine/LNAAs ratios, further sensitivity analyses were performed (Table 7). In sum, the model predicting executive function performance by serum tyrosine ratios controlling for sex/gender remained non-significant after adding the variables age, BMI and SES. Interestingly, the variable sex/gender remained as a significant predictor in all models despite that the overall models were not superior to the null model.

Table 7: Model: Executive Attention and Serum tyr/LNAAs ratios

1. Conflict Effect = $\beta_0 + \beta_1$ serum tyr/LNAAs ratio + β_2 sex/gender + β_3 age + ε		
$R_{adj}^2 = 0.062$	F(3,53) = 2.238	p = 0.09
2. Conflict Effect = $\beta_0 + \beta_1$ serum tyr/LNAAs ratio + β_2 sex/gender + β_3 age + β_4 BMI + ε		
$R_{adj}^2 = 0.046$	F(4, 52) = 1.675	p = 0 .17
3. Conflict Effect = $\beta_0 + \beta_1$ serum tyr/LNAAs ratio + β_2 sex/gender + β_3 age + β_4 BMI + β_5 SES + ε		
$R_{adj}^2 = 0.003$	F(5, 43) = 1.031	p = 0.41

Further sensitivity analyses were also performed regarding the regression model predicting serum tyrosine levels (TYR) by dietary TYR intake (Table 8). After adding each additional variable, the model remained significant overall. However, neither age, BMI, nor SES were shown to be significant predictors of absolute serum TYR levels. In addition, the explained variance of the model and the statistical significance of the variable sex/gender decreased as the number of variables increased.

Table 8: Models: Dietary - Serum tyr Relationship

1. Serum tyr Level = $\beta_0 + \beta_1$ Dietary tyr Intake + β_2 sex/gender + β_3 age + ε		
$R_{adj}^2 = 0.23$	$F(3,54) = 6.78$	$p < 0.001$
2. Serum tyr Level = $\beta_0 + \beta_1$ Dietary tyr Intake + β_2 sex/gender + β_3 age + β_4 BMI + ε		
$R_{adj}^2 = 0.22$	$F(4, 53) = 5.03$	$p = 0.0016$
3. Serum tyr Level = $\beta_0 + \beta_1$ Dietary Tyrosine Intake + β_2 sex/gender + β_3 age + β_4 BMI + β_5 SES + ε		
$R_{adj}^2 = 0.15$	$F(5, 44) = 2.67$	$p = 0.034$

Dietary Tyrosine Intake and Executive Attention Performance

We used linear regression to examine whether daily dietary tyr intake (adjusted for body weight) was linked to executive attention performance when controlling for total energy intake. Again, the overall regression model did not indicate a link between dietary tyr intake adjusted for body weight and executive attention performance ($R_{adj}^2 = -0.02$, $F(2, 55) = 0.35$, $p = 0.71$), indicating that differences in executive attention performance could not be explained by differences in energy intake adjusted dietary tyr intake ($\beta = -0.047$, $p < 0.77$).

Correlation of Tyrosine Markers

Dietary tyr intake did not correlate with neither absolute tyr levels, nor relative serum tyr/LNAAs ratios, nor when tyr intake was adjusted for energy intake, nor body weight (all $R < 0.2$, all $p > 0.14$) (Figure 5). However, higher absolute serum tyr levels related to higher relative serum tyr ratios (please note that due to a somewhat skewed distribution of residuals, statistics may be inaccurate: $R = 0.52$, $p = 2.6e\text{-}05$) (Figure 6).

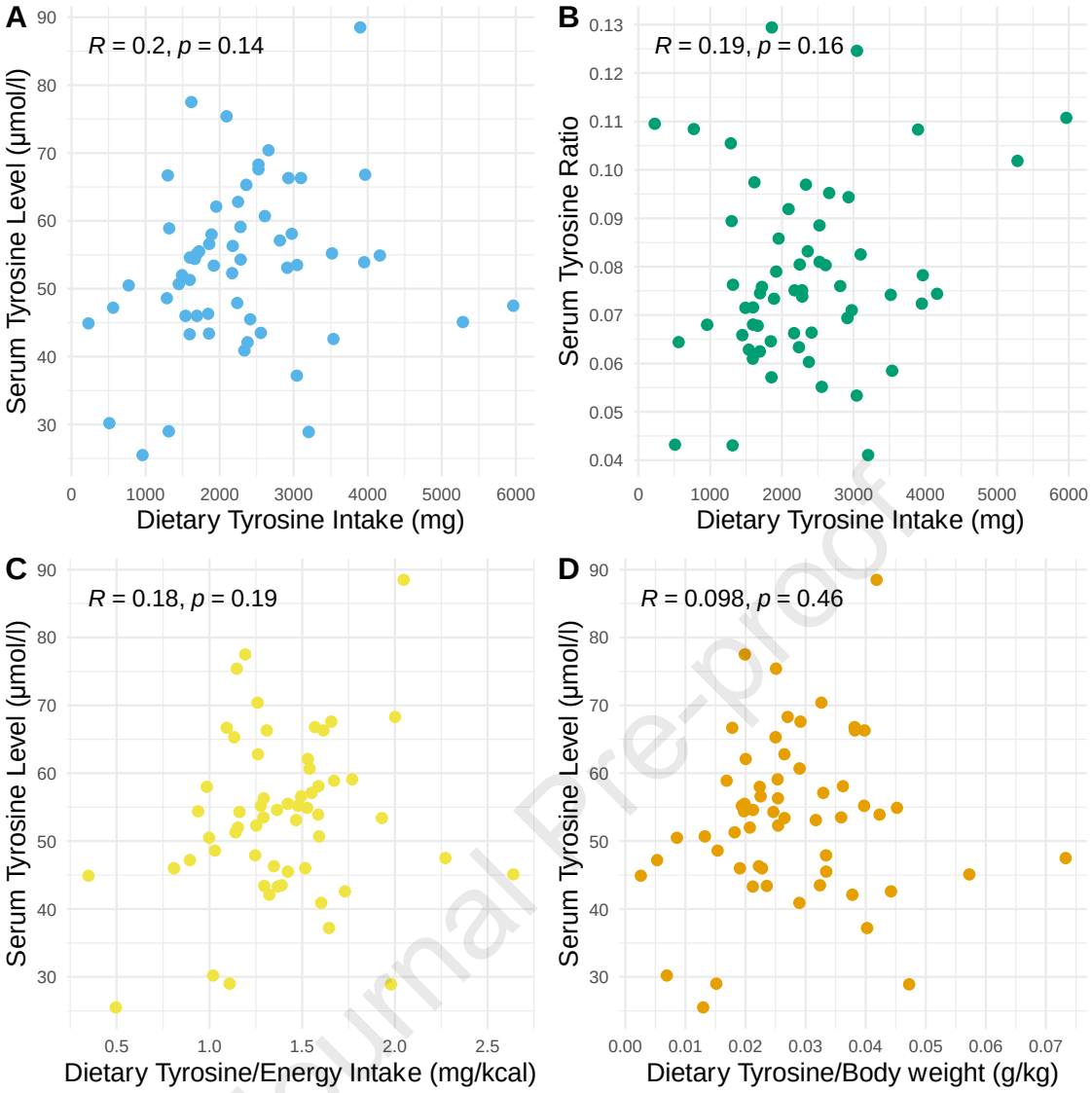


Figure 5: Correlations of (A) dietary tyrosine intake and absolute serum tyrosine levels, (B) dietary tyrosine intake and relative serum tyrosine/LNAA ratios, (C) dietary tyrosine intake adjusted for energy intake and absolute serum tyrosine levels, (D) dietary tyrosine intake adjusted for body weight and absolute serum tyrosine levels. Abbreviations: LNAA; large neutral amino acids; R, Pearson's Correlation Coefficients; p, p-value.

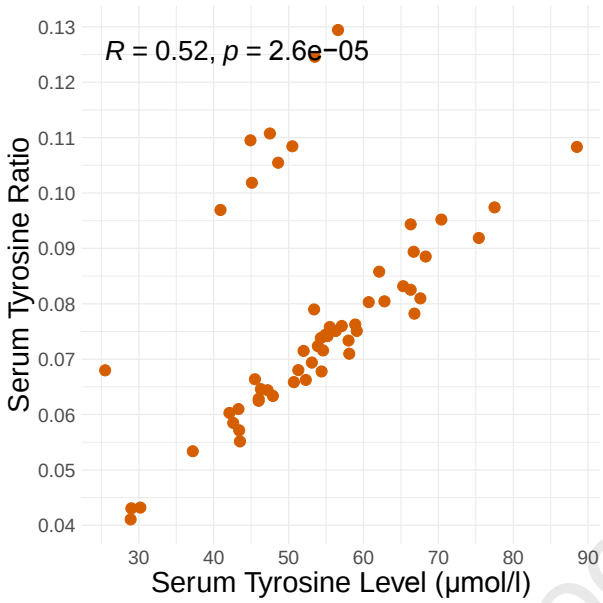


Figure 6: Correlation of absolute serum tyrosine levels and relative serum tyrosine/LNAA ratios. Abbreviations: LNAA; large neutral amino acids; R, Pearson's Correlation Coefficients; p, p-value

According to the criterion of the interquartile rule, we identified two outliers of the tyr/LNAAs ratio with values > 0.12. After exclusion of those outliers, the correlation of higher absolute serum tyr levels with higher relative serum tyr ratios did not attenuate (R = 0.59, p = 2e-06).

Sex/Gender Differences

We observed significant sex/gender differences in dietary tyr intake with men presenting higher intake than women (W = 236, p = 0.02) (Figure 7). However, this difference attenuated when dietary tyr intake was adjusted for total energy intake (W = 285, p = 0.09). Note that total energy intake was significantly higher in the male sex/gender group (W = 252, p = 0.03) (Figure 7).

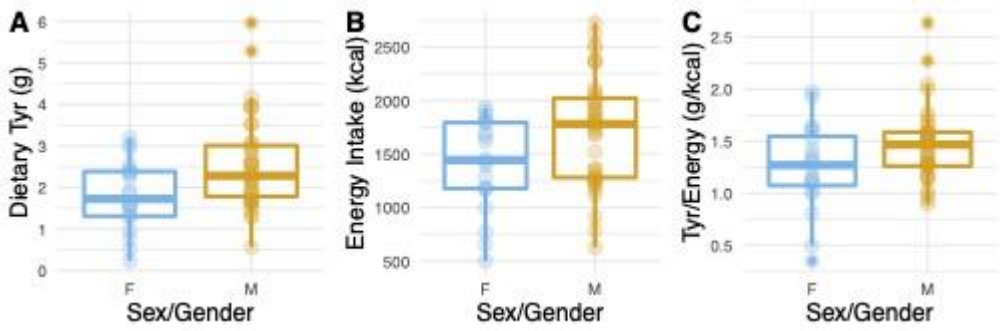


Figure 7: Sex/gender group differences regarding absolute dietary tyrosine intake (W = 236, p = 0.02, **A**), in total energy intake (W = 252, p = 0.03, **B**), and dietary tyrosine intake accounting for energy intake (W

= 285, p = 0.09, **C**). Abbreviations: Tyr, Tyrosine; TYR/Energy, Dietary Tyrosine Intake adjusted for total energy intake. Boxplots depict median as line and Q1 and Q3 as boxes.

Furthermore, the male sex/gender group showed on average slightly better executive attention performance operationalized as conflict effects based on reaction times (W = 493, p = 0.04). Note that the female sex/gender group was significantly younger than the male sex/gender group (W = 211, p = 4e-3). Moreover, our results showed that the male sex/gender group had significantly higher serum tyr markers than the female sex/gender group, both in terms of absolute and serum tyr/LNAAs ratios (all W > 232, all p < 0.02) (**Error! Reference source not found.**). The two sex/gender groups did not differ significantly in neither SES scores nor BMI (all W < 331, all p > 0.35).

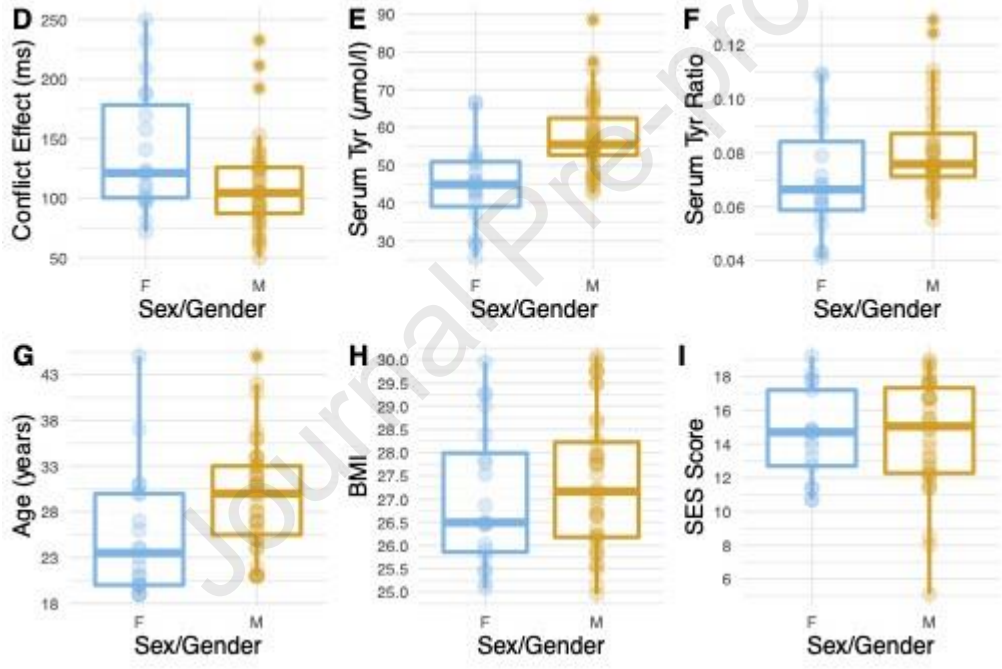


Figure 8: Significant sex/gender group differences in executive attention performance (i.e., conflict effect) (Figure D), absolute serum tyrosine levels (Figure E), relative serum tyrosine ratios (Figure F) and age (Figure G). Non-significant sex/gender group differences in BMI (Figure H) and SES Score (Figure I). Abbreviations: Tyr, Tyrosine; BMI, Body Mass Index; SES, Socio-Economic Status. Boxplots depict median as line and Q1 and Q3 as boxes.

In the female sex/gender group, we observed that neither serum tyr/LNAAs ratios nor age were related to conflict effects (R_{adj}^2 = 0.01, F(2, 15) = 1.098, p < 0.36). In the male sex/gender group, however, lower serum tyr ratio significantly predicted more pronounced conflict effects (β = -907, p < 0.01), when taking the effect of age into account (β = 3.39, p < 0.001).

Table 9: Coefficients of the Serum Tyrosine Ratio – Executive Attention Performance Regression Model controlling for age (only male sex/gender group). Abbreviations: Tyr, Tyrosine; Std. Error, Standard Error.

	Estimate	**Std. Error**	**t-value**	**Pr(>|t|)**
Intercept	82.7669	33.1454	2.497	0.017234
Serum TYR Ratio	-906.9508	324.5920	-2.794	**0.008288**
Age	3.3922	0.9263	3.662	**0.000798**

According to the model, conflict effects deteriorated by 3.39 ms RT with each additional year of life (Table 9). In contrast, the positive influence of tyr in terms of an improvement of executive attention performance by more than 900 ms per increase of 1 unit in the tyr/LNAAs ratio appeared surprisingly large. However, a tyr/LNAAs ratio of 2 means that twice as much tyr must be present in the blood relative to the sum of all other LNAAs. Therefore, this number represents a rather theoretical value.

Age Relationships

Higher age was associated with higher dietary tyr intake in our sample (Table 10 & Figure 9), and the effect of age on executive attention performance was dependent on sex/gender (Figure 10 & Table 12).

Table 10: Simple Linear Regression Models: Age Relationships

1. Dietary tyr Intake = $\beta_0 + \beta_1$ age + ε		
$R_{adj}^2 = 0.10$	F(1,57) = 7.57	p = 7.9e-3
2. Serum tyr Level = $\beta_0 + \beta_1$ age + ε		
$R_{adj}^2 = 0.016$	F(1,56) = 1.92	p = 0.17
3. Executive attention Performance/Conflict Effect = $\beta_0 + \beta_1$ age + ε		
$R_{adj}^2 = -0.017$	F(1, 56) = 0.07	p = 0.79

Table 11: Multiple Regression Models: Age Relationships

1. Dietary tyr Intake = $\beta_0 + \beta_1$ age + β_2 sex/gender + β_3 age*sex/gender+ ε		
$R_{adj}^2 = 0.13$	F(3,55) = 3.88	p = 0.014
2. Serum tyr Level = $\beta_0 + \beta_1$ age + β_2 sex/gender + β_3 age*sex/gender + ε		
$R_{adj}^2 = 0.23$	F(3, 54) = 6.78	p = 6e-4
3. Executive attention Performance/Conflict Effect = $\beta_0 + \beta_1$ age + β_2 sex/gender + β_3		
$R_{adj}^2 = 0.15$	F (3, 54) = 4.48	p = 6.9e-3

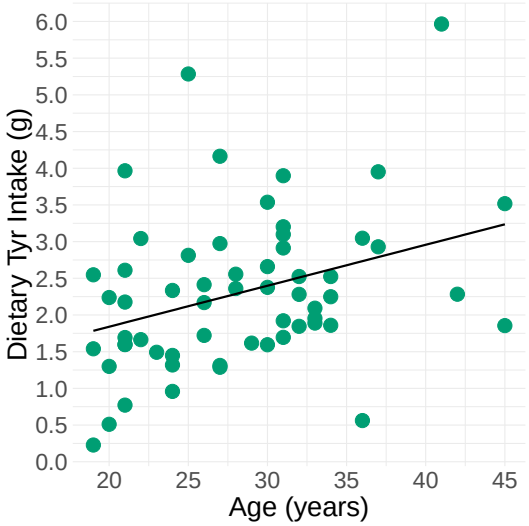


Figure 9: Age - Dietary Tyrosine Intake Relationship. The regression line is indicated in black. Abbreviations: Tyr, Tyrosine.

Table 12: Coefficients of the Age - Executive Attention Performance Regression Model (with age:sex/gender interaction). Abbreviations: Std. Error, Standard Error.

	Estimate	**Std. Error**	**t-value**	**Pr(>|t|)**
Intercept	177.56	37.04	4.8	1.32e-05
Age	-1.48	1.42	-1.04	0.30
Sex/gender (male)	-148.08	50.57	-2.93	**4.98e-3**
Age: Sex/gender	4.19	1.82	2.30	**0.025**

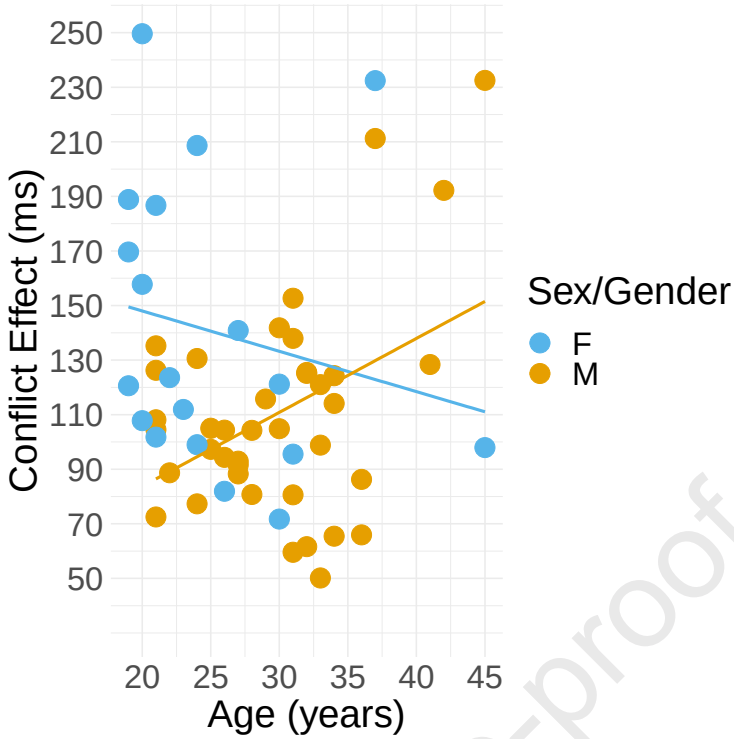


Figure 10: Moderation of the association between age and executive attention performance by sex/gender group. Abbreviations: F, female sex/gender group; M, male sex/gender group).

After excluding the oldest female participant (age = 45) to account for a possible bias due to outlier effects, the model still remained significant (R_{adj}^2 = 0.15, F(3, 53) = 4.34, p-value = 7.9e-04) but with sex/gender only as a significant predictor (β = -134, p = 0.029).

Regarding age-structure correlations, we found that higher age related significantly to lower FA values in seven clusters (TFCE, p_{FWE} > 1.8e-4), Figure 11), with the largest cluster (number of voxels = 35226) widely distributed across the brain (Figure 12).

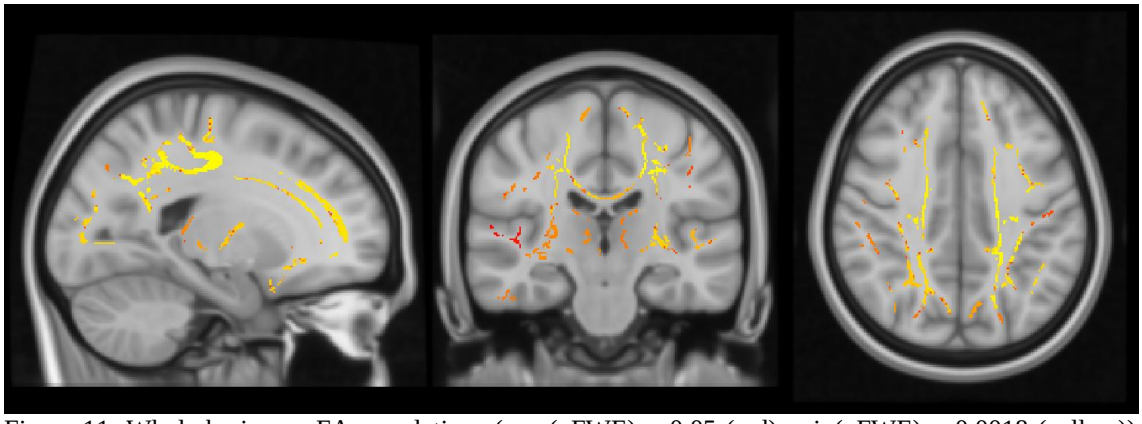


Figure 11: Whole-brain age-FA correlations (max(pFWE) = 0.05 (red), min(pFWE) = 0.0018 (yellow)) overlaid on the MNI152 template (coordinates of max. voxel. x = -20, y = -22, z = 39). Abbreviations: FA, fractional anisotropy; FWE, family-wise error corrected.

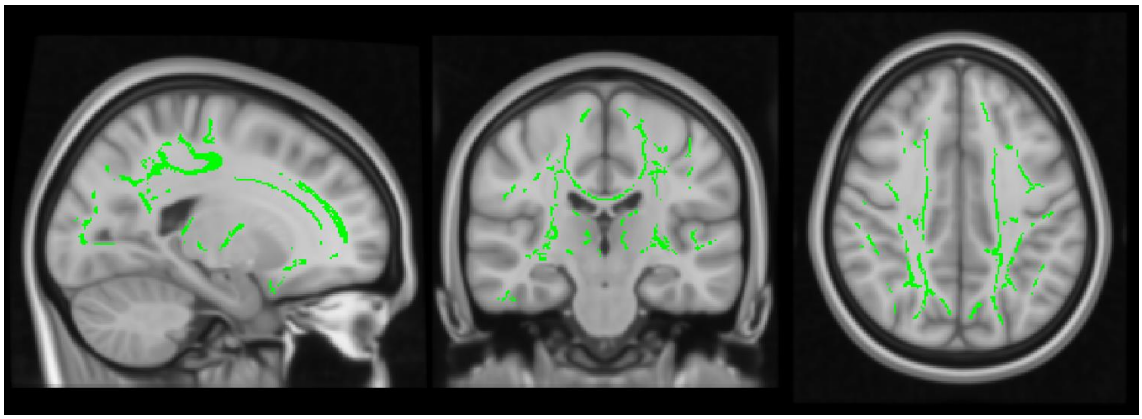


Figure 12: Maximal age-associated cluster (pFWE < 0.05; number of voxels = 35226) overlaid on the MNI152 template (coordinates of max. voxel. x = -20, y = -22, z = 39). Abbreviations: FWE, family-wise error corrected.

Discussion

In this cross-sectional analysis in 59 healthy, overweight adults, our pre-registered confirmatory analyses did not support any of the four hypotheses raised. Neither a relationship between dietary tyr intake and serum tyr levels nor between serum tyr/LNAAs ratios and executive attention performance could be demonstrated. In addition, whole-brain correlation analysis revealed no structure-function associations between white matter microstructure and executive attention performance. Therefore, no further moderation analyses were performed. Finally, the results of the pre-registered exploratory analysis also did not indicate an association between self-reported dietary tyr intake and cognitive performance in our sample. Further exploratory analysis indicated that dietary and serum tyr as well as conflict effects were higher in the male sex/gender group and that older age was associated with higher dietary tyr intake and lower fractional anisotropy in a widespread cluster across the brain. Finally, a higher relative serum tyr/LNAA concentration was linked to better executive attention performance in the male sex/gender group when negative age effects were taken into account.

Dietary and serum tyr

The measured dietary and serum tyr levels resembled those already described in studies with much larger sample sizes. For example, Kühn et al. reported a mean dietary tyr intake of 2.85 g per day, irrespective of the lower mean BMI (M =23.39 kg/m^2) of the sample (341 younger adults, 53% women, mean age: 31, recruited from the Berlin Aging Study II (Kühn et al., 2019). Furthermore, mean serum tyr level of 53.37 µmol/l in our sample

is close to the value obtained in a recently published large epidemiological study (M= 59.7 µmol/l, SD = 16.7, 1324 adults, 87% women, mean age: 44, recruited from the Australian Children's B Cohort) in a sample with similar median BMI (26.54 kg/m^2) (Andraos et al., 2021). The similarity of our sample to larger studies supports the reliability of our measurements and the methodology we used. Moreover, the result patterns of the ANT are largely consistent with those reported by the original study (Fan et al., 2002) indicating that the ANT has been properly performed and analyzed. However, analysis of the error rate data showed a ceiling effect. This ceiling effect might occur as our sample is healthy, young to middle-aged and presents with a medium to high socioeconomic status.

With respect to the methods, self-reported data have been severely criticized as reliable measure of dietary behavior; especially with respect to energy underreporting due to recall biases (Subar et al., 2015). Moreover, the correlation of self-reported dietary intake with nutritional biomarkers has also been problematized (Naska et al., 2017). In particular, short-term concentration biomarkers (e.g.; serum concentrations) are affected by individual differences in metabolism and socio-demographical, behavioral or health-related characteristics leading to inconsistent findings in diet-related research. Thus, it has been suggested to validate the applied nutrition questionnaires by employing multiple methods simultaneously and incorporating new technologies (Naska et al., 2017).

Sample size was not powered to the current cross-sectional analysis, and might have been too low to detect the hypothesized effects. We propose larger samples, data pooling and a priori power analyses to circumvent underpowered analyses.

Executive attention and white matter microstructure

We could not confirm the findings of two cross-sectional studies examining the association between self-reported dietary tyr intake and cognitive performance (Hensel et al., 2019; Kühn et al., 2019). Both studies measured working memory and were based on large sample sizes (n > 280). In contrast, our pre-registered exploratory regression analysis did not demonstrate a relationship between dietary tyr intake and executive attention possibly due to a lack of power. The power calculation was based on effects regarding the intervention study. Another possibility for the lack of a relationship could be the differences in DA processing between executive attention and working memory.

Considering the null findings of the whole-brain voxel-wise correlation analysis, it could be argued that DTI analyses are more sensitive to group analyses and comparisons of

patient vs. non-patient groups rather than at the individual level in correlation analyses (Op de Beeck & Nakatani, 2019). Moreover, we decided against a region of interest (ROI) approach and in favor of a whole-brain analysis to explore structure-function relationships without local restriction, although previous literature suggested the anterior corona radiata (ACR) as interesting ROI regrading executive attention performance (Niogi et al., 2010; Yin et al., 2013). Thus, the whole-brain analysis potentially suffered from lower statistical power. In further analyses, we aim to employ a ROI approach to increase statistical power by decreasing corrections for multiple comparisons (Saxe et al., 2006). By defining ROIs in advance, we would need fewer statistical tests and subsequently fewer corrections for multiple comparisons.

Exploratory findings

Considering exploratory analyses, sex/gender emerged as significant predictor of serum tyr concentrations. This unexpected finding also suggests that other relevant aspects influencing the variables of interest should be included in the analyses to elucidate the link between diet and cognition. Exploratory analyses showed sex/gender-specific differences with respect to various variables of interest: an effect of age on dietary tyr intake and sex/gender-age interaction effects in relation to executive attention performance. In addition, whole-brain correlation analysis showed that older age was associated with lower FA in a widespread cluster. Interestingly, we demonstrated a significant association between relative tyr serum levels and executive attention performance in the male sex/gender group only when taking negative age effects on white matter into account.

Correlation analysis of various dietary and serum tyr markers showed no significant associations. Thus, the results call a direct relationship between self-reported subjective measures of dietary tyr intake and objectively measured serum tyr levels into question. However, based on these null results, tools like FFQ based on self-report should not be doubted as a reliable method for measuring dietary tyr intake but should rather be used as an opportunity to implement recommendations to improve future studies of self-reported dietary measures. In contrast to the non-significant diet-serum associations, we demonstrated a moderate to strong correlation between the two serum markers, suggesting that individuals with higher tyr levels also had higher levels of all other six LNAAs.

Sex/gender differences in tyr - cognition relation

In line with our findings, several studies have previously reported sex/gender differences in eating behavior, food choices, and dietary strategies (Arganini et al., 2012; Grzymisławska et al., 2020). Food intake for males and females differed not only in terms of quantity and quality, but also in terms of frequency, timing, and location of meals. For example, women are more likely to eat foods with higher fiber content (e.g., fruits and vegetables), while men tend to consume more dietary supplements. A reciprocal model of the relationship between sex/gender and diet has been proposed, shaped by the interplay of physiological, psychological, and sociocultural factors (Grzymisławska et al., 2020). Another limitation to nutritional biomarker-related research is the lack of consideration of the variable sex/gender (Song et al., 2018). A recent review emphasizes the need to consider sex/gender differences in nutrition-related research because of sex/gender differences in serum metabolite concentrations and amino acids (AA) level dynamics during the menstrual cycle (Brennan & Gibbons, 2020). An epidemiological study reporting higher plasma tyr levels in men points to research indicating higher insulin concentrations and insulin sensitivity in women (Andraos et al., 2021). These differences might be related to sex/gender differences in the amount and distribution of adipose tissue (Valencak et al., 2017). Insulin promotes the uptake of AA in peripheral tissues and thus decreases AA concentrations in blood and uptake at the blood-brain barrier (John D. Fernstrom, 2013). Strang and colleagues justified the selection of exclusively male subjects with sex/gender differences in metabolism (Strang et al., 2017) based on differences in abdominal adipose tissue. Sex/gender differences may also explain some of the previously published null results, e.g. no intervention effect of tyr supplementation on executive attention in females only (Frings et al., 2020).

Our results showed higher serum tyr for the male sex/gender group compared to the female sex/gender group, which is consistent with previous studies (Andraos et al., 2021; Darst et al., 2019). The male sex/gender group showed better executive attention performance, but only in terms of significantly lower conflict effects based on reaction times. However, accuracy scores did not significantly differ between the two sex/gender groups. This pattern is also consistent with the current literature on sex/gender differences in cognition. A literature review concluded that there is little to no evidence for a consistent difference in attention, impulsive action, decision making, and working memory (Grissom & Reyes, 2019). Therein, differences in slower reaction times and a tendency of females to avoid negative consequences in decision making were reported.

In addition, men and women seemed to differ in their working memory strategies and underlying neural activity patterns, possibly due to differences in neurotransmitter systems and structural brain development. In sum, the sex/gender differences found in our study align well with previous research findings.

Age influence on tyr - cognition relation

In addition to sex/gender, age seems to be relevant for the link between tyr in blood and executive attention. The positive association between serum tyr/LNAAs ratios and executive attention performance in the male sex/gender group was only significant when age was included as a control variable to account for negative age effects on task performance. We also showed that higher age was associated with higher dietary tyr intake. However, we were not able to confirm the interaction effects of sex/gender and age already described in previous research. Inconclusively, one study reported sex/gender effects (i.e. significant higher protein intake in male subjects) and sex/gender-age interactions with respect to dietary protein intake (Hone et al., 2020). By contrast, two other studies did not report any effect of age or sex/gender on dietary try (Hensel et al., 2019; Kühn et al., 2019). A longitudinal study showed increasing plasma tyr levels with increasing age (Darst et al., 2019) and another could demonstrate age differences in baseline serum tyr levels and in dose-dependent responses to oral tyr administration (van de Rest et al., 2017), yet both studies were conducted in older populations. Contrary to previous findings, we could not identify any age effect or age-sex/gender interaction with respect to serum tyr levels, presumably due to the young to middle-aged sample.

ANT performance

In contrast to previous studies (Gamboz et al., 2010; Jennings et al., 2007), we could not establish an effect of age on executive attention performance. Nevertheless, we found and interaction effect of age and sex/gender, revealing that the effect of age is only present in the male sex/gender group. Although previous studies found slower reaction times for executive function in older participants (mean age: 69.14/67.9), conflict effects did not differ significantly when controlling for general slowing in processing speed (Gamboz et al., 2010; Jennings et al., 2007). Our analysis revealed no significant relationship between age and reaction times (although we did not even correct for general slowing with age). The lack of an age effect on reaction times is presumably owed to the small age range and relatively young age of our sample. Importantly, our results regarding age effects on

executive attention performance (in the male sex/gender group) should be interpreted with caution as we did not control for general slowing with age. This might be the main reason for reduced performance with higher age (Rey-Mermet & Gade, 2018) and should be included in future analyses.

Our whole-brain correlation analyses indicated a negative, locally non-specific association between age and white matter microstructure showing FA decreases with aging. This finding replicates the well-established age-related decline in white matter integrity (Cox et al., 2016; Vinke et al., 2018), starting already in young adulthood (Giorgio et al., 2010; Kodiweera et al., 2016).

Limitations

Besides considerations for interpreting results mentioned above, there are limitations in the study design. First, meals consumed just before ANT may have influenced task performance by either stimulating effects (e.g., coffee) or digestion-related sedative effects (e.g., burgers). Second, indirect effects of AA content and macronutrient composition relating to lower serum tyr may have not been traceable due to the too short time interval between food intake and ANT. Indeed, previously it has been shown that although the plasma tyr/LNAAs ratios increase linearly after a meal, it takes up to two hours to reach highest levels (Strang et al., 2017), whereas in our design only 30 minutes had passed. In addition, additional time passes until tyr crosses the blood-brain barrier and is converted to DA; however, evidence is missing on how long transport and DA synthesis take in humans.

Next to confounding factors, differences in study procedure should be considered. For instance, testing sessions were scheduled at constant morning slots per participant, neglecting that serum tyr and tyr/LNAAs ratios vary throughout the day dependent on the amount of protein/tyr consumed (J D Fernstrom et al., 1979). Interestingly, serum tyr levels at 7 am were almost the same for diets different in protein content and tyr/LNAAs ratios converged again in the afternoon. The main limitation of the theoretical foundation concerns the reduction of relevant influencing factors and their interrelationships, which led to a simplistic and mechanistic model. For instance, with respect to dopaminergic neuromodulation, Cools points to three key principles (i.e., regional specialization, self-regulation, and baseline dependence) that indicate that the link between DA availability in the brain and cognitive function is not a one-way, monocausal, linear relationship

(Cools, 2019). Moreover, it has been shown that chronically higher DA levels may lead to long-term adaptive changes in the dopaminergic system in terms of receptor or transporter expression and receptor sensitivity, which in turn may attenuate acute DA depletion effects (Hartmann et al., 2020). Also, brain DA in humans is mostly measured using proxy markers such as precursor availability, and not directly using PET imaging, tracing techniques or manipulation by dopaminergic drugs. Also, while we did not perform further mediation analyses because a lack of main effects, we cannot exclude that other unknown confounding factors might have masked such an effect.

Conclusions and outlook

In summary, non-pre-registered exploratory analyses revealed multiple sex/gender and age effects which are largely consistent with previous research, yet which might have possibly confounded the outcome of our analyses (Figure 14). Further exploration of sex/gender differences as imperfect proxies for yet unknown underlying biological and non-biological mechanisms is important, at least as a transitional solution to ensure equality in medical treatment and basic research for different sex/gender groups. Future neuroscientific research should consider differences in biological and non-biological mechanisms related to sex/gender when designing nutrition-related studies.

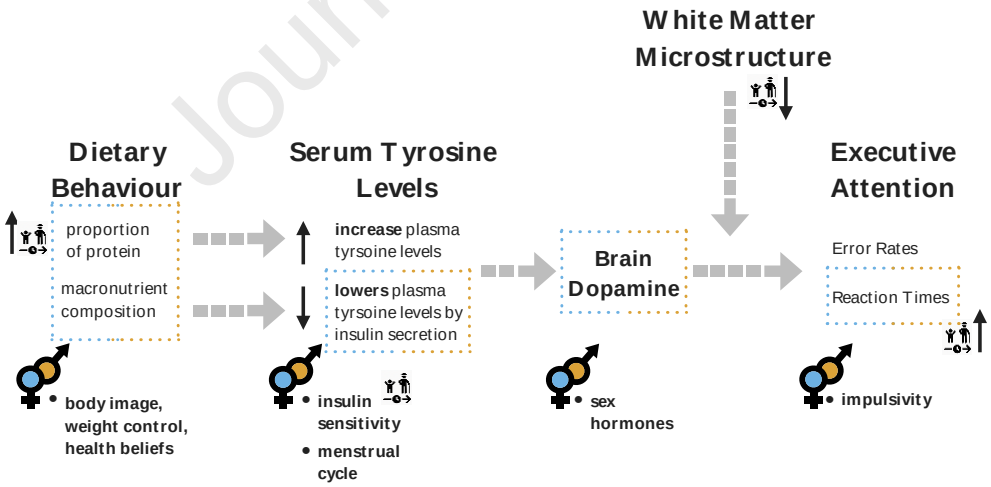


Figure 13: Aspects of sex/gender differences and age effects regarding the link between nutrition and cognition.

Ethical statement

This study was performed in compliance with the Helsinki Declaration guidelines. The institutional ethics board of the Medical Faculty of the University of Leipzig, Germany, raised no concerns regarding the study protocol (228/18-ek) and all participants provided written informed consent. They received reimbursement for participation.

Funding

Open Access funding enabled and organized by Projekt DEAL. This work was supported by grants of the German Research Foundation no. WI 3342/3-1 and 209933838 CRC1052-03 A1 (AVW), by the German Federal Environmental Foundation (EM), and by the Max Planck Society.

Author contributions

Conceptualization, AKB, AVW, EM; methodology, AKB, AVW, EM, FB, RT; formal analysis, AKB; statistical advice: FB; data curation, AKB; data visualization, AKB; writing—original draft preparation, AKB; writing—review and editing, AVW, EM, RT; project administration, AVW, AV, JS. All authors have read and agreed to the published version of the manuscript.

Acknowledgements

We thank all individuals for participating in the study and the medical staff for collecting blood samples. We also thank Anja Willenberg and the team of the Institute for Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics (ILM) Leipzig University, Leipzig, for help in blood parameter analysis, Hendrik Hartmann for providing insights on considerations in dopaminergic markers and H. Lina Schaare for supporting data analysis regarding the Attention Network Test.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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List of abbreviations

executive attention	Executive Attention
FA	Fractional Anisotropy
DTI	Diffusion Tensor Imaging
DA	Dopamine
ANT	Attention Network Theory
RT	Reaction Time
ER	Error Rate
ACC	Anterior Cingulate Cortex
VTA	Ventral Tegmental Area
LNAA	large neutral amino acids
BOLD	blood oxygen level dependent
OSF	Open Science Framework
COS	Center for Open Science
BMI	Body-Mass-Index
SES	Socio-Economic Status
MRI	Magnetic Resonance Imaging
FFQ	German Food Frequency Questionnaire
TR	Repetition time
TE	Echo Time
FOV	Field-of-view
DW- MRI	Diffusion-weighted magnetic resonance imaging
GRAPPA	GeneRalized Autocalibrating Partial Parallel Acquisition
FSL	FMRIB Software Library
TBSS	Tract-based spatial statistic
ANOVA	analysis of variance
TFCE	Threshold-Free Cluster Enhancement
FWE	Family wise error
SD	standard deviation
tyr	tyr
AA	amino acids

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1. Appendix

1.1. Pre-registered Analyses

ANT: Analysis of Variance (ANOVA)

Performing and correctly interpreting the results of an ANOVA requires that the assumption of normality and homoscedasticity is met.

First, the normal distribution of the standardized residuals was visually examined by plotting a histogram of standardized residuals and the Quantile-Quantile Plot based on both RT and ER data. Although the histogram of the RT data exhibits a slight skewness (Figure 14) and the data deviate from the reference line at the right edge of the Q-Q plot (Figure 15), we conclude that the visualization of the residuals sufficiently supports the normality assumption.

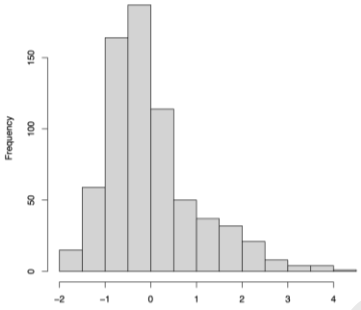

Figure 14: Histogram of standardized residuals (reaction times)

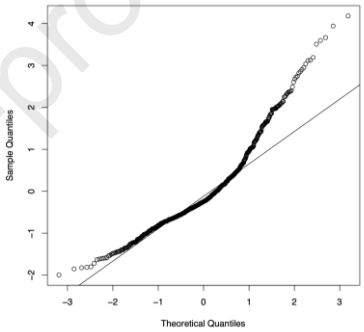

Figure 15: Quantile-Quantile Plot (reaction times)

However, the normality assumption is unambiguously violated with respect to the ER data (Figure 16 & Figure 17).

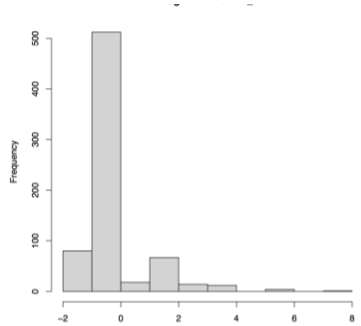

Figure 16: Histogram of standardized residuals (error rates)

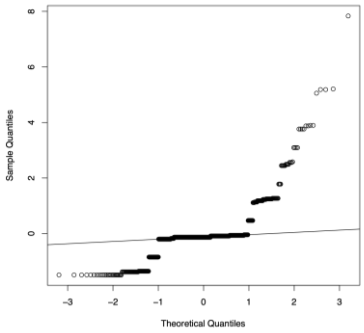

Figure 17: Quantile-Quantile Plot (error rates)

Second, the normality assumption was also tested analytically using the Shapiro-Wilk normality test (Shapiro & Wilk, 1965). The results for both RT (W = 0.92063, p-value < 2.2e-16) and ER (W = 0.70485, p-value < 2.2e-16) demonstrate that the null hypothesis (normality assumption) should be rejected. However, the results of analytical tests such as the Shapiro-Wilk normality test should be evaluated with caution, as even small deviations can lead to a rejection of the null hypothesis.

Third, homogeneity of variance was checked as well. Homoscedasticity concerns the assumption of equal or similar variances with respect to the different factors being compared. This assumption can be tested either visually or by Levene's test (Levene, 1960). Regarding the RT data, both visual inspection (Figure 18) and Levene's test ($F(11,684) = 1.0253$, $p = 0.4217$) confirms that the variance between factors is not significantly different i.e., the variances are homogeneous. However, regarding the ER data, both visual inspection (Figure 19) and Levene's test ($F(11, 696) = 27.698$, $p < 2.2e-16$) indicate a lack of homogeneity; the p-value is smaller than the significance level of 0.05. Thus, the second assumption for a two-way ANOVA of the ER data could not be met either.

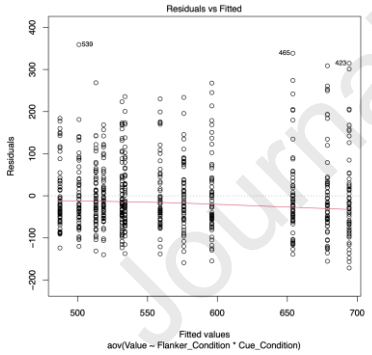

Figure 18: Residuals vs. Fitted plot (reaction times)

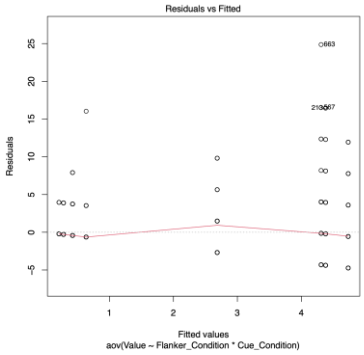

Figure 19: Residuals vs. Fitted plot (error rates)

Dietary – Serum Tyrosine Relationship

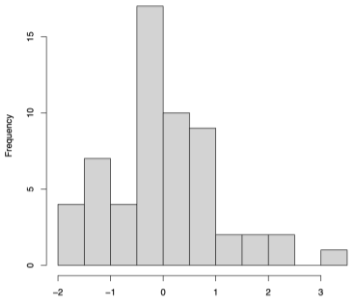

Figure 20: Histogram of standardized residuals: Dietary Tyrosine - Serum Tyrosine

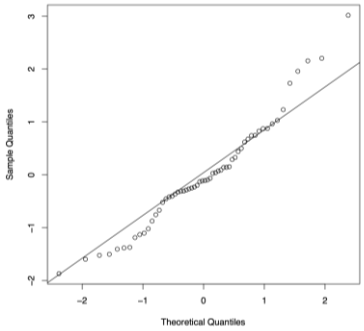

Figure 21: Normal Quantile-Quantile Plot: Dietary Tyrosine - Serum Tyrosine

Serum Tyrosine Ratio and Executive Attention Performance

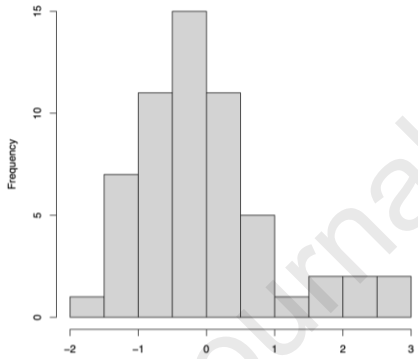

Figure 22: Histogram of standardized residuals: Serum Tyrosine/LNAA - EA Performance. Abbreviations: LNAA, large neutral amino acids; EA, executive attention.

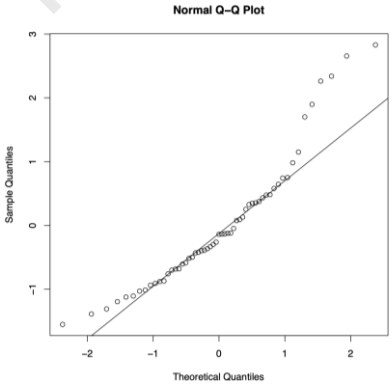

Figure 23: Normal Quantile-Quantile Plot: Serum Tyrosine/LNAA - EA Performance. Abbreviations: LNAA, large neutral amino acids; EA, executive attention.

Dietary Tyrosine Intake and Executive Attention

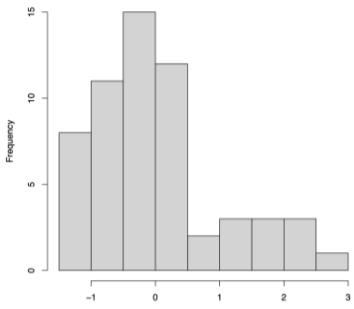

Figure 24: Histogram of standardized residuals: Dietary TYR/body weight - EA performance. Abbreviations: TYR, tyrosine; EA, executive attention.

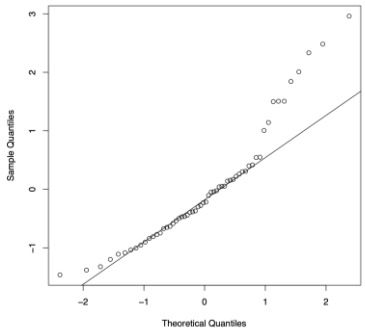

Figure 25: Normal Quantile-Quantile Plot: Dietary TYR/body weigh - EA performance. Abbreviations: TYR, tyrosine; EA, executive attention.

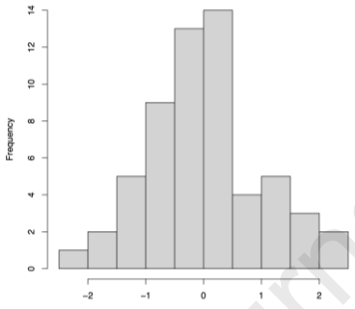

Figure 26: Histogram of standardized residuals: Dietary TYR/body weigh - EA performance (log-transformed data). Abbreviations: TYR, tyrosine; EA, executive attention.

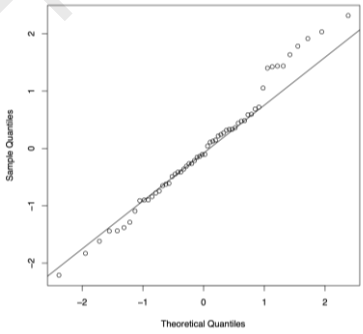

Figure 27: Normal Quantile-Quantile Plot: Dietary TYR/body weigh - EA performance (log-transformed data). Abbreviations: TYR, tyrosine; EA, executive attention.

1.2. Non-pre-registered Analyses

Sex/gender Differences in Variables of Interest

We plotted the histograms of the variable of interest. The visualization shows that the normality assumption is not met for almost all variables.

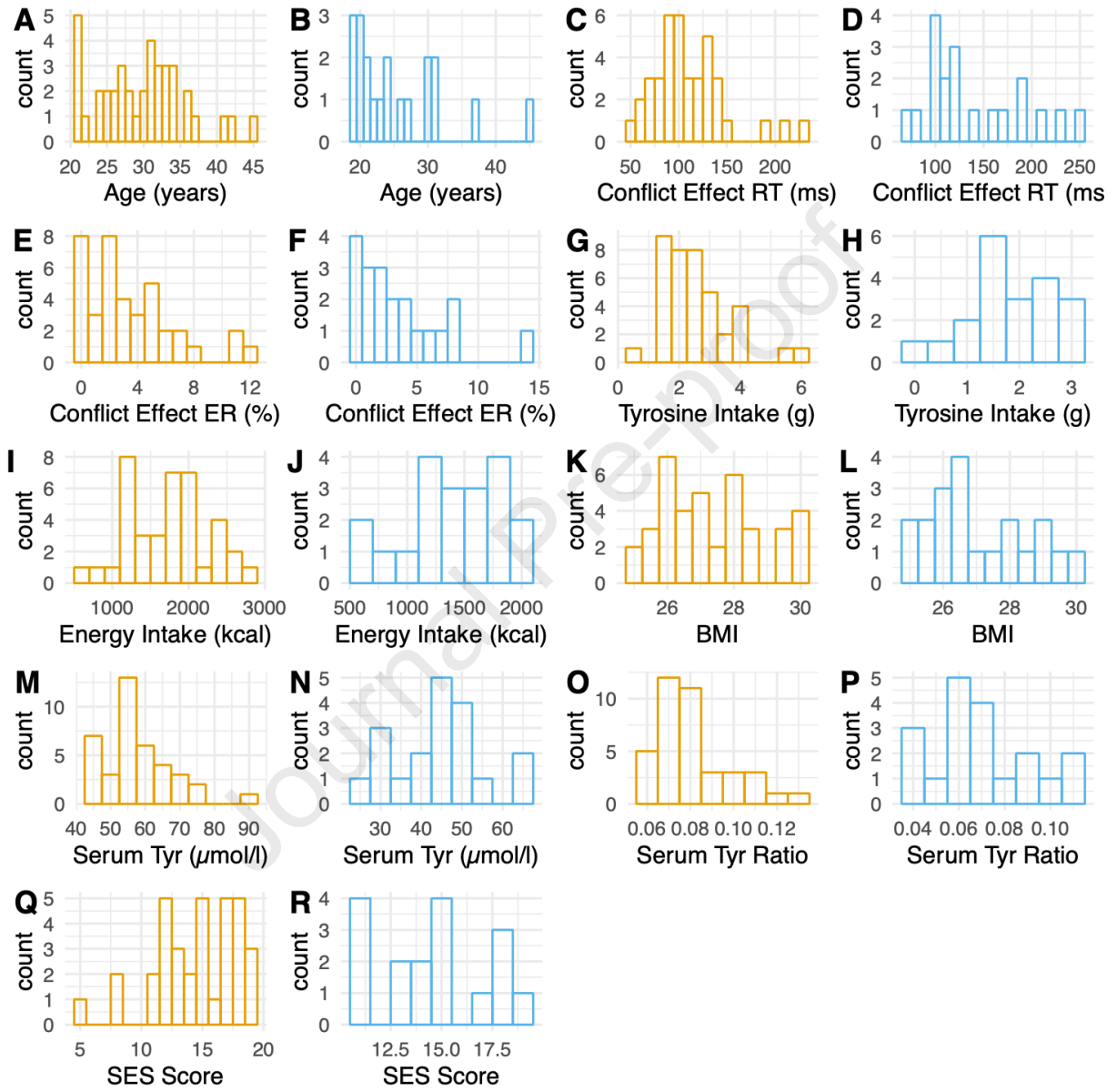

Figure 28: Histograms of variables of interest (blue: female sex/gender group, orange: male sex/gender group). Abbreviations: BMI, body mass index; TYR, tyrosine; SES, socio-economic status.

Regression Analysis per sex/gender

Female sex/gender group

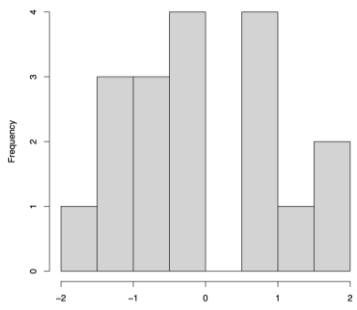

Figure 29: Histogram of standardized residuals: Serum tyrosine/LNAA ratio– EA (female*). Abbreviations: LNAA, large neutral amino acids; EA, executive attention.

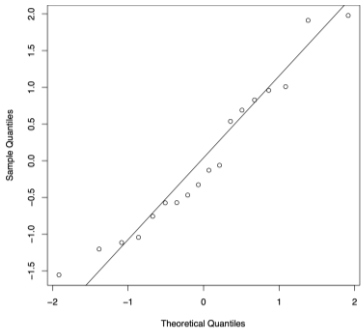

Figure 30: Normal Quantile-Quantile Plot: Serum tyrosine/LNAA ratio - EA (female*). Abbreviations: LNAA, large neutral amino acids; EA, executive attention.

Male sex/gender group

With regard to the significant multiple regression model examining whether serum tyr ratios significantly predicted executive attention performance in the male sex/gender group (when controlling for age), the normal distribution assumption was checked. First, the normal distribution of the standardized residuals was examined graphically. Both, the histogram and the Quantile-Quantile-Plot sufficiently support the normality assumption of the residuals; besides deviations on the outer edges. Secondly, the normality assumption was tested analytically using the Shapiro-Wilk normality test. The results also support that the null hypothesis of normal distribution cannot be rejected (W = 0.97719, p-value = 0.6021).

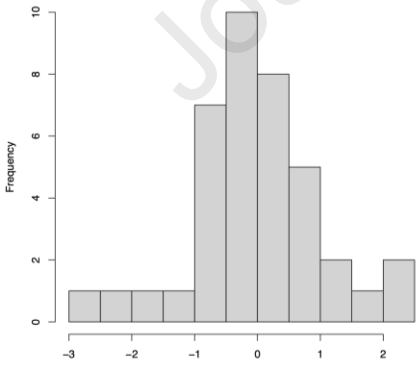

Figure 31: Histogram of standardized residuals: Serum tyrosine/LNAA ratio - EA (male*). Abbreviations: LNAA, large neutral amino acids; EA, executive attention.

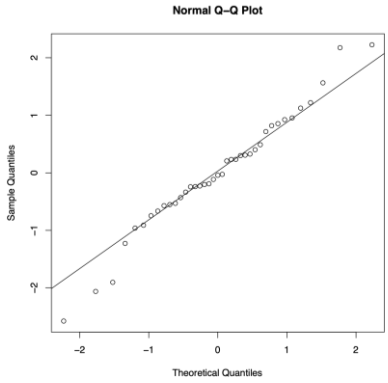

Figure 32: Normal Quantile-Quantile Plot: Serum tyrosine/LNAA ratio - EA (male*). Abbreviations: LNAA, large neutral amino acids; EA, executive attention.

Age-Relationships

Checking Normality assumption visually and by analytical test:

Regression model: Age - executive attention (W = 0.90476, p-value = 0.0002519) – no normal distribution

Regression Model: Age - Diet (W = 0.94139, p-value = 0.00683) – no normal distribution

Regression Model: Age - Serum tyr (W = 0.98677, p-value = 0.7789) - normal distribution

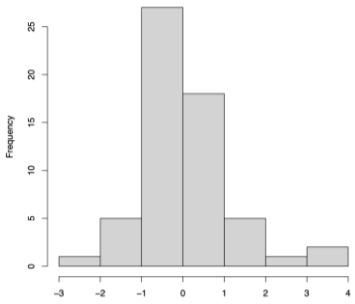

Figure 33: Histogram of standardized residuals: Age - Dietary TYR. Abbreviations: TYR, tyrosine.

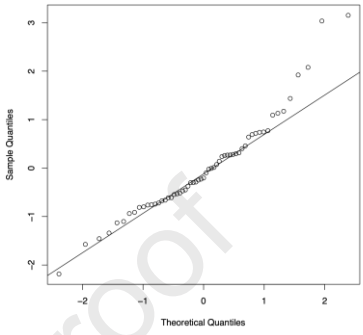

Figure 34: Normal Quantile-Quantile Plot: Age - Dietary TYR intake. Abbreviations: TYR, tyrosine.

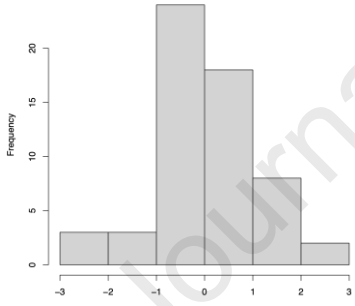

Figure 35: Histogram of standardized residuals: Age - Serum TYR levels. Abbreviations: TYR, tyrosine.

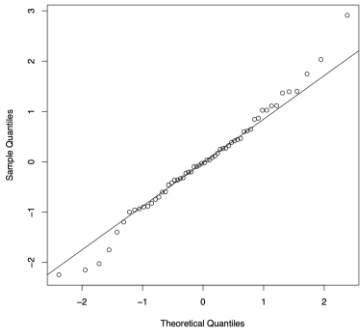

Figure 36: Normal Quantile-Quantile Plot: Age - Serum Tyrosine levels.

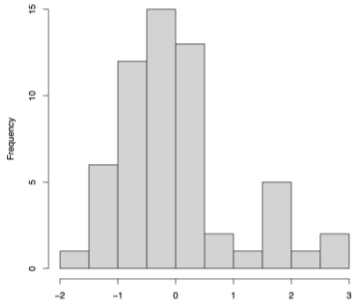

Figure 37: Histogram of standardized residuals: Age - EA performance. Abbreviations: EA, executive attention.

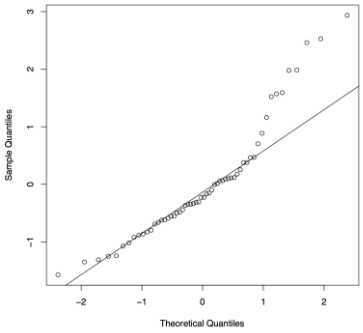

Figure 38: Normal Quantile-Quantile Plot: Age - Executive Attention Performance

Age: sex/gender interaction – executive attention performance

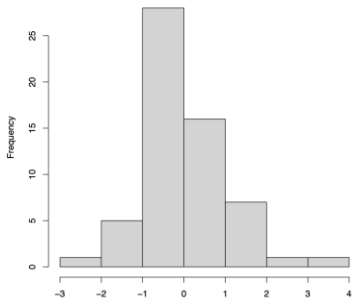

Figure 39: Histogram of standardized residuals: Diet TYR - Age:Sex/gender. Abbreviations: TYR, tyrosine.

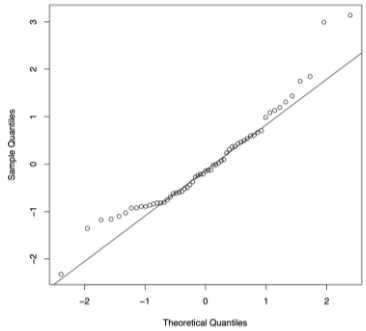

Figure 40: Normal Quantile-Quantile Plot: Diet TYR - Age:Sex/gender. Abbreviations: TYR, tyrosine.

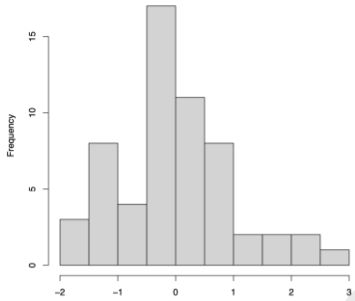

Figure 41: Histogram of standardized residuals: Serum TYR - Age:Sex/gender. Abbreviations: TYR, tyrosine.

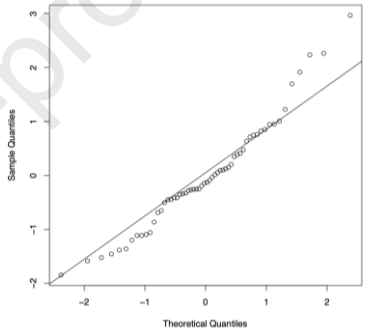

Figure 42: Normal Quantile-Quantile Plot: Serum TYR - Age:Sex/gender. Abbreviations: TYR, tyrosine.

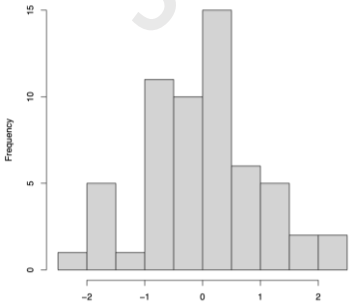

Figure 43: Histogram of standardized residuals: EA - Age:Sex/gender (log-transformed data). Abbreviations: EA, executive attention.

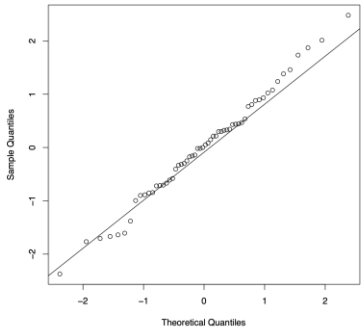

Figure 44: Normal Quantile-Quantile Plot: EA - Age:Sex/gender (log-transformed data). Abbreviations: EA, executive attention.

Conflict Effect ER

Conflict Effect computed based on Error Rate data. We performed non-parametric Mann-Whitney U/Wilcoxon rank sum tests. The results show no significant sex/gender difference in executive attention performance based on error rate data (W = 391.5, p-value = 0.9807).

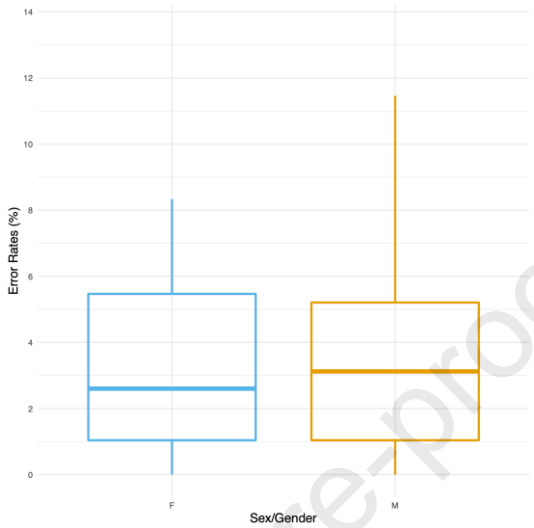

Figure 45: Sex/Gender group difference in conflict effects ER (%). Abbreviations: ER, error rates.

SI Table 1: Summary statistics of error rates as a function of cue condition and flanker type (in %). Abbreviations: n, number of subjects; sd, standard deviation; se, standard error.

Flanker	Cue	n	min	max	median	mean	sd	se
neutral	center	59	0	16.67	0	0.636	2.425	0.316
neutral	double	59	0	4.17	0	0.212	0.924	0.12
neutral	no	59	0	4.17	0	0.283	1.057	0.138
neutral	spatial	59	0	8.33	0	0.424	1.488	0.194
congruent	center	59	0	8.33	0	0.424	1.676	0.218
congruent	double	59	0	4.17	0	0.424	1.271	0.165
congruent	no	59	0	4.17	0	0.283	1.057	0.138
congruent	spatial	59	0	8.33	0	0.424	1.488	0.194
incongruent	center	59	0	16.67	4.17	4.732	5.274	0.687
incongruent	double	59	0	20.83	4.17	4.379	5.494	0.715
incongruent	no	59	0	29.17	4.17	4.308	5.788	0.754
incongruent	spatial	59	0	12.5	0	2.684	3.692	0.481

SI Table 2: Summary statistics of reaction times as a function of cue condition and flanker type (in ms). Abbreviations: n, number of subjects; sd, standard deviation; se, standard error.

Flanker	Cue	n	min	max	median	mean	sd	se
neutral	center	58	378.542	687.182	506.667	518.568	67.643	8.882
neutral	double	58	381.739	781.417	498.25	513.064	72.065	9.463
neutral	no	58	421.042	789.174	527.938	559.064	83.628	10.981
neutral	spatial	58	363.542	671.25	465.042	487.396	74.811	9.823
congruent	center	58	396.625	769.571	511.386	533.881	80.019	10.507
congruent	double	58	408.375	755	512.896	531.725	80.762	10.605
congruent	no	58	416.875	809.625	561.146	575.956	78.947	10.366
congruent	spatial	58	381.042	860.042	478.896	500.999	82.927	10.889
incongruent	center	58	523.095	987.522	655.318	678.685	106.213	13.947
incongruent	double	58	515	992.522	631.487	653.986	101.173	13.285
incongruent	no	58	522.818	1009.042	674.718	694.28	107.627	14.132
incongruent	spatial	58	441.19	863.667	569.87	595.979	92.928	12.202

Ethical statement

This study was performed in compliance with the Helsinki Declaration guidelines. The institutional ethics board of the Medical Faculty of the University of Leipzig, Germany, raised no concerns regarding the study protocol (228/18-ek) and all participants provided written informed consent. They received reimbursement for participation.

Funding
Open Access funding enabled and organized by Projekt DEAL. All funding was provided by the Max Planck Society.

Author contributions
Conceptualization, AKB, AVW, EM; methodology, AKB, AVW, EM, FB, RT; formal analysis, AKB; statistical advice: FB; data curation, AKB; data visualization, AKB; writing—original draft preparation, AKB; writing—review and editing, AVW, EM, RT; project administration, AVW, AV, JS. All authors have read and agreed to the published version of the manuscript.

Acknowledgements
We thank all individuals for participating in the study and the medical staff for collecting blood samples. Also we thank Hendrik Hartmann for providing insights on considerations in dopaminergic markers and Lina Schaare for supporting data analysis regarding the Attention Network Test.

Declaration of competing interest
The authors have no conflicts of interest to disclose.

Conflict of Interest declaration
The authors declare no conflict of interest.