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REVIEW ARTICLE

Literature review on the role of dietary protein and amino acids in cognitive functioning and cognitive decline

Ondine van de Rest · Nikita L. van der Zwaluw · Lisette C. P. G. M. de Groot

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Abstract As the population of elderly people is growing rapidly, the number of individuals with dementia and cognitive impairment is also increasing. One of the preventive measures against cognitive decline is diet and different dietary factors have already been investigated. This review provides an overview of studies on dietary protein and cognitive functioning and cognitive decline. Also studies on the individual amino acids that are related to brain function, tryptophan and tyrosine, are discussed. Overall, the role of dietary protein intake on cognitive functioning as well as cognitive decline has hardly been studied; we found eight observational studies and three intervention studies. More studies investigated the role of tryptophan (14 studies) and tyrosine (nine studies) in relation to cognitive functioning, but all these studies were performed in young adult populations and mostly under special conditions. Research in elderly populations, in particular, is warranted. Also more research is needed to come to definitive conclusions and specific recommendations regarding protein intake or intake of specific amino acids for maintaining optimal cognitive functioning.

Keywords Dietary protein · Amino acids · Tyrosine · Tryptophan · Dementia · Cognitive functioning · Cognitive decline

O. van de Rest (✉) · N. L. van der Zwaluw · L. C. P. G. M. de Groot
Division of Human Nutrition, Wageningen University, Bomenweg 4, P.O. Box 8129, 6700 EV Wageningen, The Netherlands
e-mail: Ondine.vandeRest@wur.nl

Introduction

The number of people living with dementia worldwide is currently estimated at 35.6 million. This number will double by 2,030 and more than triple by 2,050 (World Health Organization and Alzheimer's Disease International 2012). This will impose a major burden on society and the health-care system. At present, there is no treatment known that can stop or cure the progression of dementia and treatment only induces minor cognitive improvements in some patients (Klafki et al. 2006; Hansen et al. 2008; Raina et al. 2008). Moreover, by the time a person shows symptoms of dementia, the brain has already accumulated extensive neuropathology of amyloid plaques and neurofibrillary tangles, which is a process that is irreversible. Therefore, it is important to focus on ways to prevent or postpone the process of cognitive decline.

One of the preventive measures against cognitive decline is diet and different dietary factors have already been investigated. Protein and its constituent amino acids are indispensable components of the human diet. Proteins are essential to maintain cellular integrity and function, also for brain cells. Low protein intakes are associated with a higher frailty risk (Beasley et al. 2010) and physical frailty is a predictor of cognitive decline and Alzheimer's disease (AD) (Buchman et al. 2007; Auyeung et al. 2011). Protein supplementation has been shown to be a promising nutritional strategy to improve functional performance in frail elderly and it may as well improve mental performance (Tieland et al. 2012), especially since mental performance is positively related to physical fitness (Colcombe and Kramer 2003). Data from the USDA showed that $\approx$40 % of individuals aged $\geq$70 years consumed less than the Recommended Dietary Allowance (RDA) for protein and $\approx$16 % consumed $<$75 % of the

RDA (USDA Agricultural Research Service 2013). A positive role of protein intake beyond the RDA on several age-related health outcomes, among which cognitive decline, has been suggested by an increasing number of studies.

An association between protein intake and cognitive functioning may specifically be due to certain amino acids that are common constituents of protein-rich foods. Of the individual amino acids related to brain function, the main interest is in two of the large neutral amino acids (LNAAs): tyrosine and tryptophan. Tryptophan is found in nearly all protein containing foods and is the precursor of the neurotransmitter serotonin. The functioning of the serotonergic system in relation to cognitive functioning has been studied using acute tryptophan depletion (ATD). The effects of ATD on cognitive functioning have been reviewed in detail; based on a total of 66 studies, Mendelsohn concluded that ATD impairs the consolidation of episodic memory for verbal information (Mendelsohn et al. 2009). Other types of memory, such as semantic memory and working memory, as well as attention and executive functioning seem to be less or not affected by ATD. Serotonergic stimulation by increasing tryptophan levels may mirror the effects of ATD and evoke beneficial cognitive changes. Tyrosine is one of the conditionally essential amino acids and is the precursor of the catecholine neurotransmitters dopamine (DA), norepinephrine and epinephrine (Fernstrom and Fernstrom 2007). These tyrosine-dependent neurotransmitters affect a variety of central and peripheral functions and particularly the DA neurons located in the prefrontal cortex are susceptible because of their rapid firing rate. These DA neurons are involved in among others stress response and working memory (Tam and Roth 1997). Stressful conditions and aging are both characterized by neurotransmitter depletion and impaired behavioral and cognitive functioning, which may be restored by increasing the availability of the precursor tyrosine.

Unlike almost all other neurotransmitter biosynthetic pathways, concentrations of brain tryptophan as well as brain tyrosine are readily modified by dietary intake. This relation is observed when either tryptophan or tyrosine is administered directly (Ashcroft et al. 1965), or by consumption of protein-containing foods or other amino acids that share the competitive transporter for uptake into the brain from the blood (Fernstrom and Fernstrom 1987; Fernstrom and Fernstrom 1995). Consequently, these concentrations and thus the availability of tryptophan or tyrosine to brain neurons also modify the synthesis rates and release of the neurotransmitters they are precursors for; i.e., serotonin and the catecholamine neurotransmitters, respectively (Fernstrom 1983). The changes in neurotransmitter synthesis are thought to be functionally important, because they occur very rapidly. For example, after injection of tryptophan or other LNAAs, neuronal serotonin release changes within 60–90 min in the rat hippocampus (Sharp et al. 1992). However, the LNAAs tryptophan, tyrosine and phenylalanine and also the branched-chain amino acids leucine, isoleucine and valine enter the brain via the same transporter located at the BBB. This transporter is saturable and competitive, so raising the blood concentration of one LNAA raises the brain uptake of that LNAA, but reduces those of the others (Fernstrom 2013).

Despite several plausible pathways that would suggest a role for protein intake on cognitive performance, this relation has barely been studied. The current literature review focuses on studies describing the role of total protein and the amino acids tryptophan and tyrosine in relation to cognitive functioning, cognitive decline, and dementia.

Methods

Pubmed was searched up to June 2013 for papers that matched with (combinations of) the following search terms: cognition, cognitive functioning, cognitive decline, memory, attention, executive functioning, mental health, dementia, brain, protein, amino acids, tyrosine, and tryptophan. The search was restricted to papers of studies that were performed in humans and were written in English. In addition, lists of references in the identified publications were searched for additional relevant articles.

Results

Our search yielded a total of eight observational studies that examined the association between dietary protein and cognitive functioning, of which four were cross-sectional, one prospective and three case–control studies. We found three intervention studies on the effect of protein consumption on cognitive functioning. On the effects of individual amino acids on cognitive functioning, a total of 23 studies were found, of which 14 investigated tryptophan loading effects and nine the effect of tyrosine on cognitive functioning.

Evidence for a role of dietary protein in relation to cognitive functioning

Evidence from observational studies

Eight observational studies investigated the association between protein intake and cognitive performance (Table 1). The largest, most recent and only prospective study (median follow-up 3.7 years) has been performed in

Table 1 Summary of observational studies assessing the association between protein intake and cognitive performance in elderly populations

Author, year (study)	Study population (*n*)	Design	Nutritional status	Measure(s) of cognitive function	Covariate(s)	Results
Roberts et al. (2012) (Mayo Clinic Study of Aging)	Population-based prospective cohort of elderly, 70–89 years ($n = 937$)	Prospective: follow-up 3.7 (2.5–3.9) years	128-item FFQ	CDR, short test of mental status, nine tests to assess four cognitive domains: memory, executive function, language, visuospatial skills	Gender, education, propensity to participate at baseline, total caloric intake, APOEε4 status, type II diabetes, BMI, smoking, depressive symptoms, exercise, stroke, marital status, alcohol intake, occupation	High % protein intake was associated with a reduced risk of MCI or dementia [upper quartile 0.79 (0.52–1.20), p trend 0.03) in the fully adjusted models
Salerno-Kennedy and Cashman (2007)	First-degree blood relatives of AD patients, mean age 57.7 (SD 9.4) years ($n = 44$)	Cross-sectional	Semi-quantitative FFQ	MMSE	No adjustment	No significant difference in protein intake between normal (>24) and low (17–24) MMSE scores ($p = 0.13$)
La Rue et al. (1997)	Elderly community residents, 66–90 years ($n = 137$)	Cross-sectional	3-day dietary records	Abstraction Scale, Logical Memory and Visual Reproduction test, Rey-Osterrieth Complex Figure test	Body weight	Higher protein intake significantly correlates with memory scores on the Rey-Osterrieth Recall and Logical memory tests ($r = 0.19$ and $r = 0.20$, $p < 0.05$)
Ortega et al. (1997)	Non-cognitively impaired elderly, 65–90 years ($n = 260$)	Cross-sectional	7-day weighed food records	MMSE, PMSQ	No adjustment	No difference in protein intake between adequate (≥28) and unsatisfactory (<28) MMSE scores and PMSQ results (PMSQ > 0 or = 0)
Goodwin et al. (1983)	Non-institutionalized men and women, >60 years ($n = 260$)	Cross-sectional	3-day food records	Wechsler Memory test, Halstead-Reitan Categories test	No adjustment	Lower protein intake was associated with lower scores on memory tests ($p < 0.01$)

FFQ Food Frequency Questionnaire, *CDR* Clinical Dementia Rating Scale, *AD* Alzheimer's disease, *MMSE* Mini-Mental State Examination, *PMSQ* Pfeiffer's Mental Status Questionnaire

Table 2 Summary of case–control studies assessing the association between protein intake and cognitive performance in elderly populations

Study/ author, year	Study population (n)	Nutritional status	Results
Winograd et al. (1991)	Community-dwelling patients with SDAT ($n = 35$) and healthy controls ($n = 29$)	3-day estimated dietary record	No difference in protein intake between cases and controls. Cognitive function also did not correlate with protein intake
Nes et al. (1988)	Independently living, demented elderly ($n = 16$) and a sex and age-matched control group	3-day weighed dietary record	Women with dementia had lower protein intakes ($p < 0.05$). Serum levels of protein were not different
Thomas et al. (1986)	Severely demented patients ($n = 23$) and matched aged controls	3-day weighed intake	Lower mean protein intake in the patient group. Also reduced plasma tryptophan concentrations

SDAT Senile dementia of the Alzheimer type

Table 3 Summary of intervention studies assessing the effect of protein on cognitive performance

Author, year	Study population (n)	Design and intervention	Measure(s) of cognitive function	Results
Jakobsen et al. (2011)	Young, healthy males, 19–31 years ($n = 23$)	Randomized intervention with usual versus a high protein diet for 3 weeks	ACE, reaction time (three tests from the TAP	High protein diet had a positive effect on reaction time (estimated difference -25.5 ± 11.6 ms; 95 % CI -49.7 to -1.2, $p = 0.04$)
Fischer et al. (2002)	Young, healthy male students ($n = 15$)	Cross-over design with three different carbohydrate to protein ratios	Choice reaction time, combi test, multitask test	Improved overall cognitive performance, shorter choice reaction time [$F(3,33) = 2.9$, $p < 0.05$] and better accuracy in short-term memory [$F(2,19) = 3.6$, $p < 0.05$] after the protein-rich meal
Kaplan et al. (2001)	Elderly men and women, 61–79 years ($n = 22$)	Cross-over design with a high protein (whey) drink, high carbohydrate drink, high fat drink or placebo	RAVLT, Trails A and B, attention test	All drinks improved immediate (p trend $= 0.04$) and delayed recall ($p < 0.0001$) compared to placebo. Protein reduced the rate of forgetting ($p = 0.002$)

ACE Addenbrooke Cognitive Examination, *TAP* Testbattery for attentional performance, *RAVLT* Rey auditory verbal learning test

937 elderly in whom a higher protein intake was associated with a 21 % reduced risk of MCI or dementia after adjustment for multiple variables [HR 0.79 (95 % CI 0.52–1.20), p trend $= 0.03$) (Roberts et al. 2012). In a small study in first-degree blood relatives of AD patients ($n = 44$), no difference in protein intake was found between individuals with normal (MMSE > 24) and individuals with low Mini-Mental State Examination (MMSE) scores ($p = 0.13$) (Salerno-Kennedy and Cashman 2007). Conversely, La Rue et al. found a significant positive correlation between two different memory scores and protein intake ($r = 0.19$ and $r = 0.20$, respectively, after adjustment for body weight, $p < 0.05$) in 137 elderly community residents (La Rue et al. 1997). In another study, performed in non-cognitively impaired elderly, also no difference in protein intake was observed between subjects with adequate and with non-adequate scores on the MMSE and Pfeiffer's Mental Status Questionnaire (PMSQ) (Ortega et al. 1997). Goodwin and colleagues showed that older adults with the lowest 5 and 10 % of intake protein intakes had lower scores on verbal memory tests than elderly in the top 90 % ($p < 0.01$) (Goodwin et al. 1983).

Three case–control studies were performed (Table 2), of which two observed lower protein intakes in demented patients compared to age-matched controls ($p < 0.05$) (Thomas et al. 1986; Nes et al. 1988). The third study showed no difference in protein intake (Winograd et al. 1991).

Evidence from clinical trials

Only three intervention studies have been performed, of which one in elderly (Kaplan et al. 2001) and two in healthy young adults (Table 3) (Fischer et al. 2002; Jakobsen et al. 2011). A high protein diet improved reaction time in healthy young men after 3 weeks of intervention (estimated difference -25.5 ± 11.6 ms; 95 %CI -49.7 to -1.2, $p = 0.04$) (Jakobsen et al. 2011). However, the authors of this study suggested that the beneficial effect may also have been due to elevated levels of vitamin D, B2, B6 and B12 intake compared to the control group.

Table 4 Summary of intervention studies assessing the effect of tryptophan on cognitive performance

Author, year	Study population (n)	Design and intervention	Measure(s) of cognitive function	Results
Morgan et al. (2007)	Healthy subjects, 24–33 years ($n = 8$)	Randomized, double-blind, placebo-controlled, cross-over design using 30 mg/kg body mass tryptophan	Modified version of the counting Stroop test	Non-significant trend for slower reaction time after tryptophan intake
Dougherty et al. (2007)	Healthy adults, 21–40 years ($n = 18$)	Double-blind, placebo-controlled, cross-over design, 50 g tryptophan	Immediate memory task (impulsivity)	Less commission errors after the tryptophan load compared to tryptophan depletion ($p = 0.008$)
Booij et al. (2006)	Recovered depressed patients ($n = 23$) and healthy matched controls ($n = 20$), 18–65 years	Randomized, double-blind cross-over design. Intervention with meals rich in tryptophan-rich α-lactalbumin or casein protein	Sternberg memory scanning task, abstract patterns recognition task, Stroop color word task, left/right choice reaction time, tower of London	Tryptophan-rich meal improved abstract visual memory [$F(4,38) = 3.06$, $p = 0.03$] and impaired simple motor performance [$F(2,39) = 3.47$, $p = 0.02$]
Schmitt et al. (2005)	Females with premenstrual symptoms, 18–45 years ($n = 16$)	Double-blind, placebo-controlled, cross-over design using 40 g α-lactalbumin or casein protein drink	Word learning test, abstract visual pattern learning task, computerized tower of London	In the premenstrual phase α-lactalbumin improved long-term memory for abstract figures, but not for words, no effects on planning function
Markus et al. (2005)	Healthy subjects with ($n = 14$) or without ($n = 14$) mild sleep complaints, mean age 22 years	Double-blind, placebo-controlled, cross-over study. Evening diet containing either tryptophan-rich α-lactalbumin or trytophan-low protein	Continuous performance task	Tryptophan-rich meal improved reaction time ($p = 0.014$) and reduced the number of errors ($p = 0.048$) in subjects with sleep complaints
Sobczak et al. (2003)	Healthy first-degree relatives of bipolar patients ($n = 30$) and matched controls ($n = 15$), mean age 41 years	Double-blind, placebo-controlled, cross-over design using an intravenous tryptophan challenge	Computerized tower of London, Go/No go task, Stroop color word task, left/right choice reaction, dichotic listening task, motor choice reaction	In both groups, tryptophan impaired memory [delayed recall $F(1,43) = 7.76$, $p < 0.01$] and recognition [$F(1,43) = 4.15$, $p < 0.05$)] and psychomotor performance [$F(3,40) = 21.50$, $p < 0.01$]
Markus et al. (2002)	High-($n = 23$) and low-($n = 29$) stress-prone subjects	Double-blind, placebo-controlled, cross-over design. 40 g α-lactalbumin-rich drink or sodium caseinate	Sternberg memory scanning	Memory scanning improved after the α-lactalbumin-rich drink ($p = 0.019$), but only in the high-stress subjects
Luciana et al. (2001)	Healthy adults, 18–31 years ($n = 19$)	Double-blind, placebo-controlled, cross-over design, liquid mixture with 10.3 g L-tryptophan	Spatial working memory, affective working memory, verbal fluency, digit span, spatial span, letter cancellation task, finger tapping task, grooved pegboard test	Reduction in working memory for verbal and affective stimuli compared to tryptophan depletion and subtle impairment in fine motor coordination and enhancement of attention
Markus et al. (1999)	High-($n = 22$) and low ($n = 21$) stress-prone subjects, 19–26 years	Double-blind, placebo-controlled, cross-over study comparing a carbohydrate-rich/protein-poor versus a carbohydrate-poor/protein-rich diet	Sternberg memory scanning task	Improved memory scanning with carbohydrate-rich/protein-poor diet, but only in high-stress subjects
Cunliffe et al. (1998)	Healthy volunteers ($n = 6$)	Double-blind, placebo-controlled, cross-over design with 30 mg/kg body weight tryptophan or placebo	Simple reaction time	Tryptophan slowed reaction time performance

Table 4 continued

Author, year	Study population (n)	Design and intervention	Measure(s) of cognitive function	Results
Markus et al. (1998)	Subjects with high ($n = 24$) or low stress-proneness ($n = 24$), 18–25 years	Double-blind, placebo-controlled, cross-over design with a carbohydrate-rich/protein-poor versus a carbohydrate-poor/protein-rich food	Sternberg memory scanning task	Reaction time was impaired after the carbohydrate-rich/protein-poor food [$F(1,46) = 6.780$, $p = 0.012$] compared to the reaction time after the carbohydrate-poor/protein-rich food
Sayegh et al. (1995)	Premenstrual women with premenstrual syndrome, 18–45 years ($n = 24$)	Double-blind, placebo-controlled, cross-over study with a carbohydrate-rich beverage compared to two isocaloric products	Verbal recognition memory, verbal retrieval	Improved verbal-recognition memory ($p < 0.05$)
Winokur et al. (1986)	Healthy males ($n = 11$)	Double-blind, placebo-controlled, cross-over design with 5, 7.5, and 10 g of L-tryptophan or saline were administered by infusion	Symbol copying test	Tryptophan caused a dose-dependent impairment in psychomotor performance
Lieberman et al. (1985)	Healthy men, 18–45 years ($n = 20$)	Double-blind, placebo-controlled, cross-over design, 50 mg/kg tryptophan or 100 mg/kg tyrosine	Simple auditory reaction time, two-choice visual reaction time, grooved pegboard test, Thurstone tapping test	Tryptophan increased reaction time ($p < 0.05$) compared to tyrosine. No changes of tryptophan supplementation compared to placebo

Fisher and colleagues showed an improvement in overall cognitive performance, particularly a shorter choice reaction time [$F(3,33) = 2.9$, $p < 0.05$] and better accuracy in short-term memory [$F(2,19) = 3.6$, $p < 0.05$] after a protein-rich meal compared to a high carbohydrate meal in healthy male students (Fischer et al. 2002). In another repeated measures cross-over study, 22 elderly men and women consumed a high protein (whey protein isolate), a high carbohydrate (glucose), a high fat (safflower oil), or a placebo drink (Kaplan et al. 2001). All drinks, so also the high protein drink, improved immediate (p trend $= 0.04$) and delayed recall ($p < 0.0001$) compared to placebo and the protein drink additionally reduced the rate of forgetting ($p = 0.002$).

Evidence for a role of individual amino acids in relation to cognitive functioning

Tryptophan

A total of 14 studies were found that investigated the effect of extra tryptophan administration on cognitive functioning (Table 4). Increasing tryptophan levels were achieved by administration of pure tryptophan (seven studies), through consumption of tryptophan-rich α-lactalbumin (four studies) or by increasing carbohydrate intake (three studies). All these methods increase the tryptophan/LNAA ratio and thereby increase brain tryptophan resulting in an increase in serotonin synthesis and activity.

All studies that administrated pure tryptophan were performed in healthy, young adults (Lieberman et al. 1985; Winokur et al. 1986; Cunliffe et al. 1998; Luciana et al. 2001; Dougherty et al. 2007; Morgan et al. 2007) and one in first-degree relatives of bipolar disorder patients (Sobczak et al. 2003). Psychomotor performance was impaired after tryptophan administration in five of the seven studies, whereas Dougherty only observed less commission errors after the tryptophan load (Dougherty et al. 2007) and Lieberman observed no changes at all (Lieberman et al. 1985). Impaired memory function was found in the studies of Sobczak and Luciana (Luciana et al. 2001; Sobczak et al. 2003).

A diet enriched with α-lactalbumin improved abstract visual memory ($F(3,38) = 3.06$, $p = 0.03$) in recovered depressed patients and in the matched controls (Booij et al. 2006) and also improved memory functions in females with premenstrual symptoms (Schmitt et al. 2005) and stress-vulnerable subjects (Markus et al. 2002). Evening intake of α-lactalbumin has been shown to improve morning alertness as measured with improved reaction time ($p < 0.014$) and a reduced number of errors ($p < 0.048$) in subjects with sleep complaints (Markus et al. 2005). In contrast, in the study of Booij et al. a detrimental effect was found on simple motor performance [$F(2,39) = 3.47$, $p = 0.02$]. This controversy was probably caused by improved sleep due to increased tryptophan levels in the evening, whereas increased tryptophan levels during the day made sleepy and, therefore, slow in motor performance.

Table 5 Summary of intervention studies assessing the effect of tyrosine on cognitive performance under stress conditions

Author, year	Study population (n)	Design and intervention	Measure(s) of cognitive function	Results
Mahoney et al. (2007)	Military members, 18–35 years ($n = 19$)	Double-blind, cross-over design with three test conditions: cold exposure (10 °C) with or without tyrosine supplementation (300 mg/kg body weight) versus control (35 °C/placebo)	Visual vigilance, 4-choice visual reaction time, delayed match-to-sample	After consumption of tyrosine, more correct responses on match-to-sample memory measure and less study time ($p < 0.05$) during cold exposure compared to placebo
Magill et al. (2003)	Healthy young men, 18–35 years ($n = 76$)	Tests were performed several times before, during and after sleep deprivation and medication. On medication day subjects received either tyrosine (150 mg/kg), caffeine (300 mg/70 kg), phentermine (37.5 mg) or D-amphetamine (20 mg) or placebo	Visual scanning, running memory, logical reasoning, mathematical processing, Stroop color word task, four-choice serial reaction time, time wall take, pursuit tracking, visual vigilance, Trails (B) task, long-term memory	Tyrosine improved performance on several tests, although less effective than D-amphetamine
Thomas et al. (1999)	Men and women, 20–38 years ($n = 20$)	Double-blind, cross-over design, 150 mg/kg tyrosine or placebo, multi-tasking environment	Sternberg memory task, arithmetic task, cursor reset task, tone detection	Tyrosine enhanced accuracy and decreased frequency of retrieval on the working memory task. No changes on the other tasks of the multiple task or simple task battery
Deijen et al. (1999)	Cadets, 19–26 years ($n = 21$)	Double-blind design with a protein-rich drink containing 2 g of tyrosine or an iso-caloric carbohydrate drink for 5 consecutive days during a combat training course	Four computer tasks from the Taskomat battery: memory comparison task, tracking task, continuous memory task, double task	The group with the tyrosine-rich drink performed better on the memory and tracking task
Neri et al. (1995)	US marines, 18–25 years ($n = 21$)	Double-blind design, 150 mg/kg tyrosine or placebo during 1 night's sleep loss	Psychomotor task, high-event rate vigilance task	Tyrosine improved performance on a psychomotor task and a high-event rate vigilance task
Deijen and Orlebeke (1994)	Healthy young subjects, 23–35 years ($n = 16$)	Double-blind, cross-over design, 100 mg/kg tyrosine or placebo during exposure of 90 dB noise	Cognitrone, Vienna determination unit, vigilance/peripheral perception, Stroop color word test, digit span	Significant treatment effects of tyrosine on the digit span [$F(1,15) = 3.46$, $p < 0.05$] and Stroop task [$F(1,15) = 4.18$, $p < 0.03$]
Shurtleff et al. (1994)	Healthy male volunteers, 23–37 years ($n = 8$)	Double-blind, cross-over design, four condition test block: 150 mg/kg tyrosine at 4 or 22 °C and placebo at 4 or 22 °C.	Delayed matching-to-sample task	Tyrosine reversed cold-induced working memory deficit ($p = 0.0001$)
Banderet and Lieberman (1989)	Male US army militaries, 18–20 years ($n = 23$)	Double-blind, placebo-controlled, cross-over design, 100 mg/kg tyrosine or placebo during 4.5-h exposure to cold and hypoxia (15 °C and 4,200 m or 15 °C and 4,700 m)	Sustained attention task, applying prior knowledge to problems, processing spatial and verbal information, performing mathematical calculations, making decisions, summing problems with 2-digit numbers, sequence coding, map compass applications, number comparison task, pattern recognition, tower task, choice reaction time, dual task vigilance task	Treatment with tyrosine reversed adverse effect of cold and high altitude on all cognitive function tests in either or both the lesser or greater environmental stressor
Lieberman et al. (1985)	Healthy men, 18–45 years ($n = 20$)	Double-blind, placebo-controlled, cross-over design, 50 mg/kg tryptophan or 100 mg/kg tyrosine or placebo	Simple auditory reaction time, two-choice visual reaction time, grooved pegboard test, thurstone tapping test	No effect of tyrosine supplementation compared to placebo on any of the cognitive tests. Only significant decrease in reaction time compared to tryptophan ($p < 0.05$)

The three studies comparing carbohydrate-poor, protein-rich food with carbohydrate-rich, protein-poor food showed similar results as the studies that administered pure tryptophan or α-lactalbumin. Verbal recognition memory (Sayegh et al. 1995) and memory scanning (Markus et al. 1999) improved after the carbohydrate-rich food, but in the latter study only in stress-prone subjects. In stress-prone subjects, reaction time was impaired after the carbohydrate-poor/protein-rich food compared to carbohydrate-rich, protein-poor food (Markus et al. 1998).

Tyrosine

We found nine studies that investigated the effects of tyrosine administration (Table 5). These effects have mainly been investigated in healthy humans under acute stressful conditions such as cold-induced stress, loud noise disturbance, or a multitasking environment. Tyrosine is expected to be particularly beneficial under these conditions, because stress depletes brain dopamine and norepinephrine and causes a decline in cognitive function. Most of the studies, except the study from Lieberman et al. (1985), observed improvements in cognitive functioning on at least some of the cognitive tests that were performed after tyrosine administration under these stressful conditions (Banderet and Lieberman 1989; Deijen and Orlebeke 1994; Deijen et al. 1999). Tyrosine improved the working memory deficit that is induced by cold-stress (Shurtleff et al. 1994; Mahoney et al. 2007) and also in the multitask environment (Thomas et al. 1999) with the loud noise stressor (Deijen and Orlebeke 1994) and under a combination of stressful conditions (Deijen et al. 1999), beneficial effects on working memory were observed. In addition, beneficial effects on reaction time were observed in some studies (Banderet and Lieberman 1989; Deijen and Orlebeke 1994; Mahoney et al. 2007). Another critical condition where tyrosine may affect cognitive performance is after sleep deprivation, where, in particular, effects on psychomotor time and vigilance were found (Neri et al. 1995; Magill et al. 2003).

All results of tyrosine supplementation on cognitive functioning described thus far are from studies performed in relatively highly demanding conditions. Potential effects under normal circumstances are not clear, because they have not been investigated thus far. In relation to age-related cognitive decline, tyrosine effects are also very interesting, because aging is associated with a loss of dopamine. Findings from studies in aging monkeys showed a dopamine decline in the brain, especially in the prefrontal cortex (Goldman-Rakic and Brown 1981; Arnsten et al. 1995). These findings merit further research of tyrosine supplementation in elderly populations.

Conclusion and perspectives

In this literature review, studies that examined the role of total protein and some individual amino acids in relation to cognitive functioning, cognitive decline, and dementia were described. The studies on protein intake and cognitive performance were performed in elderly, community-dwelling populations. Two case–control studies were performed in demented elderly. Although there are only very few observational studies and associations were not very strong, in some studies already small differences in intake were associated with cognitive decline. Moreover, elderly people may be particularly vulnerable to inadequate amounts of protein, because their reduced reservoir in the form of skeletal muscle mass leads to a reduced whole-body protein synthesis, which in turn may lead to decreased capacity to adapt to decreased dietary protein intake and reduced availability of neurotransmitter precursors (Young 1990). These findings merit further research on the association between cognitive functioning and protein status in elderly populations who are cognitively impaired and/or at risk of malnutrition. In particular, more prospective studies and clinical trials are warranted. Most of the studies performed so far were cross-sectional and, therefore, it is not clear whether the difference in intake preceded impaired cognition or whether it was the result of impaired cognition. In observational studies, also relevant confounding factors should be taken into account, which was not always done in the described studies.

The effect of total protein on cognitive functioning is probably attributed to specific amino acids that are common constituents of protein-rich foods, such as tyrosine and tryptophan. In the studies that investigated tryptophan loading, the majority of the studies showed beneficial effects on memory performance and detrimental effects on speed and motor performance. Beneficial effects on memory were typically shown in vulnerable subjects, such as depressed or stress-vulnerable individuals and women with premenstrual complaints. In these individuals, serotonergic disturbances causing a hypo-serotonergic state have been shown. Tryptophan loading then moves serotonin towards the optimal level and improves performance, whereas serotonin levels in healthy subjects are moved beyond the optimal level and have no or a detrimental effect on performance. It would be very interesting to examine the effects of tryptophan in elderly, because serotonin activity also declines with aging (McEntee and Crook 1991). Impairments in speed-related tasks may be due to the sleep promoting effects of tryptophan (Pilcher and Huffcutt 1996). This knowledge could be applied to determine the best timing of tryptophan administration. When given before going to bed, it may induce a better sleep and a subsequent better performance on speed-related

tasks the following morning, but when given during daytime and investigating acute tryptophan effects, the speed slows down because of sleepiness. Increases in plasma tryptophan were achieved, giving tryptophan the advantage in competition with other LNAA for access to the brain. Methods to increase tryptophan levels and also the amounts of tryptophan raising agents that were used were very heterogeneous and are, therefore, difficult to compare and translate into a general advice on dosage. Furthermore, research on the long-term effects of tryptophan and α-lactalbumin needs to be performed, because also this information is lacking (Booij et al. 2006).

All studies performed on tyrosine effects were clinical studies, mostly placebo-controlled, and involved young men and women, often soldiers. There are no data on the actions of tyrosine in elderly or cognitively impaired individuals, but effects in younger adults under stressful conditions are pretty consistent and promising. Aging can be seen as comparable physical state as stress, as both are characterized by a decline in dopamine concentrations (Backman et al. 2006). For tyrosine, it is known that an effect on cognitive functioning could be found 60–90 min after ingestion and lasts for about 3 h (Deijen and Orlebeke 1994). Usually an amount of 150 mg/kg was used, which is based on animal studies where clear dose–response relationships have been observed (Yeghiayan et al. 2001). To date, it has been difficult to show this in humans. Also for the other amino acids and total protein intake, it would be useful to know how much is needed to elicit a particular effect. Furthermore, it is not known how often the treatment should be given to maintain the observed effect. In addition, especially for tyrosine it is important to know whether the effect persists if the treatment is provided chronically, since neurons can become unresponsive to additional tyrosine if their firing frequency slows tolerance may develop.

We usually consume proteins with heterogeneous amounts of amino acids, which makes it more complicated to disentangle specific effects of individual amino acids. Moreover, the availability of the specific precursor amino acids for brain neurotransmitters is highly dependent on each other, because the amino acids are competing with the same carrier to enter the BBB. To increase and maximise availability of tyrosine or tryptophan, keeping the right ratio between the amino acid of interest and its competing amino acids has to be taken into account in supplementation studies.

Similar to the research field of other nutritional effects on cognitive functioning, also in the field of the impact of protein a large and heterogeneous battery of neuropsychological tests has been used. This heterogeneity hampers a good comparison of studies.

The number of studies on protein intake in relation to cognitive functioning is unexpectedly small and many of the studies have already been performed quite long ago. All together, the total body of evidence is limited and the results are mixed. Therefore, no firm conclusions on the impact of protein intake on cognitive functioning can be drawn. With respect to tryptophan and tyrosine, the evidence in subjects that are vulnerable with respect to neurotransmitter concentrations is quite consistent. Evidence in elderly populations is lacking and due to the declines in serotonin as well as dopamine with aging, this would be a very interesting research group for new studies. All together, the available evidence together with the plausibility of the mechanisms behind the associations merits further research in the field of protein and amino acids in relation to cognitive functioning.

Conflict of interest The authors declare that they have no conflict of interest and all authors have contributed to and approved the final version of the manuscript.

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