RESEARCH PAPER

The effects of interactions between selenium and zinc serum concentration and *SEP15* and *SLC30A3* gene polymorphisms on memory scores in a population of mature and elderly adults

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Abstract Memory deficits are common during aging, but little is known about the impact of environmental and genetic variables on memory. The genes *SLC30A3* and *SEP15* are, respectively, responsible for transporting zinc and selenium, micronutrients that are neuroprotective agents. The aim of this study was to investigate the effect of nutrigenetic interactions on the memory scores of volunteers more than 50 years old. For this cross-sectional study, 240 individuals were enrolled. Micronutrient dosage was determined using atomic absorption spectrophotometry. The SNPs rs5859, rs5854, and rs561104 in *SEP15* and rs73924411 and rs11126936 in *SLC30A3* were determined by real-time PCR. The evaluations of verbal and visual memory were performed using the Weschler Memory Scale-revised and the Rey's verbal learning test. A gene versus nutrient interaction was observed for *SLC30A3* rs73924411 and zinc concentration. Carriers of the T allele had higher scores for short-term and long-term verbal memories than CC homozygotes only when zinc serum concentration was below the recommended level (p value for the interaction for short-term verbal memory = 0.011, p value for the interaction for long-term verbal memory = 0.039). For *SEP15*, C carriers of the rs5845 SNP allele had higher verbal learning memory scores than TT homozygotes (0.13 ± 1.13 vs. -1.10 ± 1.20, $p = 0.034$). Our results suggest the influence of genetic polymorphisms on memory score and identify gene versus nutrient interactions between zinc serum concentration and memory score.

Keywords Memory · Zinc · Selenium · *SLC30A3* · *SEP15* and polymorphism

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Introduction

There is a global consensus that aging may be associated with a rapid cognitive decline. Age-associated memory impairment (AAMI) was first described by Crook et al. (1986) at the National Institute of Mental Health (NIMH) and is not considered a pathological condition (Crook et al. 1986). This classification is assigned to individuals who exhibit memory impairment but no strong deficit, once there is no independence compromise, may be described as memory loss or develop into serious diseases, such as Alzheimer's disease.

Although it is well established that the mnemonics processes decline with age, it has become clear that both genetic

and environmental factors influence the development of these phenotypes (Nilsson et al. 2002; Benton et al. 2005). Although the findings are not unanimous, observational studies generally identify a positive correlation between memory score and dietary antioxidant intake (Kesse-Guyot et al. 2011). The micronutrients selenium and zinc are important antioxidants, and each element must be transported to perform its brain functions. *SEP15* is responsible for the transport of selenium, and single nucleotide polymorphisms (SNPs) are linked to changes in selenium serum concentration. Two SNPs in the 3′ untranslated region of *SEP15* (rs5859, G>A and rs5845, C>T) and the SNP rs561104 (T>C) in first intron were found to decrease the efficiency of the selenocysteine insertion sequence element at higher concentrations of selenium (Hu et al. 2001; Penney et al. 2010). The interaction of zinc with specific gene products makes it an important biochemical mediator and gives it the potential to have regulatory functions. The zinc transporter gene *SLC30A3* is expressed in regions of the brain that are important for steps in memory formation, specially the cerebral cortex and hippocampus (Seve et al. 2004; Frederickson et al. 2005). Besides, data from experimental studies addressing the effect of ZnT3 ablation in ZnT3 knock-out mice demonstrated that these animals exhibit age-dependent deficits in learning and memory, leading a cognitive loss (Adlard et al. 2010), abnormalities in associative fear memory and extinction (Martel et al. 2010), and that ZnT3 is required for hippocampus-dependent memory (Sindreu et al. 2011). Considering the relevance of *SLC30A3* gene on memory and cognition, two commonly occurring SNPs in this gene, rs11126936 (A>G) and rs73924411 (C>T), were selected for analysis. They were located at two separated haplotypes of *SLC30A3* gene (the rs73924411 located at intron 6 is whiting a 3 kb haplotype that extends from exon 2 to exon 8 and rs11126936, located at intron 1, on a separate haplotype; http://hapmap.ncbi.nlm.nih.gov).

To date, few studies have addressed associations between *SLC30A3* and *SEP15* gene polymorphisms, and this work is one of the first to investigate the neurobiological influences of these polymorphisms and their interactions with zinc and selenium serum concentrations. The aim of the study was to investigate the influence of select nutrigenetic interactions on memory scores in individuals over 50 years old.

Methodology

Study design and subjects

The sample was composed of men and women (313 individuals in total) who were selected according to the inclusion criteria for memory decline associated with age that are as follows: minimum age of 50 years, absence of dementia, owning intellect enough to continue production, present complaint of progressive memory loss, show objective evidence of memory deficits on tests of specific performance as determined by the National Institute of Mental Health (NIMH; Emery 2011). The volunteers were recruited through advertisements and interviewed at Feevale University and the Federal University of Health Sciences of Porto Alegre (Rio Grande do Sul, Brazil). This cross-sectional study involved collecting blood and information about lifestyle and evaluating neurocognitive tests for memory. The volunteers were asked about the occurrence of neurological disease or psychiatric disorders and the use of anxiolytic drugs. The Beck Depression and Anxiety Inventory and the Lipp Inventory of Stress were used to exclude volunteers who presented the indicated symptoms. Volunteers were excluded when presenting with lower estimate intellectual function (QI) ≤70, and individuals who use vitamin supplements containing the micronutrients of interest were also excluded.

Using these exclusion criteria, 73 individuals were removed from the study. The Ethics Committee of Feevale University and the Federal University of Health Sciences of Porto Alegre approved the study protocol. Written and signed consent was required from every subject included in the study.

Neuropsychological measures

Evaluations of verbal and visual memory were performed using the Weschler Memory Scale-revised (WMS-R; Weschler 1987). For each test, the final data were transformed into standard deviations of the mean as a function of age, resulting in a range from −4 to +4. Memory was considered to be in deficit only when scores were below −1, i.e., individuals with values of −1 or below exhibited a disorder in forming the specific memory or learning ability under evaluation. To assess verbal learning and the ability to store new information, we used Rey's verbal learning test. Scores were recorded as a function of age, just as in the WMS-R testing battery. Evaluations lasted an average of 1 h and were conducted by psychology students trained and supervised by professors from both universities.

Selenium and zinc serum concentrations

For the analysis of selenium and zinc serum micronutrients, blood was stored in metal-free tubes (BD Vacutainer®, Trace Elements Serum). Blood was allowed to clot at room temperature for 30 min according to the manufacturer's instructions. Once the blood had clotted completely, it was centrifuged for 10 min at 2,500 rpm. After centrifugation,

the serum was fractionated into specific transport tubes and frozen at −80 °C until the completion of concentration measurements. The samples were sent to a third-party laboratory that analyzed the samples using standardized methods, as previously described (Jacobson and Lockitch 1988; Rodriguez et al. 1989). Serum zinc concentrations were measured by atomic absorption spectrometry by flame with standard curve from 0.2 to 1.5 mg/L and linearity from 0.2 to 1.5 mg/L, and a detection limit of 0.01 mg/L. Selenium concentration was measured by for atomic absorption spectrometry in a graphite furnace, with a linearity of 40 µg/dL, standard curve from 4 to 40 µg/dL, and a detection limit of 0.1 µg/dL. Serum reference values were 0.70–1.50 mg/L for zinc and 4.6–14.3 µg/dL for selenium (Wu and Tietz 2006). For both zinc and selenium, levels below the cutoff concentrations were considered low, levels between the reference values were considered normal, and values above the cutoffs were considered high. These cutoff points were established in order to determine differences in serum concentrations between genotype groups on memory scores. Zinc concentrations were measured for 110 samples, while selenium concentrations were measured for 70 samples because the amount of serum obtained after centrifugation was insufficient to allow for the measurement of both micronutrients. The blood samples were taken in the afternoon, since during the overnight fast the concentration of serum zinc increases slightly, so the highest levels of the day are generally seen in the morning (Couturier et al. 1988). In addition, in following the meal, there is an immediate injection increase, after which the concentration declines progressively for the next 4 h. Thus, the collection was performed 2 h after the last meal (Hambidge et al. 1989).

DNA extraction and genotyping

Genomic DNA was isolated from peripheral blood leukocytes using a standard salting-out procedure (Lahiri and Nurnberg 1991). DNA quality and purity were analyzed by spectrophotometry using the Nanodrop ND-1000. The *SEP15* SNPs rs5859, rs5854, and rs561104 and the *SLC30A3* SNPs rs73924411 and rs11126936 were identified by allelic discrimination using the TaqMan 5′ nuclease assay (Real-Time PCR, Applied Biosystems, California, USA).

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation. Allele frequencies were estimated by gene counting. The agreement of genotype frequencies with Hardy–Weinberg equilibrium expectations was tested using χ^2 tests. Genotype distributions between groups

(normal or deficit) were compared by χ^2 or Fisher's exact test. After adjustment for gender and level of education through linear regression, specific memory scores (short-term and long-term verbal memories, short-term and long-term visual memories and verbal learning) were compared among genotypes by Student's t test or ANOVA. The effects of the interaction of zinc or selenium serum concentration with gene polymorphisms on specific memory scores were measured using general linear models. Corrections for multiple testing were performed using the Benjamini–Hochberg method for the calculation of false discovery ratio (FDR) p values, and corrected p values were also inserted in tables and text when significant p values were detected in analyses. A $p < 0.05$ was considered significant. Statistical analysis was performed using SPSS19.0 for Windows®.

Results

Characteristics of study population

The average memory scores and socio-demographic and lifestyle characteristics of the study population are described in Table 1. After application of the exclusion criteria, 240 subjects remained in the study, with a mean age of

Table 1 Demographic characteristics of the study group

Characteristic	
Total number of subjects	240
Age (years)	63.37 ± 8.05
Gender (% men)	59 (24.6)
Years of education	10.69 ± 4.55
Hormonal replacement therapy, women only (%)	64 (26.7)
Age at completion of education (years)	27 ± 13.82
Years without studying	35.15 ± 17.78
Cigarette smoking	
Never	169 (70.4)
Past	61 (25.4)
Current	9 (3.8)
Alcohol consumption	
Yes	131 (54.6)
No	109 (45.4)
Memory scores	
Short-term verbal memory	0.016 ± 1.056
Long-term verbal memory	−0.013 ± 0.57
Short-term visual memory	−0.007 ± 1.316
Long-term visual memory	−0.117 ± 1.269
Verbal learning test	−0.010 ± 1.266

The values shown are mean ± standard deviation or numbers and percentages in parentheses

63.37 ± 8.05 years. Of those, 75.4 % were women, 26.7 % of whom were on hormonal replacement therapy. Overall, deficits in short-term verbal, long-term verbal, short-term visual, and long-term visual memories were observed in 19.6, 10.0, 22.9, and 26.3 %, respectively. Verbal learning deficits were observed in 20.8 % of the sample population (data not shown).

Association of SEP15 and SLC30A3 gene polymorphisms and memory deficit

Genotypic frequencies for the total sample population and frequencies within groups with deficits in specific memories are shown in Table 2. The genotypic frequencies observed did not show statistically significant differences compared to those expected under Hardy–Weinberg equilibrium. The observed allelic frequencies in this study were similar to those reported in SNP databases (Entrez SNP and International HapMap Project) and in previous studies analyzing European or European-derived populations. Univariate analysis demonstrated that the frequency of the TT genotype for the rs11126936 polymorphism is higher in subjects with deficits in verbal learning memory than in the group with normal scores ($p = 0.013$, corrected $p = 0.065$). For this polymorphism, T allele was more frequently observed among subjects with deficits in verbal learning memory than in the group with normal scores ($p = 0.011$, corrected $p = 0.055$). We found no other significant differences in genotype or allele frequencies between the investigated polymorphisms and the presence of memory deficits.

SEP15 and SLC30A3 gene polymorphisms, memory scores and micronutrient serum concentrations

After adjusting each specific type of memory for level of education and gender, a significant association was found between SEP15 rs5845 SNP and scores for verbal learning memory. Allele C carriers had higher memory scores than TT homozygotes (0.13 ± 1.13 vs. -1.10 ± 1.20, $p = 0.034$, corrected $p = 0.170$, data not shown). With regard to zinc and selenium serum concentrations, a genotype versus nutrient interaction was observed only between SLC30A3 rs73924411 and zinc concentration. Allele T carriers ($n = 27$) had higher scores for short-term and long-term verbal memories than CC homozygotes ($n = 84$) only when zinc serum concentration was below the recommended level (p value for interaction with short-term verbal memory $= 0.011$, Fig. 1a; p value for interaction with long-term verbal memory $= 0.039$, Fig. 1b). The same was not observed for SEP15 polymorphisms and selenium serum concentration (data not shown).

Discussion

The aim of this study was to investigate whether SNPs in SLC30A3 and SEP15 influence memory scores in volunteers over 50 years old. Additionally, we investigated the influence of interactions between zinc and selenium serum concentration and genetic profile on different types of memory. Our findings suggest a nutrient-dependent interaction between SLC30A3 and memory and a higher frequency of the TT genotype of the rs11126936 polymorphism in individuals with memory deficits. Moreover, our data indicate an influence of SEP15 rs5845 on verbal learning memory that is independent of serum concentration.

With regard to the zinc micronutrient, in our study we identified a possible gene versus nutrient interaction for the SLC30A3 rs73924411 polymorphism. In CC homozygotes with zinc serum concentrations below the recommended values, there was a negative effect on memory, with individuals scoring lower on tests for short-term and long-term verbal memories (Fig. 1a, b). These data indicate that current dietary recommendations should be revised for the prevention of memory deficits for CC homozygotes. Additionally, it is know that, during aging, changes occur in the absorption of micronutrients, and micronutrient and vitamin deficiencies are common in the elderly. This fact becomes especially worrisome for those rs73924411 CC homozygotes that already have lower zinc serum concentrations. In addition, our data indicate that current recommendations may be detrimental to T allele carriers: this genotypic group had higher mean memory scores only when serum levels were below the recommended value. This result indicates that, for T carriers, there may be a type of neurotoxicity induced by high zinc serum concentration, but experimental studies are needed in vivo and in vitro to clarify this interaction and to unravel the underlying molecular mechanisms. Besides, further longitudinal studies are needed to elucidate how the genetic variation contributes to individual differences in memory function and provide evidence of the effect of gene polymorphisms on the regulation of zinc homeostasis and what are the phenotypic consequences of this gene–nutrient interaction.

For the SLC30A3 rs11126936 polymorphism, homozygotes for the T allele were more frequently observed among subjects with deficits in verbal learning memory. This result suggests that this genotypic group presents a higher risk for developing deficits in verbal learning memory and that this risk is independent of zinc serum concentrations. To date, only one study evaluated the association of this SNP and central nervous system-related phenotypes. Perez-Becerril et al. (2013) described a gender-specific association of allele T with schizophrenia (Perez-Becerril et al. 2013). The zinc plays essential roles

Table 2 Genotype frequencies of SEP15 and SLC30A3 polymorphisms according to the presence of memory deficits

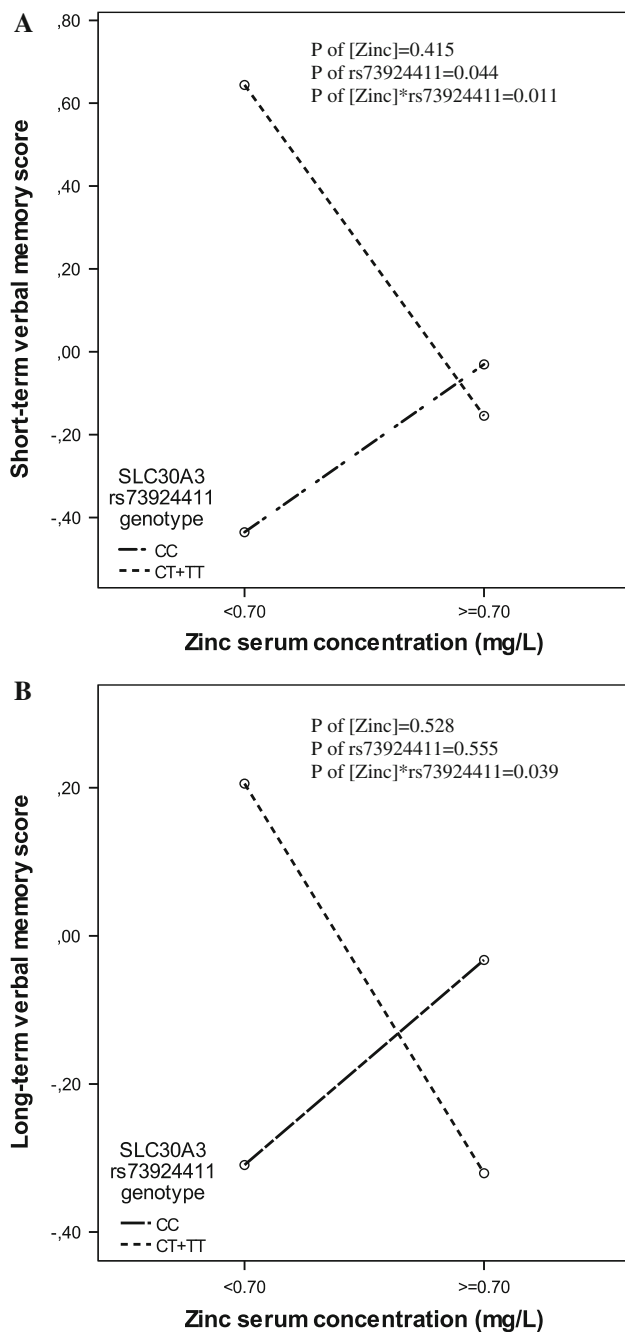| Genotype	Overall n (%)	Short-term verbal		Long-term verbal		Short-term visual		Long-term visual		Verbal learning memory	
		Normal n (%)	Deficit n (%)	Normal n (%)	Deficit n (%)	Normal n (%)	Deficit n (%)	Normal n (%)	Deficit n (%)	Normal n (%)	Deficit n (%)
SEP15											
rs561104											
CC	33 (13.8)	28 (14.5)	5 (10.6)	32 (14.8)	1 (4.2)	29 (15.7)	4 (7.3)	26 (14.7)	7 (11.1)	24 (12.6)	9 (18.0)
CT	118 (49.2)	90 (46.6)	28 (59.6)	105 (48.6)	13 (54.2)	87 (47.0)	31 (56.4)	86 (48.6)	32 (50.8)	94 (49.5)	24 (48.0)
TT	89 (37.1)	75 (38.9)	14 (29.8)	79 (36.6)	10 (41.7)	69 (37.3)	20 (36.4)	65 (36.7)	24 (38.1)	72 (37.9)	17 (34.0)
p		0.281		0.356		0.230		0.778		0.604	
rs5859											
GG	138 (57.5)	110 (57.0)	28 (59.6)	123 (56.9)	15 (62.5)	106 (57.3)	32 (58.2)	102 (57.6)	36 (57.1)	110 (57.9)	28 (56.0)
AG	91 (37.9)	74 (38.3)	17 (36.2)	82 (38.0)	9 (37.5)	69 (37.3)	22 (40.0)	69 (39.0)	22 (34.9)	72 (37.9)	19 (38.0)
AA	11 (4.6)	9 (4.7)	2 (4.3)	11 (5.1)	0 (0)	10 (5.4)	1 (1.8)	6 (3.4)	5 (7.9)	8 (4.2)	3 (6.0)
p		0.949		0.512		0.528		0.317		0.860	
rs5845											
GG	145 (60.4)	115 (59.6)	30 (63.8)	130 (60.2)	15 (62.5)	108 (58.4)	37 (67.3)	105 (59.3)	40 (63.5)	113 (59.5)	32 (64.0)
AG	89 (37.1)	73 (37.8)	16 (34.0)	80 (37.0)	9 (37.5)	71 (38.4)	18 (32.7)	69 (39.0)	20 (31.7)	74 (38.9)	15 (30.0)
AA	6 (2.5)	5 (2.6)	1 (2.1)	6 (2.8)	0 (0)	6 (3.2)	0 (0)	3 (1.7)	3 (4.8)	3 (1.6)	3 (6.0)
p		0.291		0.687		0.259		0.281		0.130	
SLC30A3											
rs11126936											
GG	119 (49.6)	99 (51.3)	20 (42.6)	109 (50.5)	10 (41.7)	89 (48.1)	30 (54.5)	86 (48.6)	33 (52.4)	99 (52.1)	20 (40.0)
GT	92 (38.3)	71 (36.8)	21 (44.7)	81 (37.5)	11 (45.8)	74 (40.0)	18 (32.7)	69 (39.0)	23 (36.5)	74 (38.9)	18 (36.0)
TT	29 (12.1)	23 (11.9)	6 (12.8)	26 (12.0)	3 (12.5)	22 (11.9)	7 (12.7)	22 (12.4)	7 (11.1)	17 (8.9)	12 (24.0)
p		0.544		0.693		0.618		0.871		**0.013***	
rs73924411											
CC	198 (82.5)	160 (82.9)	38 (80.9)	181 (83.8)	17 (70.8)	156 (84.3)	42 (76.4)	150 (84.7)	48 (76.2)	154 (81.1)	44 (88.0)
CT	41 (17.1)	32 (16.6)	9 (19.1)	34 (15.7)	7 (29.2)	28 (15.1)	13 (23.6)	26 (14.7)	15 (23.8)	35 (18.4)	6 (12.0)
TT	1 (0.4)	1 (0.5)	0 (0)	1 (0.5)	0 (0)	1 (0.5)	0 (0)	1 (0.6)	0 (0)	1 (0.5)	0 (0)
p		0.409		0.243		0.299		0.220		0.484	

* Corrected p = 0.065

Fig. 1 Interaction between zinc serum concentration and rs73924411 polymorphism on short-term (**a**) and long-term verbal (**b**) memory scores

which predicts activity in mnemonic processes (Sindreu and Storm 2011). The neurological mechanisms by how zinc participates in the development stages of mnemonic processes have not been fully clarified. However, the bond among zinc and glutamatergic neurotransmission allows this element modulates the overall brain excitability, from its interaction with different channels and calcium voltage-dependent synaptic targets (Frederickson et al. 2005). Regarding the metabolism of zinc, these are influenced by the diet and the tissue-specific expression of proteins required for its transport (Blanchard and Cousins 2000; Briefel et al. 2000). The ZnT3 protein (encoded by the *SLC30A3* gene) belongs to a class of proteins whose function is to lower the intracellular zinc concentrations, facilitating efflux of intracellular vesicles in the cytoplasm and/or extracellular spaces, and plays a particularly important role in neuronal zinc regulation. This protein is responsible for the accumulation of free zinc in glutamate-containing vesicles found in the hippocampus and cortex (Gower-Winte and Levenson 2012). The *SLC30A3* gene is expressed in brain regions important for cognitive development and development of different kinds of memory, such as the hippocampus, cerebral cortex, and amygdale (Seve et al. 2004), and ZnT3 knock-out mice exhibit cognitive loss, alterations in memory and may represent a phenocopy for memory deficits of Alzheimer's disease (Adlard et al. 2010; Martel et al. 2010; Sindreu et al. 2011).

Despite the identification of locations important for studies related to memory, no previous work has identified the potential neurobiological influences and phenotypic consequences of genetic polymorphisms. Because ours is the first such study, the results of interactions with memory and serum concentrations could be compared with other data in the literature. Therefore, it is essential to the development of scientific research to unravel the function of the gene *SLC30A3* and its polymorphisms on human memory.

Our results additionally indicate that the *SEP15* polymorphism rs5845 is associated with lower scores in verbal learning memory. In TT homozygotes, memory scores were lower than those with the C allele. The SNP rs5845 is present in the 3′UTR of *SEP15* gene, which is a region responsible for the incorporation of selenium in selenoproteins; therefore, this SNP has the potential to affect the expression of the 15 kDa selenoprotein (Papp et al. 2007). Indeed, minor allelic variants of *SEP15* rs5845 have been shown to have functional consequences. These SNPs have been reported to affect breast cancer risk (Hu et al. 2001) and the risk of lung cancer in smokers (Jablonska et al. 2008) and also to influence the risk of rectal cancer in men (Sutherland et al. 2010). It is important highlight that these studies cited also serve to illustrate the absence of neurobiological studies for *SEP15* gene. Furthermore, our study

in the central nervous system across the lifespan from neonatal brain development as well as for maintenance of brain function in adults, such that deficiency or excess of zinc has been shown to contribute to alterations in behavior, abnormal central nervous system development, and neurological disease (Bhatnagar and Taneja 2001; Frederickson et al. 2005). Therefore, it is not surprising that zinc in brain plays an important role in neuronal plasticity,

sample is small to determine the actual influence of genotype on memory scores and the consequence of this gene–nutrient interaction. Moreover, due to the small sample size of our study, it was not possible to determine with certainty the effects produced by polymorphisms in relation to serum concentration of the elements selenium and zinc and memory scores.

The complaints of the elderly related to memory should not be considered only as a phenomenon related to age. Instead, these claims deserve to be considered as an early sign of dementia. Because memory deficits have less obvious impacts on quality of life than other typical diseases of old age, research into memory problems has been limited. As a result, little is known about the factors that produce such declines in some individuals and not others. In exploring this issue, the relationship between diet and cognitive function has piqued the interest of researchers (Smith and Blumenthal 2010), and several observational studies have shown that variations in dietary practices and nutrient intake are predictive of memory decline (Barberger-Gateau et al. 2002; Akbaraly et al. 2007). Among the micronutrients, selenium and zinc are among the most studied in the elderly population, with both neuroprotective and antioxidant effects having been reported (Kesse-Guyot et al. 2011). However, it is important to note that the relationship between genes and nutrients has not been investigated in terms of memory deficits in the elderly. Even more novel is the study of the functional relationship between SLC30A3 and serum concentrations of zinc. Currently, we know very little about the mechanisms of associations between diet and memory at the molecular level. Understanding the molecular and genetic mechanisms that the brain uses to control the homeostasis of zinc and selenium and determine which genes are associated with changes in memory scores is a challenging task and crucial to the development of strategies for prevention and treatment for age-associated memory impairment (AAMI).

Traditionally, dietary recommendations have been made according to life stage and gender, with no consideration given to the important genetic markers that influence the health status of individuals (Simopoulos 2002; Van Ommen et al. 2010). In our study, we see that current dietary recommendations do not benefit individuals who are CC homozygous for SNP rs73924411, genetically seem incorporate a lower amount of zinc, and, as a result, had lower memory scores. Furthermore, for the micronutrient zinc, it was possible to observe a gene–nutrient interaction affecting memory score. Our study has limitations such as the small sample size and few SNPs investigated on each gene (SLC30A3 rs11126936, rs73924411 and SEP15, rs561104, rs5859, rs5845). Moreover, the observed associations might be spurious (type I error) due to multiple statistical comparisons, since after correction for multiple testing, observed p values do not reach statistical significance. However, when the probability of the type I error (false positive) decreases, the probability of type II error (false negative) increases. Despite some limitations of this study, our results are the first to demonstrate the influence of these polymorphisms on memory scores and micronutrient serum concentration. Thus, it is important point that further studies are needed to study with larger numbers of samples to clarify the nature of these relationships and identify the underlying molecular mechanisms by which the micronutrient selenium and zinc can affect memory. This understanding is necessary for the future union of genetic and nutritional profiles and may assist the development of a personalized diet to prevent disease progression and improve the quality of life of the elderly population.

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