ACE polymorphism and use of ACE inhibitors: effects on memory performance

Jaqueline B. Schuch · Pamela C. Constantin · Vanessa K. da Silva ·
Camila Korb · Daiani P. Bamberg · Tatiane J. da Rocha · Marilu Fiegenbaum ·
Alcyr de Oliveira Jr · Luciana A. Tisser · Fabiana M. de Andrade

Received: 10 July 2013 / Accepted: 18 March 2014 / Published online: 4 April 2014
© American Aging Association 2014

Abstract Memory is an important cognition function, being fundamental to the development and independence of individuals. Our aim was to investigate the influence apolipoprotein E (APOE) and angiotensin I-converting enzyme (ACE) polymorphism and ACE inhibitors use, besides their interaction on memory performance of healthy subjects over 50 years. The sample consisted of 205 subjects assessed for five types of episodic memory, using Wechsler Memory Scale-Revised (WMS-R), who answered a questionnaire about drug use and were assessed for the *ACE* insertion/

deletion polymorphism and *APOE* polymorphism. We found no influence of the *APOE* gene. The use of ACE inhibitors beneficially influenced learning ability scores ($p=0.02$). Besides, I allele carriers of *ACE* polymorphism showed higher verbal memory scores compared with homozygous DD. Also, we observed an interaction influencing learning ability between the *ACE* polymorphism and the use of inhibitors, the beneficial influence of the I allele was present only in individuals who make use of ACE inhibitors. We conclude that the *ACE* gene has influence on memory performance, and that this influence is modulated by ACE inhibitors use.

J. B. Schuch · P. C. Constantin · V. K. da Silva · C. Korb ·
F. M. de Andrade
Institute of Health Sciences, Universidade Feevale,
Novo Hamburgo, RS, Brazil

D. P. Bamberg · L. A. Tisser · F. M. de Andrade
Institute of Human Sciences, Letters and Arts, Universidade
Feevale, Novo Hamburgo, RS, Brazil

T. J. da Rocha · M. Fiegenbaum
Basic Health Sciences Department, Universidade Federal de
Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre,
Rio Grande do Sul, Brazil

A. de Oliveira Jr
Psychology Department, Universidade Federal de Ciências da
Saúde de Porto Alegre (UFCSPA), Porto Alegre, Rio Grande
do Sul, Brazil

F. M. de Andrade (✉)
Pró-Reitoria de Pesquisa e Inovação – PROPI, sala 201 F,
Universidade Feevale, RS 239, no. 2755, Novo Hamburgo,
RS 93352-000, Brazil
e-mail: fabiana.andrade@fevale.br

Keywords *ACE* polymorphism · ACE inhibitors ·
Pharmacogenetic interaction · Memory scores

Introduction

Memory impairment in the human aging course has high incidence of complaints. The action mechanism of this characteristic is still unclear; however, several genetic and environmental factors are involved in metabolic processes related to cognition (McDougall et al. 2006; Richard et al. 2000). Age-associated memory impairment (AAMI) was first described in 1986 by Crook et al. at the National Institute of Mental Health (NIMH) and is not regarded as a pathological condition, although there is some controversy that suffering from AAMI increases one's chances of developing dementia (Crook 2006; Goldman and Morris 2001).

A large number of candidate genes have been reported to be associated with dementia, cognition, and memory. Among these is the *apolipoprotein E* (*APOE*) $\epsilon 4$ allele. This gene is located on chromosome 19q13, and the $\epsilon 4$ isoform increases beta amyloid deposition (Rubinsztein 1995). This allele has been associated with Alzheimer's disease (AD) in a large number of studies (Saunders et al. 1993; Farrer et al. 1997; de Andrade et al. 2000; Jun et al. 2010; Elias-Sonnenschein et al. 2012; Ohara et al. 2012). Beyond this, this variant has also been associated with cognitive performance and memory by a much smaller number of studies (Schultz et al. 2008; van der Flier et al. 2008; De Blasi et al. 2009).

The angiotensin I-converting enzyme (ACE) is considered the key enzyme of the renin–angiotensin system (RAS), promoting the conversion of angiotensin I to angiotensin II. The RAS has an important role in the vascular physiology and pathology and has been associated with stroke and coronary artery disease (Markus et al. 1995; Arbustini et al. 1995). Besides, this system components act on the brain, working as nonclassical neurotransmitters on different receptors, including those associated with memory and learning, and also has effects on beta-amyloid peptide ($A\beta$) metabolism and consequently in AD (Mogi et al. 2012). The *ACE* gene, located on chromosome 17q23, has a 287-pb insertion (I)/deletion (D) polymorphism which is associated with regulation of the circulating enzyme levels (Rigat et al. 1990). Genetic studies relating *ACE* polymorphism with cognitive or memory impairment remain with inconclusive results. The D allele is associated with higher circulating levels of ACE and frequently is considered a risk factor for dementia, cognitive, and memory decline (Kehoe 2003; Bartrés-Faz et al. 2000, 2001; Stewart et al. 2004; Palumbo et al. 1999; Amouyel et al. 1996). However, the I allele has also been associated with impaired cognition (Gustafson et al. 2010), while other studies have found no association (Visscher et al. 2003; Liu et al. 2011).

The use of ACE inhibitors on hypertensive individuals was associated with improved cognitive performance and lower risk of dementia (Croog et al. 1986; Tzourio et al. 2003), and similar results were found in animal models (Hou et al. 2008). Research aiming to explain these effects have been reported. While some studies correlate the use of ACE inhibitors with decreased $A\beta$ deposition and ACE, others studies demonstrate that these inhibitors are correlated with increasing

of $A\beta$ concentrations and the onset of dementia (Hou et al. 2008; Hemming and Selkoe 2005). Due to conflicting reports, there is a need to study the ACE mechanisms and better understand its role in cognitive performance.

There are no studies investigating the association/interaction between *ACE* polymorphism and the use of ACE inhibitors on memory in healthy individuals. Thus, the aim of our study is to investigate the influence of these factors, as well as their interaction, on memory scores of healthy individuals over 50 years.

Methods

Sample

The sample consists of 205 volunteers with a minimum age of 50 years. The selection of these volunteers followed prior exclusion criteria related to previous history or diagnosis of any neurological diseases type, including Alzheimer's and Parkinson's diseases, as well as brain traumas. After, the volunteers participated in interviews and neuropsychological tests. Those that were using any kind of psychotropic medication or suffering from depression, anxiety, stress, or cognitive impairment, assessed by the tests described below, were also excluded.

Each volunteer answered a questionnaire with general information about health and lifestyle, including drug use, ACE inhibitors and level of schooling, besides hormone replacement therapy in women. The research project was approved by the Ethics Committee of Universidade Feevale, and all participants received information about the proposal, having signed an informed consent form.

Neuropsychological assessments

Verbal and visual memories were assessed using the Wechsler Memory Scale-Revised (WMS-R). The Rey Auditory-Verbal Learning Test (RAVLT) was used to assess verbal learning with the aim of measuring short-term verbal memory and the ability to store new information (Malloy-Diniz et al. 2007). Thereby, the application of these two instruments enabled the assessment of five memory measurements for each individual studied, and the final data for each test were transformed into standard deviations for the mean value

expected in each age, ranging from -4 to $+4$. According to Crook et al. (1986), memory deficit is only characterized when the scores values are equal or lower than -1 .

The following tests were used to assess the exclusion criteria: (1) For detecting mental disabilities, the subtests of the Wechsler Adult Scale-WAIS-III (Wechsler 2004) were applied with the purpose of estimating the IQ of the volunteers and excluding individuals with estimated IQ below 70. (2) The incidence and level of stress were assessed using Lipp's stress inventory for adults (Lipp 2000), and volunteers that were found to be in the "near exhaustion" and "exhaustion" stages were excluded. (3) In order to exclude individuals suffering from depression or anxiety, the Beck inventory was used (Cunha 2001).

Genotyping

Genomic DNA was extracted from whole blood (Lahiri and Nurnberger 1991) and amplified by polymerase chain reaction (PCR). *ACE* insertion/deletion polymorphism (rs1799752) was detected as previously described by Franken et al. (2004), and *APOE* polymorphism (rs429358 and rs7412) according to de Andrade et al. (2000).

Statistical analysis

Chi-square analysis was used to assess deviation from Hardy–Weinberg equilibrium. The normality of memory scores was tested using the Kolmogorov–Smirnov test, and all three of five classes presented normal distribution in the investigated sample. Besides this, those variables which did not agree with normal distribution (both visual memories) were evaluated for variance homogeneity through Levene's test and had similar variances. Therefore, all five memory classes were after all evaluated through general linear model (or analysis of covariance (ANCOVA)).

Evaluation of genetic polymorphisms and *ACE* inhibitor influences on memory performance was tested using different general linear models (ANCOVA). All initial models had gender and schooling as covariates. Besides, in *APOE* model, *ACE* genotype and *ACE* inhibitor were also used as covariates. In *ACE* genotype model, an additional covariate was also *APOE* genotype, and in *ACE* inhibitor use model, additional covariates were *ACE* and *APOE* genotypes. Gene $\times$ gene interaction was tested in the three models, and *ACE* gene $\times$

ACE inhibitor was evaluated in *ACE* genotype model. In spite of all these variables initially entered in the models, only those variables which contributed to the total $R^2 \times 100$ were maintained in the final models. Therefore, models shown in the "Results" section are those with the highest $R^2 \times 100$, and the covariates maintained in the final model are shown together with each result.

For all these analysis, subjects were grouped in *APOE*- $\epsilon 4$ carriers and noncarriers, and to the *ACE* polymorphism, they were grouped according to the presence of INS allele (II/I+ versus DD).

The entire statistical analysis was performed using the Statistical Package for the Social Sciences software (SPSS) 20. A p value equal or smaller than 0.05 was considered statistically significant. A p value ≤ 0.10 for interaction was considered significant according to Isenberg et al. (2010) and Sudore et al. (2009).

Each one of the five different memories was tested against the three independent variables (*ACE* gene, *ACE* inhibitor, and *APOE* gene), besides the interaction gene $\times$ inhibitor that yielded four different tests for each memory. However, correction for multiple comparisons was not done because each one of the statistical tests was done based on previous biological hypothesis. Therefore, a positive association detected would have a very low probability to be random.

Results

Table 1 shows the characteristics of the sample studied, which presents the mean age as 64.0 ± 8.08 years. The genotype distribution of *ACE* and *APOE* polymorphism agreed with the Hardy–Weinberg equilibrium ($p=0.98$ and $p=0.39$, respectively). The frequency of D allele was 49 %, and the frequency of $\epsilon 4$ allele was 12 %.

There were no statistically significant differences in memory scores tested between the genotype groups to *APOE* polymorphism (Table 2). Evaluation of the use of *ACE* inhibitors has shown that individuals who use inhibitors had higher learning ability scores ($p=0.02$). However, the performances of verbal and visual memories were not significantly different between groups (Table 2). It was not possible to detect any gene $\times$ gene interaction to these variables.

In order to evaluate the influence of *ACE* genotype on memory scores and its possible interaction with *ACE* inhibitors use, ANCOVA, testing the interaction between

Table 1 Characteristics of the studied sample ($n=205$)

Gender (men) ^a	49 (24)
Age ^b	64.0±8.08
Schooling ^a	10.47±4.73
ACE inhibitors use	57 (24.9)
Evaluated memories ^b	
Immediate verbal memory	0.049±1.05
Delayed verbal memory	0.055±1.05
Immediate visual memory	-0.168±1.37
Delayed visual memory	-0.245±1.30
Learning ability	-0.088±1.25
<i>APOE</i> ^a	
E2/E3	21 (10.2)
E2/E4	2 (0.9)
E3/E3	135 (65.9)
E3/E4	47 (22.9)
<i>ACE</i> ^a	
I/I	54 (25.9)
I/D	101 (49.5)
D/D	50 (24.5)

I Insertion allele, *D* deletion allele

^a n (%)

^b Mean±SD

these two variables, was used (Table 3). The evaluation of the scores of each type of memory between the *ACE* genotypes, when adjusted for gender, schooling, and $\epsilon 4$ allele presence, showed that *I* allele carriers had higher immediate ($p=0.057$) and delayed ($p=0.063$) verbal memory scores, although p values are marginal when

compared with *D* homozygotes (Table 3). No gene×drug interaction could be seen in these kinds of memories. For learning ability, similar results were found, but an interesting interaction gene×drug could be detected ($p=0.058$) showing that *ACE* genotype is very important in the performance of this kind of memory ($p=0.015$), but that the beneficial influence of *I* allele is present only in the subjects using ACE inhibitors (Fig. 1). Any isolated or interaction influence on visual memory could be seen (Table 3).

Discussion

The memory performance is crucial for normal development and a good quality of life, and its performance declines as consequence of nonpathological human aging. In this study, we examined the effects of ACE on memory, in healthy individuals during aging, comprising the evaluation of insertion/deletion polymorphism and use of inhibitors. The influence of the *APOE* polymorphism was also studied and inserted in the statistical models. Although we have not found an association to *APOE* polymorphism, some studies have shown that the $\epsilon 4$ allele is a risk factor for impaired cognitive performance, besides it is the main genetic risk factor for AD (Schultz et al. 2008; van der Flier et al. 2008; De Blasi et al. 2009; Farrer et al. 1997; de Andrade et al. 2000).

The RAS and its components acts in the brain, and angiotensin II specifically operates on the AT1 receptor, increasing blood pressure and acting as a nonclassical neurotransmitter activating brain neurons (Phillips and de Oliveira 2008). It is also involved in vascular

Table 2 Influence of *APOE* polymorphism and ACE inhibitors use on memory scores

Evaluated memories	<i>APOE</i> genotype ^a				ACE inhibitors			
	$R^2 \times 100$	E4−	E4+	<i>P</i>	$R^2 \times 100$	Yes	No	<i>p</i>
Immediate verbal	12.9 ^b	0.037±0.08	0.126±0.15	0.59	12.1 ^b	0.028±0.14	0.038±0.08	0.95
Delayed verbal	9.6 ^c	0.044±0.08	0.226±0.15	0.29	9.3 ^b	-0.066±0.15	0.083±0.08	0.37
Immediate visual	18.1 ^d	-0.079±0.10	-0.250±0.18	0.41	19.5 ^c	-0.101±0.17	-0.180±0.10	0.68
Delayed visual	15.2 ^c	-0.121±0.10	-0.321±0.17	0.31	15.3 ^c	-0.258±0.16	-0.256±0.09	0.99
Learning ability	18.8 ^d	0.013±0.09	-0.022±0.17	0.85	19.7 ^b	0.278±0.16	-0.147±0.09	0.02

^a E4− are E4 allele noncarriers (E3E3 and E2E3), while E4+ are E4 allele carriers (E3E4 and E2E4)

^b Covariates maintained in the model were gender, schooling, and ACE genotype

^c Covariates maintained in the model were gender and schooling

^d Covariates maintained in the model were gender, schooling, ACE genotype, and ACE inhibitors use

Table 3 Influence of *ACE* polymorphism and use of ACE inhibitors on memory scores

Evaluated memories		<i>ACE</i> genotype		<i>p</i> Value for <i>ACE</i> genotype comparison	<i>p</i> Value for <i>ACE</i> inhibitor use comparison
		II/I+	DD		
Immediate verbal memory					
ACE inhibitor	Yes	0.22±0.16	−0.53±0.35	0.057	0.401
	No	0.07±0.09	−0.02±0.16		
<i>P</i> (interaction)		0.126			
Delayed verbal memory					
ACE inhibitor	Yes	0.14±0.17	−0.65±0.37	0.063	0.116
	No	0.12±0.10	0.07±0.16		
<i>P</i> (interaction)		0.100			
Immediate visual memory					
ACE inhibitor	Yes	−0.04±0.20	−0.15±0.44	0.473	0.930
	No	−0.21±0.12	0.06±0.20		
<i>P</i> (interaction)		0.473			
Delayed visual memory					
ACE inhibitor	Yes	−0.25±0.19	−0.04±0.42	0.596	0.966
	No	−0.19±0.11	−0.12±0.19		
<i>P</i> (interaction)		0.787			

inflammation, cerebral blood flow, oxidative stress, cellular senescence, and cerebrovascular remodeling (Kazama et al. 2004; Mogi et al. 2012). In animal models, the role of angiotensin II in memory and cognition is contradictory, but it is suggested that their long-term effects are associated with a worse performance (Mogi et al. 2012). Another component of RAS system, the angiotensin IV, acts on the AT₄ receptor and has been associated with learning and memory, potentiating the release of acetylcholine from the hippocampus (Lee et al. 2001). Despite these data, the *ACE* influence on cognition is not fully established, and its role is evaluated in different ways including through the

insertion/deletion polymorphism of the *ACE* gene, which is associated with modulation of ACE plasmatic levels (Rigat et al. 1990).

The *ACE* allelic frequencies (49 % to D allele) in our study were similar to others Brazilian samples (Franken et al. 2004; Lucatelli et al. 2011). Individuals DD homozygotes had worse verbal memory performance compared with carriers I allele. This result is similar to the findings of previously published studies in different populations, where the D allele is associated with higher ACE levels, impaired cognitive performance, dementia, and AD (Kehoe 2003; Bartrés-Faz et al. 2001, 2000; Stewart et al. 2004; Palumbo et al. 1999; Amouyel et al. 1996). On the other side, I allele was also associated with dementia by Gustafson et al. (2010) and Lucatelli et al. (2011). Considering studies that assessed cognition or memory in healthy individuals, Visscher et al. (2003) and Liu et al. (2011) found no association to the *ACE* polymorphism. However, Richard et al. (2000) and Stewart et al. (2004) showed that the DD genotype is more frequent in those individuals with impairment cognitive, when others factors, such as *APOE* polymorphism and age, were included in analyses. The *ACE* polymorphism has also influenced the cognitive scores in individuals evaluated by the Mini-Mental State Examination, and a combined effect with the presence of at least one ε4 allele was a risk factor for cognitive

Fig. 1 Interaction between *ACE* gene and use of ACE inhibitors on learning ability scores (figure done using Excel software)

decline (Richard et al. 2000). Beyond this, an interaction between age and *ACE* genotype detected by Stewart et al. (2004) showed that with increasing age, the decline in verbal memory was stronger in individuals with the DD genotype. Therefore, when the dataset is inspected together with the present data, it looks like there are more evidences pointing to a deleterious role of D allele on memory in healthy subjects.

The evaluation of ACE inhibitors showed that the use of this drug class is beneficial to learning ability ($p=0.02$, Table 2). The results about it, in several studies, remain inconsistent, mainly due to the still-uncertain ACE role. The use of ACE inhibitors, correlated with decreased ACE levels, is related to decreased A β deposition (Hou et al. 2008). However, others studies showed association with increase of A β concentrations and earlier onset of dementia (Hemming and Selkoe 2005). This drug has also been correlated with protection for the development of dementia and AD, probably through direct effects on RAS in the brain (Tzourio et al. 2003; Ohruu et al. 2004). Despite these conflicting data, other studies have found similar results to ours, when assessing cognition instead of dementia. The use of ACE inhibitors was associated with decreased cognitive decline by Croog et al. (1986) and Hanon et al. (2004). One of the ways of explaining this kind of inconsistency can be the interaction with genetic variation, which was not tested until now.

Following this hypothesis, our analysis revealed an interaction between *ACE* genotype and use of ACE inhibitor. The learning ability performance was influenced by these factors, where the influence of I allele was advantageous only in ACE inhibitors users. Therefore, our data suggested that individuals who theoretically have lower ACE levels, because of the use of inhibitor and/or presence of I allele, present a better memory performance. The reason why this interaction was detected for learning ability (evaluated by RAVLT test) but was not detected for visual or verbal memory (evaluated by Wechsler tests) is not clear. The RAVLT method is a more specifically directed method to measure neurological function from the hippocampus (verbal memory), while Wechsler methods measure intellectual capability through a scale directed to the operational memory (Van der Elst et al. 2005). This difference between methods can be related to our ability in detecting an association with ACE (both gene and inhibitors), once this enzyme has established function exactly in the hippocampus.

Unfortunately, there are no more investigations beyond ours evaluating the interaction between these factors, especially in memory performance, making it impossible to compare our results. Most studies have indicated that high ACE levels or the presence of D allele are associated with higher risk for developing AD, dementia, or cognitive decline. There are few published studies evaluating memory performance during healthy aging and *ACE* gene, or analyzing the use of ACE inhibitors, but according to the available data and findings of various studies, the ACE has an important role in memory and cognition behavior, both in healthy subjects and in those with any associated pathology. Therefore, the replication of these data in other samples is strongly required one that can be used in the future for primary prevention of aged-associated memory impairment, increasing quality of life in aging.

References

- Amouyel P, Richard F, Cotel D, Amant C, Codron V, Helbecque N (1996) The deletion allele of the angiotensin I converting enzyme gene as a genetic susceptibility factor for cognitive impairment. *Neurosci Lett* 217:203–205
- Arbustini E, Grasso M, Fasani R, Klersy C, Diegoli M, Porcu E, Banchieri N, Fortina P, Danesino C, Specchia G (1995) Angiotensin converting enzyme gene deletion allele is independently and strongly associated with coronary atherosclerosis and myocardial infarction. *Br Heart J* 74:584–591
- Bartrés-Faz D, Junqué C, Clemente IC, López-Alomar A, Valveny N, López-Guillén A, López T, Cubells MJ, Moral P (2000) Angiotensin I converting enzyme polymorphism in humans with age-associated memory impairment: relationship with cognitive performance. *Neurosci Lett* 290:177–180
- Bartrés-Faz D, Junqué C, Clemente IC, Serra-Grabulosa JM, Guardia J, López-Alomar A, Sánchez-Aldeguer J, Mercader JM, Bargallo N, Olondo M, Moral P (2001) MRI and genetic correlates of cognitive function in elders with memory impairment. *Neurobiol Aging* 22:449–459
- Croog SH, Levine S, Testa MA, Brown B, Bulpitt CJ, Jenkins CD, Klerman GL, Williams GH (1986) The effects of antihypertensive therapy on the quality of life. *N Engl J Med* 314:1657–1664
- Crook TH (2006) The memory advantage. SelectBooks, New York
- Crook TH, Bartus RT, Ferris SH, Whitehouse P, Cohen GD, Gershon S (1986) Age-associated memory impairment: proposed diagnostic criteria and measures of clinical change—report of a National Institute of Mental Health work group. *Dev Neuropsychol* 2:261–276
- Cunha JA (2001) Manual da versão em Português das Escalas de Beck, 1st edn. Casa do Psicólogo, São Paulo

- de Andrade FM, Larrandaburu M, Callegari-Jacques SM, Gastaldo G, Hutz MH (2000) Association of apolipoprotein E polymorphism with plasma lipids and Alzheimer's disease in a Southern Brazilian population. *Br J Med Biol Res* 33: 529–537
- De Blasi S, Montesanto A, Martino C, Dato S, De Rango F, Bruni AC, Mari V, Feraco E, Passarino G (2009) APOE polymorphism affects episodic memory among non demented elderly subjects. *Exp Gerontol* 44(3):224–227
- Elias-Sonnenschein LS, Bertram L, Visser PJ (2012) Relationship between genetic risk factors and markers for Alzheimer's disease pathology. *Biomark Med* 6(4):477–495
- Farrer LA, Cupples LA, Haines J (1997) Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. *Am Med Soc* 278:1349–1356
- Franken RA, Bellesso M, Cavazin AM, Polônio IB, Mattheucci E, Varga J (2004) Associação do polimorfismo do gene da enzima conversora da angiotensina com dados ecocardiográficos em jovens normotensos filhos de hipertensos. *Rev Assoc Med Bras* 50(1):62–67
- Goldman WP, Morris JC (2001) Evidence that age-associated memory impairment is not a normal variant of aging. *Alzheimer Dis Assoc Disord* 15:72–79
- Gustafson DR, Melchior L, Eriksson E, Sundh V, Blennow K, Skoog I (2010) The ACE insertion deletion polymorphism relates to dementia by metabolic phenotype, APOEepsilon4, and age of dementia onset. *Neurobiol Aging* 31(6):910–916
- Hanon O, Seux ML, Lenoir H, Rigaud AS, Forette F (2004) Prevention of dementia and cerebroprotection with antihypertensive drugs. *Curr Hypertens Rep* 6:201–207
- Hemming ML, Selkoe DJ (2005) Amyloid beta-protein is degraded by cellular angiotensin-converting enzyme (ACE) and elevated by an ACE inhibitor. *J Biol Chem* 280(45):37644–37650
- Hou D-R, Wang Y, Zhou L, Chen K, Tian Y, Song Z, Bao J, Yang Q-D (2008) Altered angiotensin-converting enzyme and its effects in the brain in a rat model of Alzheimer Disease. *Chin Med J* 121(22):2320–2323
- Isenberg D, Appel GB, Contreras G, Dooley MA, Ginzler EM, Jayne D, Sanchez-Guerrero J, Wofsy D, Yu X, Solomons N (2010) Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study. *Rheumatology (Oxford)* 49(1):128–140
- Jun G, Naj AC, Beecham GW, Wang LS, Buross J, Gallins PJ, Buxbaum JD, Ertekin-Taner N, Fallin MD, Friedland R, Inzelberg R, Kramer P, Rogaeva E, St George-Hyslop P, Cantwell LB, Dombroski BA, Saykin AJ, Reiman EM, Bennett DA, Morris JC, Lunetta KL, Martin ER, Montine TJ, Goate AM, Blacker D, Tsuang DW, Beekly D, Cupples LA, Hakonarson H, Kukull W, Foroud TM, Haines J, Mayeux R, Farrer LA, Pericak-Vance MA, Schellenberg GD (2010) Meta-analysis confirms CR1, CLU, and PICALM as Alzheimer disease risk loci and reveals interactions with APOE genotypes. *Arch Neurol* 67(12):1473–1484
- Kazama K, Anrather J, Zhou P, Girouard H, Frys K, Milner TA, Iadecola C (2004) Angiotensin II impairs neurovascular coupling in neocortex through NADPH oxidase-derived radicals. *Circ Res* 95(10):1019–1026
- Kehoe PG (2003) The renin-angiotensin-aldosterone system and Alzheimer's disease? *Journal of the renin-angiotensin-aldosterone system. JRAAS* 4(2):80–93
- Lahiri DK, Nurnberger JI (1991) A rapid non-enzymatic method for the preparation of HMW DNA from blood for RFLP studies. *Nucleic Acids Res* 19(19):5444
- Lee J, Chai S-Y, Mendelsohn FAO, Morris MJ, Allen AM (2001) Potentiation of cholinergic transmission in the rat hippocampus by angiotensin IV and LVV-hemorphin-7. *Neuropharmacology* 40(4):618–623
- Lipp MEN (2000) Manual do inventário de sintomas de stress para adultos de Lipp. Casa do Psicólogo, São Paulo
- Liu ME, Tsai SJ, Lu T, Hong CJ, Chen MC, Lin SL, Yeh HL, Ku YC (2011) No association of angiotensin I converting enzyme I/D polymorphism with domain-specific cognitive function in aged men without dementia. *Neuromol Med* 13(3):212–216
- Lucatelli JF, Barros AC, Silva VK, Machado Fda S, Constantin PC, Dias AA, Hutz MH, de Andrade FM (2011) Genetic influences on Alzheimer's disease: evidence of interactions between the genes APOE, APOC1 and ACE in a sample population from the South of Brazil. *Neurochem Res* 36(8):1533–1539
- Malloy-Diniz LF, Lasmar VAP, Gazinelli LSR, Fuentes D, Salgado JV (2007) The Rey Auditory-Verbal Learning Test: applicability for the Brazilian elderly population. *Rev Bras Psiquiatr* 29:324–329
- Markus HS, Barley J, Lunt R, Bland JM, Jeffery S, Carter ND, Brown MM (1995) Angiotensin-converting enzyme gene deletion polymorphism. A new risk factor for lacunar stroke but not carotid atheroma. *Stroke* 26(8):1329–1333
- McDougall GJ Jr, Becker H, Arheart KL (2006) Older adults in the SeniorWISE study at risk for mild cognitive impairment. *Arch Psychiatr Nurs* 20(3):126–134
- Mogi M, Iwanami J, Horiuchi M (2012) Roles of brain angiotensin II in cognitive function and dementia. *Int J Hypertens*. doi:10.1155/2012/169649
- Ohara T, Ninomiya T, Hirakawa Y, Ashikawa K, Monji A, Kiyohara Y, Kanba S, Kubo M (2012) Association study of susceptibility genes for late-onset Alzheimer's disease in the Japanese population. *Psychiatr Genet* 22(6):290–293
- Ohrui T, Matsui T, Yamaya M, Arai H, Ebihara S, Maruyama M, Sasaki H (2004) Angiotensin-converting enzyme inhibitors and incidence of Alzheimer's disease in Japan. *JAGS* 52: 649–650
- Palumbo B, Cadini D, Nocentini G, Filipponi E, Fravolini ML, Senin U (1999) Angiotensin converting enzyme deletion allele in different kinds of dementia disorders. *Neurosci Lett* 267:97–100
- Phillips MI, de Oliveira EM (2008) Brain renin angiotensin in disease. *J Mol Med (Berl)* 86(6):715–722
- Richard F, Berr C, Amant C, Helbecque N, Amouyel P, Alperovitch A (2000) Effect of the angiotensin I-converting enzyme I/D polymorphism on cognitive decline. *Neurobiol Aging* 21:75–80
- Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F (1990) An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. *J Clin Invest* 86:1343–1346
- Rubinstein DC (1995) Apolipoprotein E: a review of its roles in lipoprotein metabolism, neuronal growth and repair as a risk for Alzheimer's disease. *Psychol Med* 25:223–229

- Saunders AM, Strittmatter WJ, Schmechel D, George-Hyslop S, Pericak-Vance MA, Joo SH, Rosi BL, Gusella JF, Crapper-MacLachlan DR, Alberts MJ, Hulette C, Crain B, Goldgaber D, Roses AD (1993) Association of apolipoprotein E allele epsilon4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* 43(8):1467–1472
- Schultz MR, Lyons MJ, Franz CE, Grant MD, Boake C, Jacobson KC, Xian H, Schellenberg GD, Eisen SA, Kremen WS (2008) Apolipoprotein E genotype and memory in the sixth decade of life. *Neurology* 70:1771–1777
- Stewart R, Powell J, Prince M, Mann A (2004) ACE genotype and cognitive decline in an African-Caribbean population. *Neurobiol Aging* 25(10):1369–1375
- Sudore RL, Landefeld CS, Perez-Stable EJ, Bibbins-Domingo K, Williams BA, Schillinger D (2009) Unraveling the relationship between literacy, language proficiency, and patient-physician communication. *Patient Educ Couns* 75(3):398–402
- Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, Chalmers J, Group. PC (2003) Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med* 163:1069–1075
- Van der Elst W, van Boxtel MP, van Breukelen GJ, Jolles J (2005) Rey's verbal learning test: normative data for 1855 healthy participants aged 24–81 years and the influence of age, sex, education, and mode of presentation. *J Int Neuropsychol Soc* 11(3):290–302
- van der Flier WM, Pijnenburg YAL, Schoonenboom SNM, Dik MG, Blankenstein MA, Scheltens P (2008) Distribution of APOE genotypes in a memory clinic cohort. *Dement Geriatr Cogn Disord* 25:433–438
- Visscher PM, Tynan M, Whiteman MC, Pattie A, White I, Hayward C, Wright AF, Starr JM, Whalley LJ, Deary IJ (2003) Lack of association between polymorphisms in angiotensin-converting-enzyme and methylenetetrahydrofolate reductase genes and normal cognitive ageing in humans. *Neurosci Lett* 347(3):175–178
- Weschler D (2004) WAIS-III: Escala de inteligência Wechsler para adultos. WMS-III: Escala de memória Wechsler—manual técnico (trans: Silva MCdVM). Casa do Psicólogo, São Paulo