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ORIGINAL ARTICLE

Blood total antioxidant status is associated with cortical glucose uptake and factors related to accelerated aging

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Abstract

Identifying cerebral vulnerability in late life is of paramount importance to prevent pathological trajectories of aging before the onset of symptoms. Considerable evidence suggests that impaired antioxidant mechanisms are a fingerprint of aging-related conditions, but there is a lack of human research linking total antioxidant capacity (TAC) measured in peripheral blood to in vivo brain changes and other factors featuring accelerated aging. To address this issue, we have assessed in cognitively normal elderly subjects ($N = 100$) correlations between serum TAC, using the oxygen radical absorbance capacity assay, surface-based cortical thickness, surface-based 18F-fluorodeoxyglucose positron emission tomography cortical uptake, and different factors associated with accelerated aging [i.e., serum homocysteine (HCY), self-reported memory problems, and self-reported patterns of physical activity]. While no relationship was observed between serum TAC and variations in cortical thickness, decreased TAC level was significantly associated with lower FDG uptake in temporal lobes bilaterally. Remarkably, decreased TAC level was linked to increased HCY concentrations, more subjective memory complaints, and lower frequency of physical activity. Overall, our results suggest that decreased serum TAC level may be helpful to detect vulnerable trajectories of aging.

Keywords Aging · Blood total antioxidant capacity · Cortical thickness · FDG-PET · Homocysteine · Subjective memory complaints · Physical activity

Introduction

The growth of aging population is a worldwide phenomenon that impacts all sectors of society. Particularly, increased life expectancy brings higher healthcare requirements due to a rise in the prevalence of chronic diseases (United Nations 2017). Despite the remarkable variability among individuals in the rate of biological aging, evidence suggests that non-communicable chronic conditions, such as cognitive frailty and Alzheimer's disease (AD), accelerate aging and are leading causes of disability among the elderly (Morley et al. 2015). Therefore, searching for reliable predictors of vulnerability in aging will have undoubted benefits for public health.

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There is an urgent need to develop cost-effective and minimally invasive biomarkers able to identify, before symptoms appear, individuals who can benefit from prophylactic interventions and/or early-stage treatments aimed at modifying the course of aging (Bürkle et al. 2015). The progressive decline in physiological functions that characterize aging is not only manifested in the central nervous system but also seems to be partly encoded in blood signatures (Wyss-Coray 2016). Consequently, blood-based fingerprints of aging-related vulnerability should appear in tandem with in vivo brain changes favoring the emergence of non-invasive biomarkers able to anticipate pathological aging.

One factor with the capacity to weaken neuronal health is oxidative stress (OS), which arises from an imbalance between increased production of reactive oxygen species (ROS) and decreased antioxidant mechanisms. Excessive ROS has detrimental effects on target cellular components such as DNA, proteins, and membrane lipids, ultimately leading to cell damage and gradual impairment of physiological systems (Kohen and Nyska 2002). Among the mechanisms against OS, the one involving antioxidant defenses

is particularly important due to its role at removing pro-oxidant compounds, which in turn contributes to neutralize unwanted ROS and maintain redox homoeostasis.

Compared to other organs, the brain produces elevated levels of ROS due to its high requirements for oxygen consumption, intense production of reactive oxygen metabolites, high content of polyunsaturated fatty acids, relatively low antioxidant capacity, low repair mechanism activity and non-replicating nature of neurons (Evans 1993). Therefore, aged neurons are naturally overexposed to an environment with considerable OS, favoring subtle alterations in neuronal physiology, dysfunctions of neural circuits, and increasing the susceptibility of vulnerable neurons to neuropathology (Bell 2013). Evidence indicates that cerebral antioxidant capacity decreases with age in both experimental models (Siqueira et al. 2005) and humans (Venkateshappa et al. 2012). However, there is a lack of human research supporting the link between blood total antioxidant capacity (TAC) and in vivo brain changes in the elderly, which may have significant implications to identify vulnerability in aging using non-invasive biomarkers.

Previous research has shown, on the one hand, that the blood–brain barrier (BBB) contains appreciable amounts of antioxidants to protect against oxidative damage (Shukla et al. 1995), and on the other, that aging itself is the most important risk factor for BBB damage through disruption of tight junction proteins and dysregulation of transport systems (Enciu et al. 2013). Consequently, aging-related BBB breakdown may facilitate a more permissive exchange of oxidative molecules from the brain to the periphery and vice versa (Grammas et al. 2011). Additionally, research with mouse models of accelerated aging has revealed associations between lower cerebral glucose consumption and increased OS (Borras et al. 2009). On the basis of the data reviewed here, our working hypothesis is that serum TAC reductions parallel antioxidant deficits of the aged brain. Particularly, we expect that decreased TAC level is accompanied by reductions in cortical glucose uptake, uncovering initial dysfunctions of neural metabolic networks that may precede structural changes in the aging neocortex. If confirmed, lower TAC level should further correlate with other signatures of vulnerable aging. We, therefore, predict that decreased serum TAC is linked to the elevation of homocysteine (HCY), poorer subjective memory, and lower frequency of self-reported physical activity, three well-known factors associated with accelerated aging (e.g., Mattson and Arumugam 2018; Cantero et al. 2016; Lehmann et al. 1999). To assess these predictions, serum TAC level was correlated with patterns of surface-based cortical thickness/cortical glucose metabolism obtained with high-resolution magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), respectively. We further examined whether serum TAC was associated with variations in serum HCY, subjective memory complaints, and/or self-reported patterns of physical activity in cognitively normal elderly subjects.

Materials and methods

Subjects

One hundred normal elderly subjects, recruited from senior citizen's associations, health screening programs, and hospital outpatient services, participated in the study. They showed normal cognitive performance in the neuropsychological tests relative to appropriate reference values for age and education level. Table 1 contains demographic, neuropsychological and clinical data of this cohort. Individuals with medical conditions and/or history of conditions that may affect brain structure or function (e.g., neurodegenerative diseases, stroke, head trauma, hydrocephalus, and/or intracranial mass) were not included in the study. All subjects showed a global score of 0 (no dementia) in the Clinical Dementia Rating (CDR), normal global cognitive status in the Mini-Mental State Examination (MMSE) (scores ≥ 26) as well as normal independent function-assessed by the Spanish version of the Interview for Deterioration in Daily Living Activities (Böhm et al. 1998). Depression was excluded (scores ≤ 5) by the shorter version of the Geriatric Depression Scale (Yesavage et al. 1983). All participants gave informed consent to the experimental protocol approved by the Ethical Committee for Human Research at

Table 1 Characteristics of the study sample

Age	68.9 ± 3.8 (62–78)
Sex (M/F)	58/42
Education (years)	11 ± 4.7 (3–19)
CDR	0
TAC (μmol/L)	413.7 ± 193.4 (70–918)
HCY (μmol/L)	15.1 ± 5.5 (7–28)
PhysAct	22.8 ± 17.5 (0–98)
MMSE	29.2 ± 1.3 (26–30)
MFQ	18.1 ± 3.4 (8–24)
FCSRT	41.4 ± 5.4 (25–48)
TOL	402 ± 140 (134–824)
BNT	51.9 ± 4.8 (35–59)

Results are expressed as mean ± standard deviation, range (min–max)

M males, *F* females, *CDR* clinical dementia rating, *TAC* total antioxidant capacity measured in serum with the oxygen radical absorbance capacity (ORAC) assay, *HCY* serum homocysteine, *PhysAct* self-reported physical activity, *MMSE* Mini Mental State Examination, *MFQ* Memory Functioning Questionnaire, *FCSRT* Free and Cued Selective Reminding Test, *TOL* Tower of London, *BNT* Boston Naming Test

the University Pablo de Olavide according to the principles outlined in the Declaration of Helsinki.

Neuropsychological assessment and self-reported physical activity

A neuropsychological battery covering memory, executive functioning and language was administered to all participants. Subjective memory was evaluated with the Memory Functioning Questionnaire (MFQ), while objective memory was assessed with the Free and Cued Selective Reminding Test (FCSRT). The Tower of London (TOL) and the Boston Naming Test (BNT) were administered to evaluate the executive function and naming ability, respectively.

Self-reported patterns of physical activity were evaluated with the Godin Leisure-Time Exercise Questionnaire (GLTEQ) (Godin and Shephard 1985). The GLTEQ assesses patterns of exercise behavior during leisure time, by asking the number of times an individual performs strenuous, moderate, and mild exercise for more than 15 min during free time in a typical week.

Measures of TAC and HCY

Overnight fasting blood samples for measuring TAC and HCY were collected at the same time in all participants, stored at – 80 °C, and thawed immediately before assay. To estimate serum TAC level, we employed an improved oxygen radical absorbance capacity (ORAC) assay with fluorescein as the fluorescent probe. This methodology provides a direct measure of hydrophilic chain-breaking antioxidant capacity against peroxyl radicals and takes into account both the inhibition time and the inhibition percentage of free radical action (Ou et al. 2001). The serum non-protein fraction was used in the ORAC assay by diluting the serum with perchloric acid. Fluorescence was measured at 37° C on a Victor X3 multilabel plate reader spectrophotometer (PerkinElmer, USA) at 485 nm and 535 nm wavelengths for excitation and emission, respectively. Trolox, a water-soluble vitamin E analog, was used as standard, and ORAC was expressed as Trolox equivalents in micromole per liter of serum (µmol/L). ORAC level was calculated using a regression equation between the Trolox concentration and the net area under the fluorescein decay curve. Reactions were carried out in triplicate and coefficients of variation were below 10%. Since over half of the antioxidant capacity of the human blood is due to uric acid, uric acid levels were obtained by enzymatic methods and subtracted from ORAC value for statistical purposes.

Serum HCY level (µmol/L) was also measured in each participant using standard enzymatic methods (A15 Random Access Analyzer, Biosystems, Spain).

MRI and FDG-PET acquisition

Structural brain images were acquired on a Philips Achieva 3 T MRI scanner equipped with an 8-channel phased-array head coil (Philips, Best, The Netherlands). A whole-brain T1-weighted magnetization prepared rapid gradient echo (MPRAGE) was obtained with the following parameters: sagittal slice orientation, repetition time (TR) = 2300 ms, echo time (TE) = 4.5 ms, matrix = 320 × 320, flip angle = 8°, voxel size = 0.8 mm isotropic, no gap between slices, acquisition time = 9.1 min). Head motion was controlled using a head restraint system and foam padding around the subject's head.

FDG-PET brain images were acquired on a whole-body PET-TAC Siemens Biograph 16 HiREZ scanner (Siemens Medical Systems, Germany) in 3D mode. Subjects fasted for at least 8 h before PET examination, and they were scanned at the same time of the day (8:00–9:00 am). Participants were injected with 370 MBq of 2-[18F]fluoro-2-deoxy-D-glucose (FDG). FDG brain images were corrected for attenuation, scatter and decay, smoothed for uniform resolution, and reconstructed with 2.6 × 2.6 × 2 mm voxel resolution using back-projection filters.

Estimation of surface-based cortical thickness and cortical FDG uptake

MRI data were processed using the analysis pipeline of Freesurfer v6.0 (https://surfer.nmr.mgh.harvard.edu/) that involves intensity normalization, registration to Talairach, skull stripping, white matter (WM) segmentation, tessellation of WM boundaries, and automatic correction of topological defects (Fischl and Dale 2000). Pial surface misplacements and erroneous WM segmentations were manually corrected on a slice-by-slice basis to enhance the reliability of cortical thickness measurements. Cortical thickness maps were smoothed using non-linear spherical wavelet-based de-noising schemes, which have previously shown greater specificity and sensitivity at detecting local and global changes in cortical thickness (Bernal-Rusiel et al. 2008).

Partial volume correction (PVC) of FDG-PET images was performed with PMOD v3.208 (PMOD Technologies Ltd., Switzerland) using the Müller–Gartner approach, and assuming a uniform 6 mm point spread function. To map PET scans onto native cortical surfaces, FDG images were first co-registered to the corresponding T1 image for each subject using PMOD tools. Next, PVC-cortical FDG individual images were mapped into native cortical surface in Freesurfer. FDG activity assigned to each cortical surface vertex was normalized by the FDG activity of the entire cortex using an iterative vertex-based statistical method that excludes group-dependent vertices from the calculation of

global activity (Park et al. 2006). Finally, PVC-cortical FDG individual images were smoothed with non-linear spherical wavelet-based de-noising schemes (Bernal-Rusiel et al. 2008).

Statistical analyses

We first assessed whether TAC, HCY, cognitive and physical activity scores deviated from normality applying the Kolmogorov–Smirnov test with the Lilliefors correction. Linear regression analyses were conducted, after regressing out age and sex effects, to evaluate associations between TAC, HCY, cognitive scores, and self-reported physical activity. These statistical analyses were performed with SPSS v22 (SPSS Inc. Chicago, IL, USA). The Bonferroni test was used to overcome the problem of multiple testing.

Vertex-wise linear regression analyses were further performed, after regressing out age and sex effects, to determine whether TAC level was correlated with variations in cortical thickness/cortical glucose consumption. Results were corrected for multiple comparisons using a previously validated hierarchical statistical model (Bernal-Rusiel et al. 2010). This procedure first controls the family-wise error rate in significant clusters by applying random field theory over smoothed statistical maps; and next controls the false discovery rate in vertices within significant clusters over unsmoothed statistical maps. A significant cluster was defined as a contiguous set of cortical surface vertices that met the statistical threshold criteria ($p < 0.05$ after correction for multiple comparisons) and whose surface area was greater than 40 mm^2. The color scale in the figures illustrates the range of significant p values within the cluster.

Results

Relationship between TAC, HCY, cognitive function, and physical activity in aging

TAC, HCY, cognitive function, and physical activity scores were normally distributed, thus allowing for the use of parametric statistical tests. Although neither age nor sex was significantly related to TAC level, both variables were introduced as covariates in the regression model to control for their potential confounding effect. Table 2 contains the correlation matrix for all variables analyzed in this study, after adjusting for potentially confounding effects of age and sex. Regression analyses revealed that decreased TAC level was significantly correlated with higher HCY concentrations ($r = -0.3$, $F_{3,96} = 3.1$, $p = 0.03$), poorer subjective memory ($r = 0.31$, $F_{2,97} = 5.2$, $p = 0.007$), and lower frequency of physical activity ($r = 0.32$, $F_{3,96} = 3.8$, $p = 0.01$). Moreover, increased HCY and lower naming ability were associated with poorer subjective ($r = -0.39$, $F_{3,96} = 5.9$, $p = 0.01$) and objective memory ($r = 0.53$, $F_{3,96} = 12.8$, $p = 10^{-7}$), respectively, and lower naming ability was associated with worse objective memory ($r = 0.53$, $F_{3,96} = 12.8$, $p = 10^{-7}$). Figure 1 shows scatter plots of residuals for these results.

Table 2 Correlation matrix for variables included in the study

	HCY	PhyAct	MMSE	MFQ	FCSRT	TOL	BNT
TAC	**− 0.30**	**0.32**	− 0.24	**0.31**	− 0.21	− 0.28	− 0.28
	0.03*	**0.01***	0.27	**0.007***	0.18	0.84	0.16
HCY	1	0.32	− 0.26	**− 0.39**	0.20	0.30	0.25
		0.65	0.15	**0.01***	0.26	0.21	0.90
PhyAct		1	0.21	0.31	− 0.16	− 0.28	0.25
			0.70	0.53	0.90	0.64	0.90
MMSE			1	− 0.31	0.18	− 0.28	0.26
				0.80	0.41	0.54	0.50
MFQ				1	0.20	− 0.28	− 0.25
					0.25	0.93	0.51
FCSRT					1	0.28	**0.53**
						0.76	**10^{-7}***
TOL						1	− 0.29
							0.40
BNT							1

Correlations were obtained after regressing out age and sex effects. Significant correlations appear in bold marked with an asterisk ($p < 0.05$)

TAC total antioxidant capacity measured in serum with the oxygen radical absorbance capacity (ORAC) assay, *HCY* serum homocysteine, *PhysAct* self-reported physical activity, *MMSE* Mini-Mental State Examination, *MFQ* Memory Functioning Questionnaire, *FCSRT* Free and Cued Selective Reminding Test, *TOL* Tower of London, *BNT* Boston Naming Test

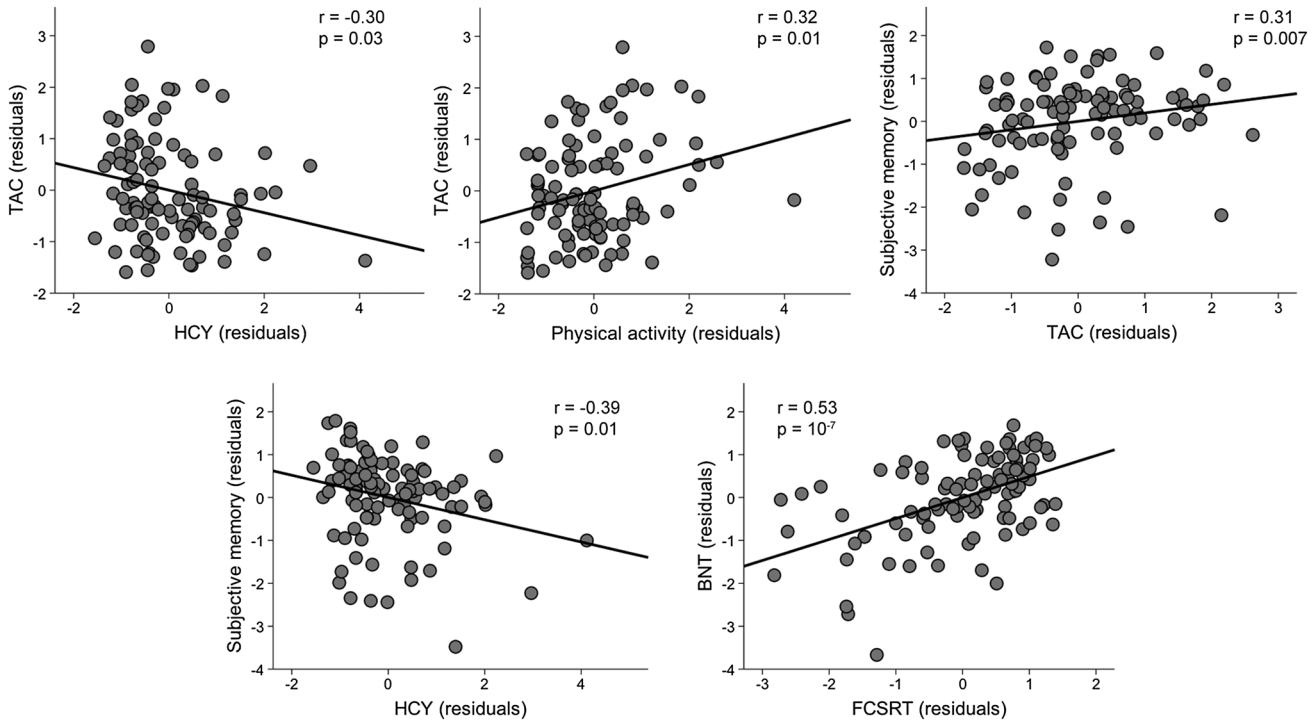

Fig. 1 Significant correlations between TAC, homocysteine, and cognitive outcomes. Variables included in the scatter plots correspond to the standardized residuals from a linear regression analysis after regressing out age and sex effects. *TAC* total antioxidant capacity measured in serum with the oxygen radical absorbance capacity (ORAC) assay, *HCY* serum homocysteine, *FCSRT* free and cued selective reminding test, *BNT* Boston naming test

Table 3 Correlations between serum TAC level and cortical FDG uptake

Cortical region	CS (mm^2)	*r*	*p*
L middle temporal	642	0.28	10^{-3}
R middle temporal	212	0.32	10^{-3}
R lateral occipital	543	0.37	10^{-5}

Correlations were obtained after regressing out age and sex effects

CS cluster size representing the spatial extent of significant correlations, *L* left, *R* right, *r* Pearson correlation coefficient, *p* exact *p* value

Relationship between TAC level and changes in cortical thickness/cortical FDG uptake in aging

We next assessed if TAC level was associated with changes in cortical thickness and/or cortical FDG uptake. Our analysis showed that decreased TAC was significantly correlated with cortical FDG reductions in the temporal lobe bilaterally. Particularly, reduced levels of serum TAC were associated with lower glucose uptake in middle temporal regions of both hemispheres (left: $p = 10^{-3}$; right: $p = 10^{-3}$) and in lateral aspects of the right occipital lobe ($p = 10^{-5}$). These results are summarized in Table 3 and illustrated in Fig. 2. No significant associations were shown between TAC level and cortical thickness. Neither did we find significant correlations between significant changes in cortical FDG uptake and thickness of the same cortical regions.

Discussion

Aged neurons become extremely vulnerable to deleterious effects of oxidative damage. While deficits of redox homeostasis in aging have been largely established in experimental models and human brain tissues, there is a lack of human evidence linking aging-related variations in blood antioxidant status to in vivo brain changes. In the present study, we have shown, for the first time, that decreased serum TAC is associated with lower glucose uptake of the temporal lobe in cognitively normal elderly subjects. Lower TAC was further linked to increased HCY, poorer subjective memory, and lower frequency of physical activity, all of them factors associated with vulnerability in aging. Altogether, these results suggest that blood TAC level combined with in vivo cerebral markers are helpful to monitor accelerated aging, which may have further implications for detecting persons at risk of developing neurodegenerative conditions.

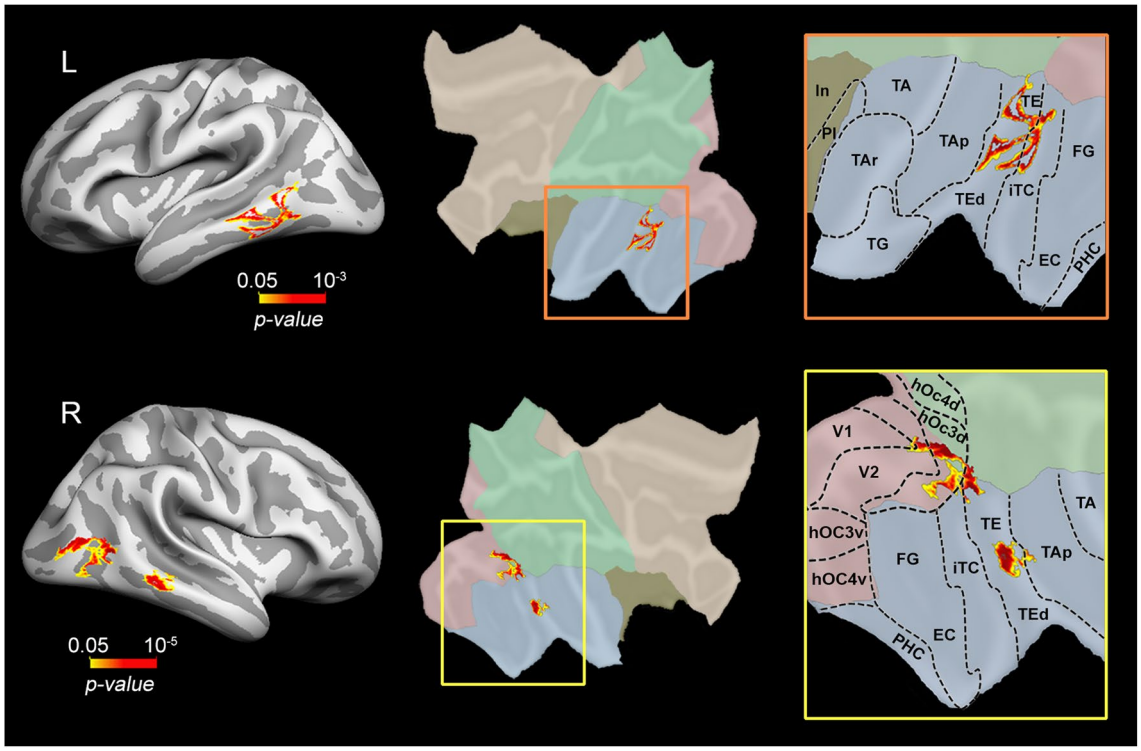

Fig. 2 Significant correlations between decreased serum TAC and reduction of cortical FDG uptake, after regressing out age and sex effects. Results were represented on inflated cortical surfaces (left column). Left (L) and right (R). Squares with colored borders on flattened cortical surfaces limit the location of significant correlations (middle column). Surfaces with colored borders were zoomed in to get a more accurate location of affected regions (right column). Abbreviations for the left middle temporal region (orange square): *PHC* parahippocampal cortex, *EC* entorhinal cortex, *FG* fusiform gyrus, *iTC* inferior temporal cortex, *TEd* temporal area dorsal, *TE* temporal area, *TAp* temporal area polisensory, *TG* temporal pole, *TAr* temporal area rostral, *TA* temporal area, *In* insula, *PI* parainsular cortex (Ding et al. 2009). Abbreviations for the right middle temporal and lateral occipital regions (yellow square): *TA* temporal area, *TAp* temporal area polisensory, *TEd* temporal area dorsal, *TE* temporal area, *iTC* inferior temporal cortex, *EC* entorhinal cortex, *FG* fusiform gyrus, *PHC* parahippocampal cortex (Ding et al. 2009), *hOC3v* ventral occipital cortex C3, *hOC4v* ventral occipital cortex C4, *V1* visual 1 area, *V2* visual 2 area (Rottschy et al. 2007), *hOc3d* dorsal occipital cortex C3, *hOc4d* dorsal occipital cortex C4 (Kujovic et al. 2013)

Serum TAC level and cortical glucose uptake in aging

Mounting evidence suggests that TAC is reduced in the aged brain, both in animals (Rodriguez-Siqueira et al. 2005) and humans (Venkateshappa et al. 2012). Aging-related antioxidant deficits mostly affect the frontal cortex and the medial temporal lobe (Rodriguez-Siqueira et al. 2005; Venkateshappa et al. 2012), making these regions more vulnerable to free radical-induced injuries and protein misfolding. However, lower antioxidant activity caused by aging and/or neurodegenerative diseases is not only circumscribed to the brain but also to blood compartments. Thus, previous research has shown that TAC measured in peripheral blood declines with age (Goraca 2004), increases in successful aging (da Cruz et al. 2014) and decays in prodromal and clinical stages of AD (Guidi et al. 2006; Sanchez-Espinosa et al. 2017; Perrotte et al. 2018). Nevertheless, the link between circulating blood TAC and in vivo brain changes had not been previously explored in human aging.

We showed that decreased serum TAC level was significantly correlated with lower glucose uptake in temporal cortices bilaterally. These findings are reminiscent of those obtained in senescence-accelerated mice, a genetically modified experimental model that shows faster senescence caused by an overproduction of ROS (Borras et al. 2009). In this study, the authors found an inverse relationship between in vivo glucose consumption and OS in the brain of these animals, results that were further substantiated by higher mitochondrial production of hydrogen peroxide and higher neuronal ROS. Mechanisms responsible for this lower cerebral glucose utilization in aging are not well understood. One possibility is that accelerated aging impairs the electron transport chain in mitochondria, affecting the cytochrome oxidase enzyme (COX, Complex IV of mitochondria electron transport chain) responsible for the oxygen activation for aerobic energy metabolism and the synthesis of

adenosine triphosphate (ATP). This cascade of events leads to increased production of ROS and disruption of energy metabolism in neurons, eventually promoting excitotoxicity and apoptosis (Wong-Riley 1989). Evidence supporting this hypothesis comes from studies that showed deficits of COX activity in the aged brain of non-human primates (Bowling et al. 1993) and in autopsied brain regions of AD (Kish et al. 1992; Simonian and Hyman 1993; Mutisya et al. 1994; Valla et al. 2001), a neurodegenerative condition characterized by deficits in neuronal glucose metabolism and mitochondrial dysfunctions (Batterfield and Halliwell 2019).

Evidence from postmortem brain tissue strongly suggests that brain glucose dysregulation is a critical event in AD pathogenesis that precedes the onset of clinical symptoms (An et al. 2018). These findings extend previous results showing that levels of glucose transporters GLUT1 and GLUT3 are decreased, especially in the cerebral cortex of AD patients (Simpson et al. 1994; Mooradian et al. 1997). The spatial distribution of GLUT1 and GLUT3 in the brain is extremely heterogeneous and may reflect the distribution of capillaries that is directly related to the local blood flow of different brain structures (Duelli and Kuschinsky 2001). More specifically, the 45 kDa GLUT1 isoform has shown to be selectively present both in the endothelium of the BBB and in astrocytes surrounding gray matter (Morgello et al. 1995), the cerebral compartment where the FDG uptake is supposed to be greater. Moreover, patients suffering the GLUT1 deficiency syndrome have shown a pronounced deficit of FDG uptake in regions of the medial temporal lobe while preserving the structural integrity of the cortical mantle (Pascual et al. 2002), as found in the present study.

Previous research suggests that impaired neuron-astrocyte signaling may also contribute to elucidate the relationship between decreased TAC and lower cortical glucose consumption in aging. Astrocytes, among other functions, provide metabolic support for neurons through GLUT1 (Kacem et al. 1998) and enhance the antioxidant potential of BBB endothelial cells (Schroeter et al. 1999). Although most of the brain's oxidative metabolism occurs in neurons, they have less antioxidant mechanisms than astrocytes. Accordingly, the high antioxidant potential of astrocytes protects neighboring neurons against oxidative stress mainly through the action of glutathione (Dringen et al. 2000; Gegg et al. 2005), the most abundant antioxidant molecule in the brain. Astrocytes respond differently in aging, showing decreased GLUT1 expression levels and, therefore, less glucose uptake (Souza et al. 2015). A pro-inflammatory environment, as occurs in aging-related conditions, leads astrocytes to switch from a resting to a reactive phenotype affecting metabolic support for neurons and decreasing antioxidant defense mechanisms (Gavillet et al. 2008). In our study, the association between decreased TAC level and lower glucose consumption in the temporal lobe could partially result from a sustained astrocyte reactive response in this cortical region, as occurs in AD models (Bogdanovic et al. 2001) and AD patients (Karelson et al. 2001).

Serum TAC level and factors promoting accelerated aging

To our knowledge, this is the first study to report an association between decreased serum TAC and risk factors associated with increased vulnerability of aging, such as higher HCY, worse subjective memory, and lower frequency of physical activity. Given the urgent need for non-invasive biomarkers accounting for different trajectories of aging, these findings may contribute to identify individuals at risk of developing pathological aging who can benefit from therapeutic strategies aimed to prevent cognitive frailty.

Evidence supports that higher HCY level increases the likelihood of death in elderly population (Gonzalez et al. 2007), and is an important risk factor for atherosclerosis (McCully 1969) and AD (Seshadri et al. 2002). The connection between HCY, vascular damage and OS has been long established (Welch et al. 1997; Kanani et al. 1999; Weiss et al. 2003; McCully 2017). The oxidized derivatives of HCY overstimulate the glutamate-binding site of the *N*-methyl-D-aspartate (NMDA), favoring mitochondrial dysfunction, increased ROS and caspase activation (Lipton et al. 1997). This cascade of events causes excitotoxicity, leading to decreased bioavailability of nitric oxide (NO) and apoptosis during the pathogenesis of atherosclerotic plaques (Lhotak et al. 2011). Decreased glutathione peroxidase-1, one of the major intracellular antioxidant enzymes, has been suggested to promote deleterious effects of HCY contributing to a pro-atherogenic state (Lubos et al. 2007). Consistent with this idea, recent findings have confirmed that aging leads to decreased NO bioavailability and increased oxidant formation, triggering redox-signaling pathways associated with endothelial NO synthase dysfunction, all these phenomena are shown to be exacerbated in aged glutathione peroxidase-1-deficient mice (Oelze et al. 2014).

Elevated HCY is further associated with deterioration of bone material properties such as collagen cross-link formation that affects the tensile strength and toughness of bone (Saito and Marumo 2018), increasing the risk of fallings/fractures (McLean et al. 2004; van Meurs et al. 2004), a leading cause of morbidity and mortality in older adults (Rubenstein 2006). It has been recently proposed that elevated HCY modulates osteoclastogenesis by enhancing the generation of ROS and decreasing the blood flow (Behera et al. 2017), thereby causing weakening of the bone and increasing the risk of osteoporosis (Sanchez-Rodriguez et al. 2007). Accordingly, previous research has found an association between low blood TAC level and reduced bone mineral density that resulted in osteoporosis in animal

models (Lean et al. 2003) and humans (Yilmaz and Eren 2009). Therefore, if confirmed in large, prospective trials, the aging-related association between decreased TAC and increased HCY reported in the present study may be helpful to identify cognitively normal elderly subjects at high risk of fallings/fractures due to moderately high level of HCY, which could be eventually reduced by folate and vitamin B12 supplementation.

Research performed in animal and cellular models of AD has shown that elevated circulating level of HCY affect redox-signaling pathways promoting brain amyloidosis and tau phosphorylation (Zhuo et al. 2010; Suszyńska-Zajczyk et al. 2014; Di Meco et al. 2019; Shirafuji et al. 2018), the two major pathological hallmarks of AD. Although much evidence supports that increased plasma concentration of HCY predicts the risk and progression of AD (Clarke et al. 1998; Seshadri et al. 2002; Hooshmand et al. 2012), few studies have documented an association between blood level of HCY and TAC in MCI/AD (Guidi et al. 2006; Sanchez-Espinosa et al. 2017). One of these studies also showed that increased HCY and lower TAC were independently associated with gray matter loss in the middle temporal lobe of MCI patients (Sanchez-Espinosa et al. 2017), the same cortical region involved in TAC-glucose uptake correlations in the present study. As TAC and cortical thickness were not correlated in our study, it is tempting to speculate that associations between decreased serum TAC and lower glucose consumption of the temporal lobe in the elderly may precede TAC-related structural deficits in the same cortical region during prodromal AD.

Our findings suggest that serum TAC and HCY combined with self-reported memory complaints may gain particular relevance to identify cognitive frailty in primary care practice; especially if one takes into account increasing evidence suggesting that self-perceived memory decline, in the absence of clinical impairment, represents one of the earliest manifestations of AD (Jessen et al. 2014). The relationship between TAC and subjective memory complaints (SMC) is supported by previous results showing a significant reduction of the cerebral metabolic rate for glucose in regions of the temporal and inferior frontal lobe in individuals with SMC when compared with demographically matched individuals with no such complaints (Mosconi et al. 2008). However, the association between HCY and memory complaints remains controversial (Hengstermann et al. 2008; Sala et al. 2008). Elevated HCY promotes atherosclerosis through increased oxidant stress, impaired endothelial function, and induction of thrombosis (McCully 1969), which may facilitate small vessel disease leading to subtle cognitive impairment in older adults (Low et al. 2019). Interestingly, only aging-related word-finding problems were associated with poorer objective memory. Evidence has shown that aging-related failures in word retrieval are related to atrophy in the insula, an area implicated in phonological production (Shafto et al. 2010). Remarkably, thinning of the insular cortex and temporal lobe precedes significant memory loss in MCI patients (Cantero et al. 2017), likely supporting naming and memory problems observed in AD. Follow up studies are clearly required to determine whether prominent naming deficits associated with volume loss of the insular cortex in cognitively normal elderly subjects predict pathological memory loss years later.

Finally, the present study also revealed a relationship between decreased serum TAC and lower frequency of physical activity, supporting the protective role of regular physical activity against OS in late life. Experimental data reveals that untrained muscles have lower amount of antioxidant enzyme activity and glutathione content, leading to impaired ROS removal (Ji et al. 1998). Thus, a sedentary lifestyle at old age is associated with reduced mitochondrial function, dysregulation of cellular redox status and chronic systemic inflammation that renders the skeletal muscle intracellular environment prone to ROS-mediated toxicity (Safdar et al. 2010). Conversely, physical exercise attenuates aging-related decline in mitochondrial function of the skeletal muscle partly due to upregulation of factors involved in promoting muscle mitochondrial biogenesis in response to exercise (Kang et al. 2013). Regular physical activity leads to increased resistance to OS even in previously sedentary elderly individuals (Done and Traustadottir 2016). Promising evidence suggests that exercise, even if initiated in advanced old age (Tolppanen et al. 2015), promotes anti-inflammatory defenses and enhances the redox state, affecting the expression of neurotrophins and, therefore, supporting normal brain function (Di Benedetto et al. 2017). Accordingly, physically fit older adults have less OS than unfit age-matched controls, likely due to greater circulating concentrations of non-enzymatic antioxidants and greater capacity to upregulate antioxidant enzymes (Traustadottir et al. 2012).

Conclusions

Tremendous effort has been made in the last decades for searching minimally invasive biomarkers able to detect how well a person is aging and/or to predict the risk of developing aging-related conditions. Here we provide evidence linking decreased serum TAC to lower glucose intake in the temporal cortex of normal elderly subjects. These observations were complemented by significant associations between lower serum TAC, higher concentrations of HCY, poorer subjective memory, and lower frequency of physical activity, all of them well-known factors associated with accelerated aging. In summary, our findings offer new insights into the ability of total antioxidant status measured in peripheral

blood for detecting vulnerability among the aged population. Further research is clearly required to establish if associations between blood TAC level and in vivo cortical glucose uptake precede pathological aging.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of Ethics Committee for Human Research of the Pablo de Olavide University and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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

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