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Cognitive decline is mediated by gray matter changes during middle age

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ABSTRACT

The present theoretical framework of Alzheimer's disease proposes that pathophysiological changes occur 10–20 years before the diagnosis of dementia. We addressed the question of how age-related changes in gray matter mediate the cognitive performance during middle age. Eighty-two participants (40–50 years, ±2) were assessed with a comprehensive neuropsychological battery covering a broad spectrum of cognitive domains and components. Mediation effects were studied with hierarchical regression and bootstrapping analysis. Results showed that more vulnerable cognitive components were related to executive functioning and in a lesser degree to processing speed. Age-related differences in gray matter mainly involved the frontal lobes. Moreover, age-related differences in visuoconstructive, visuospatial functions, reaction time, and mental flexibility and executive control were mediated by several gray matter regions. It is important to increase the knowledge of the impact of brain changes on cognitive function during middle age. To define the early stages of the aging process may allow early detection of pathologic changes and therapeutic interventions.

1. Introduction

Aging is associated with decline in cognitive functioning and brain structural changes. Regarding age-related cognitive changes, broad life-span studies have reported cognitive decline in processing speed, executive functions, attention, episodic memory (especially delayed recall), and language (lexical access and word retrieval) (Keys and White, 2000; Luo and Craik, 2008; Nilsson, 2003; Salthouse, 2009; Tisserand and Jolles, 2003). Decline in visuoperceptive, visuospatial, and visuoconstructive functions have also been reported, although they seem to begin at older ages (65 or more years). With respect to the age-related neuroanatomical changes, neuroimaging studies have consistently reported a linear decline in the gray matter volume and cortical thickness starting in the early adulthood (Abe et al., 2008; Hutton et al., 2009; Salat et al., 2004). White matter tissue shows a nonlinear evolution. White matter volume increases until the early middle-age adulthood (aged 35 years), with a period of stability and an accelerated decline only after the late middle age (aged 55–60 years). Likewise, diffusion tensor imaging studies analyzing water movement along the fiber tracks have demonstrated changes in white matter integrity early in the adulthood, although showing greater decline after the age of 60 (Abe et al., 2008; Fjell et al., 2008; Grieve et al., 2007). Interestingly, age-related decline both in gray and white matter follow a pattern of anterior-posterior gradient, with the prefrontal cortex and its cortical and subcortical circuits as the most involved regions (Bennett et al., 2009; Jernigan et al., 1991). Nevertheless, some studies have also shown age-related degeneration in posterior sensory regions (Salat et al., 2004; Ziegler et al., 2010).

Age-related cognitive and neuroanatomical changes seem to be well documented in the literature. However, the relationship between them is still poorly investigated and results are inconsistent. Most studies have focused on the white matter, but only a few have analyzed the gray matter. Findings support that age-related neuroanatomical changes contribute to the cognitive decline in executive functions, processing speed, and episodic memory. More

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specifically, age-related changes in executive functions have been linked to decline in both frontal gray and white matter (Brickman et al., 2006; Davis et al., 2009; Gunning-Dixon and Raz, 2003; Raz et al., 1998; Ziegler et al., 2010; Zimmerman et al., 2006), and to posterior visual regions when executive tasks involve visual processing (Raz et al., 1998). Moreover, temporal and posterior white matter regions have been identified in tasks of flexibility and inhibition (Kennedy and Raz, 2009; Madden et al., 2009). Age-related changes in processing speed seem to be mainly explained by degeneration in frontal regions, either gray matter or white matter (Gautam et al., 2011; Gunning-Dixon and Raz, 2000; Kennedy and Raz, 2009). Finally, age-related memory impairment appears to be associated with the volume and integrity of frontal, temporal, and parietal white matter, and the inferior longitudinal fascicle (Brickman et al., 2006; Davis et al., 2009; Gautam et al., 2011; Gunning-Dixon and Raz, 2000; Ziegler et al., 2010). Moreover, individual variability in well preserved functions such as semantic or short-term memory is accounted by variability of global and regional gray matter volume in healthy elderly individuals (Taki et al., 2011). However, other cognitive functions as attention, visuospatial, visuoconstructive abilities, and language have received almost no attention. In addition, a critical issue in most of the previously mentioned studies is that correlation analyses may not be sufficient to establish a mediation effect of neuroanatomical changes on the relationship between age and cognitive performance (Madden et al., 2009). Few studies have proven such a mediation effect by conducting hierarchical regression analyses or other mathematical methods (e.g., path analyses in Gunning-Dixon and Raz, 2003). With regard to the gray matter, only Gunning-Dixon and Raz (2003) carried out a mediation analysis. However, these authors only included 2 gray matter regions (prefrontal cortex and fusiform gyrus), and 2 cognitive tasks (a verbal working memory task and the Wisconsin Card Sorting Test). Therefore, further studies are mandatory to determine the possible involvement of the age-related gray matter changes on the age-related decline in cognition.

As we have mentioned previously, structural brain changes and some cognitive deficits start early in the middle age. Further research is warranted to improve the diagnosis, prevention, and prediction of pathologic aging at an early level. From a therapeutic point of view, to define the age at which brain structural and cognitive decline begins is also important to determine the most suitable window at which potential interventions can have greater benefits. In the case of Alzheimer's disease, the most widely validated biomarkers of Alzheimer's disease become abnormal in an ordered manner starting 10–20 years before the diagnosis of dementia (Jack et al., 2010), probably overlapping the middle-age period. In this sense, research on the middle-age adulthood is of great importance, given that it is the critical point when the first pathophysiological changes begin to take place. Therefore, it is the ideal point to implement early interventions (Center for Disease Control and Prevention, 2009).

In the present study, we examined the age-related changes in cognition and gray matter, and the relationship between them, in a large cohort of middle-aged participants. We carried out an in-depth analysis of both gray matter volume and cortical thickness through multiple structural regions covering the whole brain. Although volume and thickness are highly related markers, they represent different characteristics of the tissue, giving complementary information on processes occurring in the gray matter. Because cortical volume is a product of thickness and surface area, degenerative processes that selectively affect surface area (e.g., age-related sulcal expansion), could be related to changes in cortical volume but not in cortical thickness (Ziegler et al., 2010). A comprehensive neuropsychological battery was applied with the aim of covering the largest possible number of cognitive functions and components. Finally, hierarchical regression and bootstrapping analyses were used to investigate whether age-related gray matter changes mediated the effects of aging on cognitive functioning. We predicted a selective age-associated gray matter reduction, especially in anterior brain regions, and that this variability would be significantly associated with age-related cognitive decline, particularly in those functions mediated by more anterior brain regions such as executive functioning.

2. Methods

2.1. Participants

One hundred twenty-five early-middle-aged participants were initially enrolled. Personnel from local schools, and relatives and acquaintances of the research staff were recruited for the study. Participants initially underwent a telephonic interview to screen the following criteria: (1) age between 40 and 50 (±2); (2) preserved cognitive and functional status; (3) no neurologic or psychiatric disorders, systemic diseases with neuropsychological consequences, or substance abuse history. Once this criteria was applied, 11 participants were discarded because of: traumatic brain injury (2); cerebral tumor (2); symptomatology subjective of neurologic disease (1); systemic disease with subtle cognitive impairment (1); and depression (5). Remaining participants underwent an exhaustive interview, neuropsychological assessment, and magnetic resonance imaging (MRI) studies. After data collection, 13 participants were excluded because of anomalous neuropsychological performance (−2Sd in more than 8 variables using own sample descriptive values), and/or a pathologic MRI examination. All included participants gave their written informed consent and the study was approved by the local ethics committee.

The final sample consisted of 82 participants (51% female), all of them native Spanish speakers from the Canary Islands. Mean age was 45.07 (3.92 years), and all participants had a Mini Mental State Examination total score of 26 or greater (mean: 29.20; Sd: 1.05). Age did not correlate with the Mini Mental State Examination total score ($r = -0.118$; $p = 0.293$). Wechsler Adult Intelligence Scale (WAIS) Information subtest (Wechsler, 1997a), a measure of crystallized intelligence, was used as indicator of education. Performance in WAIS Information is not affected by the age effect. Moreover, in populations that received heterogenous formal education, as the one included in this study, these measures best represent achievements and/or usage of educative opportunities in comparison with the number of years of study or degree attained (Barnes et al., 2004; Manly et al., 1999). Mean WAIS information was 15.40 (5.80), with scores between 6 and 26. Age was neither related with WAIS information ($r = 0.054$; $p = 0.633$), nor gender ($t_{[80]} = 0.782$; $p = 0.436$). Education and gender may have a significant effect on cognitive performance and gray matter. Therefore, we entered them as confounding variables in the analyses when they were significantly correlated with cognitive performance and/or gray matter.

2.2. Cognitive assessment

Cognition was assessed using a comprehensive neuropsychological battery covering processing speed, attention, executive functions, verbal and visual episodic memory, visual abilities and language. Processing speed was measured with Choice Reaction Times from the PC-Vienna System (Schuhfried, 1992). Part A from the Trail Making Test (TMT: Reitan, 1958) and part 1 from the Color Trails Test (CTT: D'Elia and Saltz, 1989) were applied to assess attention and visual tracking-visuomotor components. Regarding

executive functions, CTT part 2 was applied to assess mental flexibility and executive control, and Digit and Visuospatial Spans from Wechsler Memory Scale (WMS-III) (Wechsler, 1997b) as working memory tasks. Digit and Visuospatial Spans include 2 modalities (verbal and visual), and 2 components (amplitude: forward; and manipulation: backward). TAVEC (Spanish version of California Verbal Learning Test [CVLT]) (Benedet and Alejandre, 1998) and Visual Reproduction from WMS-III were applied to evaluate verbal and visual episodic memory, respectively. Visual abilities were assessed by means of Block Design from WAIS-III (Wechsler, 1997a) and the Judgment of Line Orientation Test form H (JLOT: Benton et al., 1983). Finally, language functioning was assessed with Actions Gereration by Semantic Associations Test (Test de Generación de Acciones por Asociación Semántica or TGAAS), an in-house computerized task to evaluate the lexical access. TGAAS is an auditory task where participants are given 30 nouns and semantic associated actions must be generated. Moreover, 3 different categories are included: nMA (nouns without a morphologic derived action, e.g., pencil—to write), MA (nouns with a morphologic derived action, e.g., conversation—to converse), and CMA (cognitive nouns with a morphologic derived action, e.g., past—to forget). As morphologic derived actions are not allowed, those categories with morphologic derived actions entail cognitive inhibitory processes and they are thus more difficult. Stimuli are presented and responses are recorded with milliseconds precision using the E-prime v1.1 Software (Psychology Software Tools, Inc, 2002).

2.3. MRI acquisition

Participants were scanned using a 3.0 T General Electric imaging system (General Electric, Milwaukee, WI, USA) at the Hospital Universitario de Canarias, Tenerife (Spain). Three-dimensional T1-weighted FSPGR sequence (Fast Spoiled Gradient Echo) was acquired in sagittal plane with the following parameters (repetition time/echo time = 8.73/1.74 ms, inversion time = 650 ms, field of view = 250 × 250 mm, matrix 250 × 250 mm, flip angle 12°, slice thickness = 1 mm). Full brain and skull coverage was required for the MRI datasets and detailed quality control was carried out on all MR images according to previously published criteria (Simmons et al., 2009).

2.4. MRI data analysis

Cortical reconstruction and volumetric segmentation were performed using the FreeSurfer 5.1.0 image analysis suite (http://surfer.nmr.mgh.harvard.edu/), including: (1) motion correction; (2) removal of nonbrain tissue (Ségonne et al., 2004); (3) automated Talairach transformation; (4) segmentation of the subcortical structures (Fischl et al., 2004a); (5) intensity normalization (Sled et al., 1998); (6) tessellation of the gray matter white matter boundary; (7) automated topology correction (Ségonne et al., 2007); (8) surface deformation following intensity gradients to optimally place the gray and/or white and gray and/or cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al., 1999; Fischel and Dale, 2000); (9) registration to a spherical atlas (Fischl et al., 1999); (10) parcellation of the cerebral cortex into units based on gyral and sulcal structure (Desikan et al., 2006); and (11) creation of a variety of surface based data.

Visual quality control was performed on all output data. All steps involving brain extraction, automated Talairach transformation, tessellation, surfaces reconstruction, and subcortical segmentation were carefully checked. After image processing, volume and cortical thickness measures were selected for its analysis. Briefly, volume measures include cortex, cerebellum, and deep gray matter structures (Fischl et al., 2002, 2004a), and measures of 34 cortical regions in both hemispheres (Desikan et al., 2006; Fischl et al., 2004b). Cortical thickness measures include the same 34 regions for both hemispheres. In addition to these measures, total gray matter volume was calculated by adding up cortex volume, and right and left caudate, thalamus, putamen, pallidum, hippocampus, amygdala, ventral diencephalum, and accumbens volumes. All volume measures were corrected by the total intracranial volume to account for between-individuals differences (Westman et al., 2013).

2.5. Statistical analysis

According to Baron and Kenny (1986), 3 conditions are necessary to demonstrate that gray matter is a mediator of the relationship between age and cognitive performance (Fig. 1). *First*, there must be a significant association between age and cognitive performance. *Second*, a significant association between age and gray matter regions must exist as well. *Third*, for significant variables in first and second steps, gray matter should account for significant variance in cognitive performance, when age is also included in the model. A mediating relation exists when the amount of age-related variance in cognitive performance is substantially attenuated by the presence of gray matter in the model (*third* step), relative to when age is the sole independent variable (*first* step). First and second steps were tested using Pearson correlation analyses. Partial correlations were used as well to control the possible effect of gender and education. Before performing the third step, we tested the direct relationship between gray matter and cognitive performance. This strategy allowed us not only to complement the previous analyses, but also to identify significant relationships to reduce the number of models performed in the subsequent third step. The third step was conducted using hierarchical regression analyses as in previous studies (Madden et al., 2009; Salami et al., 2012). Among age, gray matter, and cognitive performance, the flow of variance is presumed unidirectional, with upstream variables having the ability to affect downstream variables, but not the other way around. In other words, in our model, age is assumed to be measured without error and not influenced either by gray matter or cognitive performance. Gray matter is positioned before age in the hierarchical model because it presumably could be affected by age but not by cognitive performance, at least under normal range of circumstances. Cognitive variables are the last level under the assumption that such cognitive functions could be influenced by both age and gray matter. We performed hierarchical regression analyses to estimate the age-related variance in cognitive performance when gray matter is entered in the first block of the model, before age, which was entered in the second block (see Fig. 1). As we wanted to further

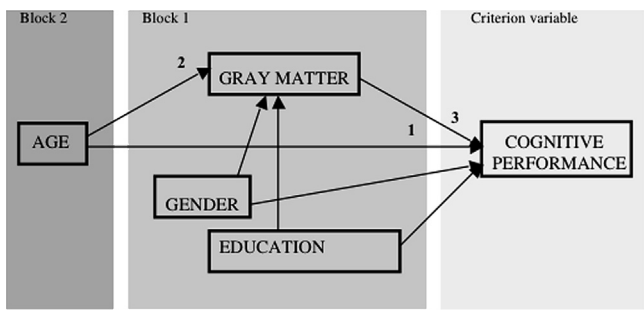

Fig. 1. Hierarchical regression model: relationship between age, gray matter and cognition, including confounding variables gender and education. Block 1 represents predictor variables entered first in the hierarchical regression model. Block 2 represents predictor variables entered after block 1 in the hierarchical regression model. Numbers represent steps in Baron and Kenny's model.

Table 1
Mediation of age-related differences in gray matter on age-related differences in cognition

Cognitive variable (Y)	Model	R^2	F	*p*	Predictors (X)	R^2	β	*p*	Mediation			
									Att.	PE	SE	BC 95% CI
Block design-complex	Right thalamus vol + age (+gender + education)	0.399	12.755	0.0001	Age	0.045	−0.211	0.024				
					Right thalamus vol	0.034	0.185	0.054	51%			NS
	Right caudal middle frontal CT + age (+gender + education)	0.405	13.114	0.0001	Age	0.038	−0.194	0.039				
					Right caudal middle frontal CT	0.040	0.201	0.032	42%	−0.131	0.078	−0.333/−0.016
	Right precentral CT + age (+gender + education)	0.409	13.308	0.0001	Age	0.038	−0.196	0.036				
					Right precentral CT	0.044	0.209	0.025	43%	−0.127	0.077	−0.345/−0.023
Block design-total WAIS score	Right caudal middle frontal CT + age (+gender + education)	0.451	15.814	0.0001	Age	0.027	−0.163	0.071				
					Right caudal middle frontal CT	0.034	0.184	0.042	37%	−0.147	0.093	−0.380/−0.010
	Right precentral CT + age (+gender + education)	0.471	17.150	0.0001	Age	0.023	−0.153	0.083				
					Right precentral CT	0.055	0.235	0.008	32%	−0.176	0.102	−0.466/−0.029
	Left caudal middle frontal CT + age (+gender + education)	0.474	17.313	0.0001	Age	0.019	−0.139	0.118				
					Left caudal middle frontal CT	0.059	0.243	0.007	27%	−0.214	0.121	−0.607/−0.052
Reaction time	Right caudal anterior cingulate vol + age (+gender + education)	0.246	6.134	0.0001	Age	0.036	0.190	0.074				
					Right caudal anterior cingulate vol	0.052	0.229	0.032	51%	1.292	0.802	0.172/3.558
CTT-2	Right thalamus vol + age (+gender + education)	0.154	3.104	0.021	Age	0.039	0.198	0.100				
					Right thalamus vol	0.037	−0.193	0.115	(58%)	0.421	0.316	0.005/1.360
	Left lingual CT + age (+education)	0.164	4.519	0.006	Age	0.045	0.213	0.063				
					Left lingual CT	0.044	−0.209	0.067	NO			NS
TAVEC first learning trial	Left caudal middle frontal CT + age (+education)	0.146	4.434	0.006	Age	0.038	−0.195	0.079				
					Left caudal middle frontal CT	0.028	0.168	0.129	NO			NS
JLOT	Left superior parietal CT + age (+gender + education)	0.328	9.403	0.0001	Age	0.029	−0.169	0.090				
					Left superior parietal CT	0.032	0.179	0.070	(46%)	−0.049	0.030	−0.123/−0.002
TGAAS correct responses	Left supramarginal vol + age (+education)	0.321	12.134	0.0001	Age	0.042	−0.283	0.041				
					Left supramarginal vol	0.030	−0.002	0.083	NO			NS
TGAAS errors	Left supramarginal vol + age (+education)	0.188	5.956	0.001	Age	0.031	−0.206	0.106				
					Left supramarginal vol	0.027	0.173	0.131	NO			NS
TGAAS CMA correct responses	Left supramarginal vol + age (+gender + education)	0.355	10.440	0.0001	Age	0.065	0.177	0.011				
					Left supramarginal vol	0.028	−0.165	0.093	NO			NS
TGAAS CMA errors	Left supramarginal vol + age (+education)	0.225	7.435	0.0001	Age	0.060	−0.254	0.023				
					Left supramarginal vol	0.025	0.167	0.137	NO			NS

Degree of attenuation = age-related variance in cognitive performance when accounting for gray matter (Table 1)/age-related variance in cognitive performance (Table 2). In brackets: mediation effect according to bootstrapping analysis but not to Baron and Kenny's model; (the mediation effect is significant when zero is not in the 95% confidence interval).

Key: Att, degree of attenuation; BC 95% CI, bias corrected 95% confidence interval; CMA, cognitive nouns with a morphologic derived action; CTT, Color Trails Test; JLOT, Judgment of Line Orientation Test; Vol, volume; WAIS, Wechsler Adult Intelligence Scale.

control the confounding effect of gender and education over cognitive functioning, we also entered these 2 variables in the first block of the regression model. Bonferroni correction was applied in all hierarchical regression analyses. Moreover, following Madden et al. (2009), we calculated the degree to which gray matter attenuates the age-related variance in cognition. We divided the unique variance in cognitive performance associated with age when gray matter is also entered in the model (Table 1), by the variance associated with age as the sole predictor (Table 2) (see Table 1, "Mediation" section). Associated point estimates and standard errors of the mediation effect were calculated with the product-of-coefficients approach (Preacher and Hayes, 2008). Confidence intervals were calculated with bootstrapping, a nonparametric resampling procedure that does not impose the assumption of normality of the sampling distribution. Bootstrapping provides the most powerful and reasonable method of obtaining confidence limits for mediation effects (Preacher and Hayes, 2008). Bias corrected 95% confidence intervals were

Table 2
Correlation between age and cognitive performance

Cognitive variable	Mean (Sd)	R^2	r	p
Reaction time	636.08 (84.16)	0.071	0.266	0.018
TMT-A	33.28 (9.58)	0.083	0.288	0.038
CTT-1	41.05 (1228)			ns
CTT-2	89.05 (28.55)	0.067	0.258	0.029
Digit-forward	8.32 (2.09)			ns
Digit-backward	5.96 (1.75)			ns
Visuospatial-forward	8.12 (1.67)			ns
Visuospatial-backward	7.84 (1.58)	0.088	−0.296	0.008
TAVEC-learning first trial	7.39 (1.71)	0.064	−0.252	0.023
TAVEC-learning total	58.37 (7.60)			ns
TAVEC-delayed recall	14.41 (1.71)			ns
TAVEC-recognition	15.70 (0.54)			ns
Visual reproduction-immediate	87.23 (9.35)			ns
Visual reproduction-delayed recall	75.87 (16.70)			ns
Visual reproduction-recognition	45.07 (2.28)			ns
Block design-simple	31.85 (0.63)			
Block design-complex	37.29 (9.04)	0.089	−0.299	0.007
Block design-total WAIS score	40.49 (11.12)	0.072	−0.269	0.016
JLOT	23.84 (3.80)	0.063	−0.251	0.025
TGAAS correct responses	24.52 (4.12)	0.086	−0.294	0.008
TGAAS errors	2.43 (3.81)	0.058	0.241	0.031
TGAAS-nMA correct responses	9.15 (1.39)			ns
TGAAS-nMA errors	0.51 (1.24)			ns
TGAAS-MA correct responses	8.64 (1.34)			ns
TGAAS-MA errors	0.42 (0.93)			ns
TGAAS-CMA correct responses	6.73 (2.19)	0.118	−0.343	0.002
TGAAS-CMA errors	1.51 (2.00)	0.098	0.313	0.005

Reaction time (milliseconds: mean); TMT and CTT (seconds); Digit and Visuospatial (correct items); TAVEC (number of correct words); Visual Reproduction (number of correct elements); Block Design (number of blocks correctly placed in simple (4 blocks) and complex (9 blocks) designs; total WAIS score as indicated in original instructions. Extended time was further included to minimize processing speed dependence); JLOT (correct responses); TGAAS (correct responses and errors).
Key: CMA, cognitive nouns with a morphologic derived action; CTT, Color Trails Test; JLOT, Judgment of Line Orientation Test; MA, nouns with a morphologic derived action; nMA, nouns without a morphologic derived action; TMT, Trail Making Test, WAIS, Wechsler Adult Intelligence Scale.

preferably used because regular confidence intervals are forced to be symmetrical, leading to estimation inaccuracies and problems with type I errors and power. All statistical analyses were performed using SPSS 20.0 for Mac, with a p value of <0.05 deemed significant.

3. Results

3.1. Age-related differences in cognitive performance

Age was significantly correlated with performance on Reaction time, TMT-A, CTT-2, Visuospatial backward, TAVEC first learning trial, Block design (number of blocks in complex designs and total WAIS score), JLOT, and TGAAS (total and cognitive nouns with a morphologic derived action condition) (Table 2). Correlation coefficients were all in the predicted directions indicating worse performance with increasing age. Effect sizes were large in all cases.

3.2. Age-related differences in gray matter

Correlation between age and total gray matter volume, and mean cortical thickness, showed a trend (gray matter volume: pr = −0.211; $p = 0.059$; mean thickness: r = −0.214; $p = 0.056$). More specific regional analyses showed significant relationships between age and both volume and cortical thickness involving mainly frontal and parietal lobes. Regarding gray matter volume, age was negatively correlated with the right thalamus (pr = −0.225; $p = 0.044$), left amygdala (r = −0.251; $p = 0.023$), left superior parietal (pr = −0.220; $p = 0.050$), and left supramarginal (r = −0.311; $p = 0.004$). Moreover, we found a positive correlation between age and the right caudal anterior cingulate (r = 0.247; $p = 0.025$). Regarding cortical thickness, age correlated negatively with the bilateral caudal middle frontal (right: r = −0.260; $p = 0.018$; left: r = −0.294; $p = 0.007$), right lateral orbitofrontal (r = −0.241; $p = 0.029$), right precentral (r = −0.253; $p = 0.022$), right rostral anterior cingulate (r = −0.231; $p = 0.037$), left postcentral (r = −0.242; $p = 0.029$), left superior parietal (r = −0.272; $p = 0.013$), and left lingual (r = −0.239; $p = 0.030$). Effect sizes were from moderate to large.

3.3. Relationship between gray matter and cognitive performance

Because the main question in this study was to find gray matter regions that mediated age-related cognitive decline, we limited the correlation between gray matter and cognition to those measures that were significantly associated with age in the previous analyses. Results are shown in Table 3 and Fig. 2. Correlations indicated that worse cognitive performance was related to less gray matter volume or cortical thickness, except in relationships involving the right caudal anterior cingulate. As volume in this structure increased with age, but performance in Reaction time got worse with age, relationships between them indicated that an age-related decline in this cognitive task was associated with greater volume. On the other hand, age-related decline in CTT-2 was related to smaller right thalamus volume and left lingual thinning. Performance on TAVEC first learning trial was associated with caudal middle frontal thinning. Decline in Block design correlated to thinning of bilateral caudal middle frontal and right precentral gyrus, and decline in the right thalamus volume. Worsening in JLOT correlated with left superior parietal thinning. Finally, worse performance in TGAAS correlated with decline in the left supramarginal volume. Effect sizes were from moderate to large in all the cases. Age-related changes in TMT-A and Visuospatial backward did not correlate with any structural region.

3.4. Mediation of age-related differences in gray matter on age-related differences in cognition

Hierarchical regression analyses were conducted to study whether gray matter tissue was a real mediator of the relationship between age and cognitive performance (Table 1 and Fig. 2). A mediating relation exists when the amount of age-related variance in cognitive performance is substantially attenuated by the presence of gray matter in the model (see Table 1, “Predictors [X]: Age”), relative to when age is the sole independent variable (see Table 2). Table 1 also represents the relationship between gray matter and cognitive performance when accounting for the age effect (see e.g., “Predictors [X]: Right thalamus vol”). Age-related decline in Block design was mediated by age-related cortical thinning in bilateral caudal middle frontal gyrus and right precentral cortex. Moreover, the right thalamus volume showed a trend ($p = 0.054$) (see Fig. 3 for an example). Age-related decline in Reaction time was mediated by age-related increase in the right caudal anterior cingulate volume. Associated degrees of attenuation ranged from 27% to 51%. Bootstrapping analyses confirmed that all these attenuations were significant (see Table 1, “BC 95% CI”). Moreover, this procedure showed that the right thalamus volume significantly mediated the age-related variance in CCT-2; and the left superior parietal thickness significantly mediated the age-related variance in JLOT (Table 1). Regarding TAVEC first learning trial and TGAAS, in spite of the significant correlation between performance in these age-declined cognitive variables and several age-declined gray matter regions, hierarchical regression and bootstrapping analyses showed no mediation effects.

Table 3
Correlation between gray matter and cognitive performance

Hemisphere	Structural region	Mean (Sd)	Cognitive variable	r	*p*
Right	Thalamus (Vol)	0.49 (0.05)	Block design (complex)	0.270	0.015
			CTT-2	−0.253	0.033
	Caudal middle frontal g. (CT)	2.51 (0.12)	Block design (complex)	0.305	0.006
			Block design total WAIS score	0.288	0.010
	Precentral g. (CT)	2.50 (0.12)	Block design (complex)	0.311	0.005
			Block design total WAIS score	0.345	0.002
	Anterior cingulate (caudal region) (Vol)	0.15 (0.03)	Reaction time	0.297	0.008
Left	Caudal middle frontal g. (CT)	2.58 (0.11)	Block design total WAIS score	0.354	0.001
			TAVEC learning trial 1	0.233	0.036
	Supramarginal g. (Vol)	0.73 (0.07)	TGAAS correct	0.269	0.016
			TGAAS errors	−0.233	0.038
			TGAAS CMA correct	0.260	0.020
			TGAAS CMA errors	−0.250	0.026
	Superior parietal g. (CT)	2.32 (0.10)	JLOT	0.260	0.020
	Lingual g. (CT)	2.13 (0.12)	CTT-2	−0.256	0.030

Key: CT, cortical thickness (mm); CTT, Color Trails Test; JLOT, Judgment of Line Orientation Test; Vol, volume (ratio, all volume measures are corrected by the total intracraneal volume); WAIS, Wechsler Adult Intelligence Scale.

4. Discussion

In the present work we aimed to study how age-related changes in gray matter mediate age-related changes in cognition during the early stage of the middle-age adulthood. To isolate the age effect, we exerted a statistical control of the confounding effect of gender and education.

Results regarding age-related differences in cognitive performance could be explained by early deficits in the executive functioning (CTT-2, Visuospatial-Backward, TAVEC-Learning first trial, Block Design complex, TGAAS), and in a lesser degree, in processing speed (Reaction time, TMT-A). Although TAVEC and Block Design are frequently considered as measures of memory and visuoconstructive functions, respectively, the first learning trial in TAVEC can also be regarded as a measure of working memory (amplitude), and Block Design has been related to executive and/or prefrontal functions (Anstey et al., 2002; Haaland et al., 2003). Likewise, TGAAS is a test of lexical access that entails cognitive inhibitory processes. Results on age-related differences in gray matter also confirmed the predicted reduction especially in anterior brain regions. Regarding the relationship between age-related differences in cognition and gray matter, mental flexibility, and executive control was related to the right thalamus volume and left lingual thickness. The poorer performance in initial learning of supra-span information was associated with reduced cortical thickness in the caudal middle frontal gyrus. Decline in visuoconstructive functions correlated with cortical thickness of the bilateral caudal middle frontal gyrus and right precentral gyrus, and the volume of the right thalamus. Worse performance in visuospatial functions correlated with the left superior parietal thickness. The linguistic component of lexical access by semantic association correlated with the left supramarginal volume. Finally, worse performance in reaction time was related to greater volume of the right caudal anterior cingulate. Moreover, hierarchical regression analyses showed a mediation effect of several frontal regions on age-related differences in visuoconstructive functions and reaction time. Bootstrapping analyses confirmed these results and added a mediation effect of the left parietal lobe and right thalamus on visuospatial functions and mental flexibility and/or executive control, respectively. These differences between methods may be explained because bootstrapping more directly addresses the mediation hypothesis. It requires one fewer test and thus type I and type II errors would be less likely (Preacher and Hayes, 2008).

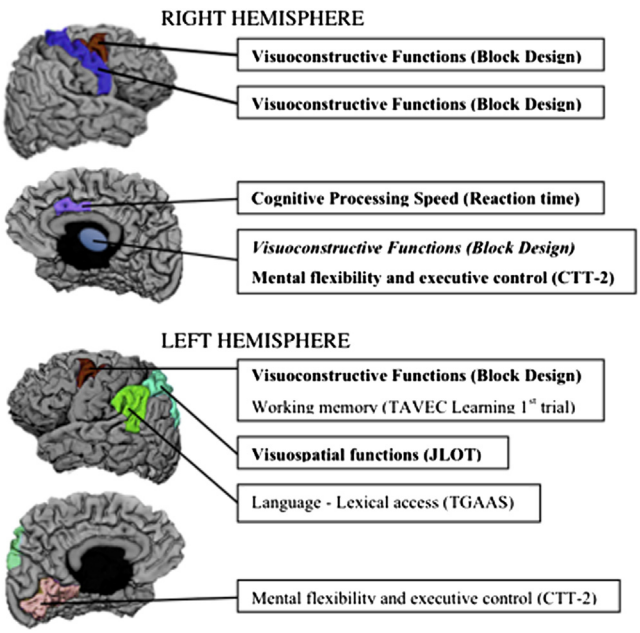

Fig. 2. Relationship between gray matter and cognitive performance. Bold: significant mediation effect of gray matter on cognitive performance (bootstrapping analyses); italics: trend for a mediation effect ($p = 0.054$).

There are almost no studies in the literature about the mediation effect of age-related gray matter changes over the age-related cognitive decline. Nevertheless, our findings are well supported by studies focusing on white matter, and more general literature resting on correlation analyses and spanning broad age ranges. In our study, Block design, as a visuoconstructive task, was mediated by the precentral gyrus and middle frontal cortex, and showed a trend for the thalamus. To our knowledge, only Salami et al. (2012) have previously studied the influence of age-related brain structural changes on Block design. However, these authors limited their analyses to the white matter tissue and failed to find any mediation effect. We can hypothesize that Block design correlated with the precentral gyrus given that motor skills are involved in its correct execution. It also correlated with the caudal middle frontal cortex, which could be explained by attending to its motor, planning, and problem solving dependency. Moreover, it has been described in the literature that Block design could be influenced by factors other than visuospatial and visuoconstructive functions in normal aging, and authors point to the executive and/or prefrontal functions

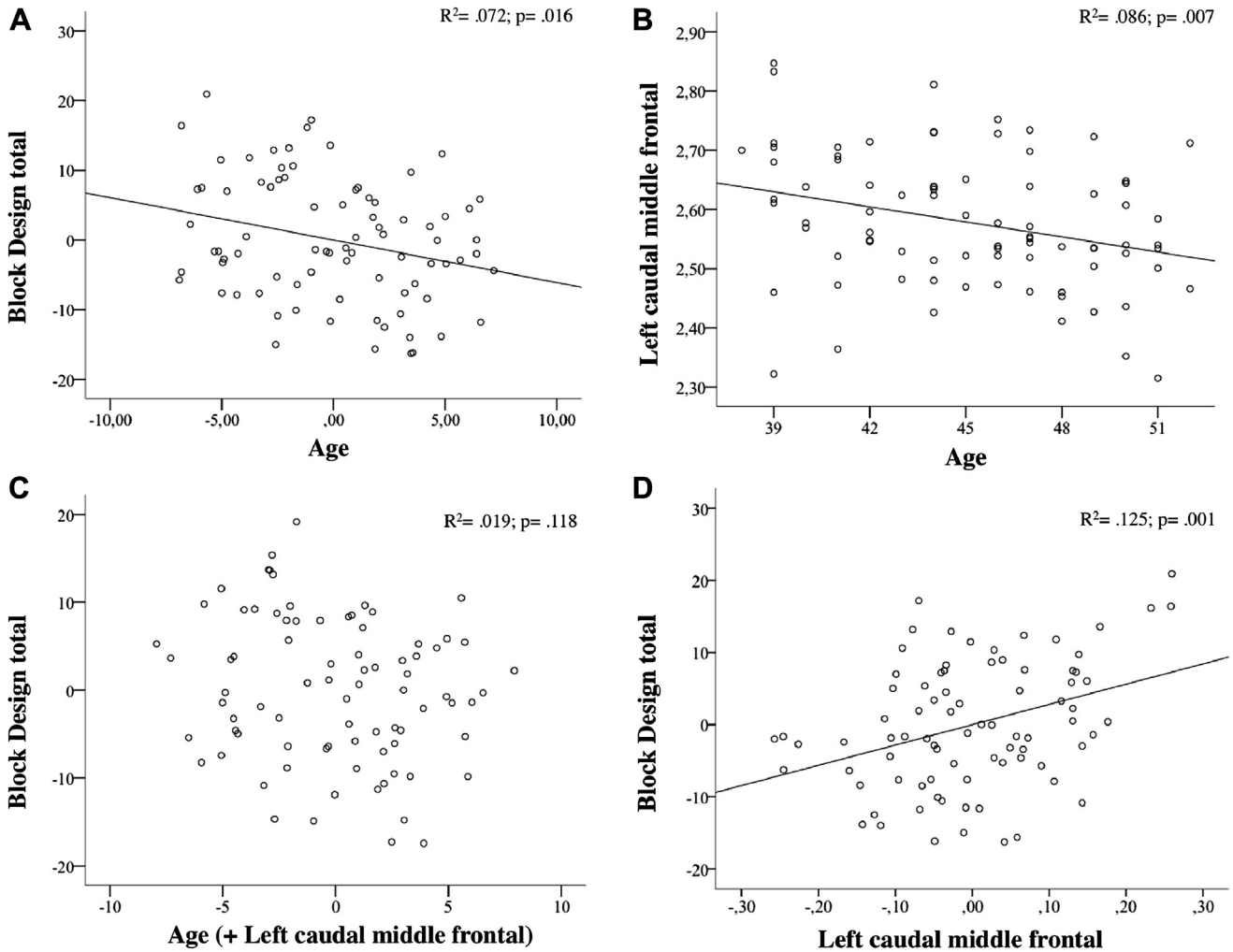

Fig. 3. Mediation effect of the left caudal middle frontal gyrus over the age-related variance in Block Design total: the amount of age-related variance in Block Design total is substantially attenuated by the presence of left caudal middle frontal in (C) ($R^2 = 0.019$), relative to when age is the sole independent variable in (A) ($R^2 = 0.072$). A: relationship between age and Block Design total (accounting for gender and education) (step 1 in Baron and Kenny's model); B: relationship between age and left caudal middle frontal (step 2 in Baron and Kenny's model); C: relationship between age and Block Design total when left caudal middle frontal is also included in the model (accounting for gender and education) (step 3 in Baron and Kenny's model); D: relationship between Block Design total and left caudal middle frontal (accounting for gender and education). Units of measurement: A, C, and D show residuals from the hierarchical regression models; B shows years (age) and cortical thickness (millimeters).

(Anstey et al., 2002; Haaland et al., 2003). Interestingly, Block design also correlated with the right thalamus. This subcortical structure is part of the dorsolateral prefrontal circuit, which connects the middle frontal cortex with the parietal cortex. Lesions in this circuit entail alterations in spatial working memory tasks.

Worse performance in reaction time was related to greater volume of the right caudal anterior cingulate. This a priori counterintuitive result can be explained because the volume in this structure increased with age in our cohort. Other authors have reported similar results (Fjell et al., 2008; Ziegler et al., 2010). It has been speculated that greater volume or thickness with age in specific cortical regions may impart some protective advantage in older adults in terms of performance in specific cognitive domains (Fjell et al., 2006). In the case of the cingulate gyrus, such possible protective advantage is not surprising as it is part of the associative cortex, which would be the best candidate to compensate age-related deficits in more primary regions. In fact, the anterior cingulate region has been related with high demanding tasks that require complex integration of different stimuli (executive attention system), solving of cognitive conflicts, planning, decision making, error monitoring, and novel responses. The reaction time task used in the present study involves maintenance of attention, requires decision making, and solving of simple cognitive conflicts. Moreover, this task creates a completely novel setting for participants, thus demanding novel responses. However, performance in reaction time got worse with age, leading to a negative mediation of the right caudal anterior cingulate on cognitive performance. As the volume of the right caudal anterior cingulate increased with age, but the performance in reaction time got worse with age, the relationship between both measures indicated that the age-related decline in this cognitive task was associated with greater volume. Our results do not seem to support a protective effect of the anterior cingulate region in reaction time performance. Instead, it might be influenced by the variability in our sample. Therefore, this finding should be confirmed in future studies.

Results presented here are novel in relation to the mediation effect of age-related changes in brain structure over cognitive functioning. To date, several authors have provided some findings regarding this relationship. However, information is still very limited and there are almost no studies, especially regarding the middle-age adulthood. As far as we know, only Brickman et al. (2006) and Gautam et al. (2011) included specific groups of

middle-aged participants in their studies. However, these studies applied brief neuropsychological batteries and analyses were focused on the white matter tissue (Brickman et al., 2006) or limited gray matter regions (Gautam et al., 2011).

Our findings show that age-related gray matter changes mediated the cognitive decline in several cognitive functions already during the middle-age adulthood. These findings contribute to advance in the knowledge about normal aging. Moreover, we believe that it is of great importance to increase the knowledge of middle-age adulthood to better define the earliest stages of the aging process. Nonetheless, we acknowledge several limitations in the present study. First, conclusions rely on cross-sectional data and, therefore, must be confirmed in longitudinal designs. Our results belong to the first phase of a longitudinal study carried out in our group. Second, we did not apply the Bonferroni correction for multiple comparisons in some of the correlational analyses. Although the likelihood of type I error increases with multiple testing, likelihood of type II error also does. As only subtle aging effects in cerebral structures and cognition were a priori expected in our sample of normal middle-aged participants, Bonferroni adjustments might cause some differences to be deemed nonsignificant because increased type II error (Perneger, 1998). Following Debette et al. (2011) study on middle age, we decided not to perform any correction and consider our study as exploratory. Therefore, our findings must be confirmed in future studies. Nonetheless, the likelihood of obtaining type I and type II errors in our correlational analyses can be appraised by having in mind the number of tests performed. Age was correlated with 27 cognitive measures, 68 cortical volumes, 14 subcortical gray matter volumes, and 68 measures of cortical thickness. These analyses were carried out to explore age-related differences in cognition and gray matter. Intermediate correlations between previously significant gray matter and cognitive measures (13 and 12 variables, respectively) were then performed to reduce the number of tests conducted in subsequent hierarchical regression analyses. It is noteworthy that all models in Table 1 except those for CCT-2 and TAVEC successfully passed the Bonferroni correction (16 models: α level adjusted to 0.0031). Moreover, we further reduced the likelihood of obtaining type I and type II errors by performing bootstrapping analyses in addition to the Baron and Kenny (1986) method. We also selected bias corrected 95% confidence intervals to reduce inaccuracies and problems with type I error (Preacher and Hayes, 2008). Finally, a last limitation is that we only studied age-related differences in gray matter. Future research in this area should include analyses of the white matter tissue as well. Although white matter volume is known not to change during middle age, diffusion tensor studies on the white matter integrity and functional magnetic resonance imaging (fMRI) studies regarding brain connectivity could add relevant information about the possible mediation effect on the age-related cognitive decline by early changes in white matter properties. Likewise, other pathophysiological mechanisms need to be explored. For instance, it would be of great interest to investigate the relationship between our findings and markers of Aβ accumulation and neuronal injury (e.g., cerebrospinal fluid Aβ_{42} and cerebrospinal fluid Tau) (Jack et al., 2010). To move forward in the study of the relationship and interaction between different markers of underlying pathology is mandatory for several reasons. First, to establish the links between the appearance of any specific marker in asymptomatic individuals and the subsequent emergence of clinical symptomatology. Second, to detect those variables that best predicts progression from preclinical to clinical stages of different neurodegenerative processes. Third, to identify possible biological targets of disease modification therapeutic interventions. This will help in the diagnosis, prevention, and prediction of pathologic aging at an early level.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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