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Cognitive decline before the age of 50 can be detected with sensitive cognitive measures

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Abstract

Background: To define the profile of age-related differences in cognition in healthy middle-aged adults in order to identify the most sensitive measures of early cognitive decline. To study whether these differences precede cognitive decline in the elderly. **Method:** 141 cognitively normal participants (101 middle-aged adults with age 40-50±2; and 40 elderly individuals with age 65±2) were assessed with a comprehensive neuropsychological protocol covering processing speed, attention, executive functions, verbal and visual episodic memory, procedural memory, visuoconstructive, visuoperceptive and visuospatial functions, and language. **Results:** Age-related differences were detected before the age of 50 in cognitive reaction time, executive control, initial learning in verbal episodic memory, complex visuoconstructive and visuospatial functions, and lexical access. These differences preceded more extensive cognitive decline present at the age of 65. **Conclusions:** Our findings suggest subtle executive dysfunction before the age of 50, together with slowing in processing speed later on in the transition to old age. This profile could be explained by changes in the frontal lobe and its connections, starting at middle-age. These findings, together with future research, may be important for the diagnosis, prognosis, and prevention of pathological aging at a very early level.

Keywords: normal aging, pathological aging, middle-age adulthood, neuropsychological tests, early cognitive decline.

Resumen

El deterioro cognitivo puede ser detectado antes de los 50 años usando medidas cognitivas sensibles. **Antecedentes:** definir el perfil de cambios cognitivos durante la adultez de mediana edad para identificar medidas sensibles al deterioro cognitivo temprano. Estudiar si estos cambios preceden el deterioro cognitivo presente en la vejez. **Método:** 141 participantes cognitivamente normales (101 adultos entre 40-50±2 años; y 40 individuos con 65±2 años) fueron evaluados mediante un amplio protocolo neuropsicológico incluyendo velocidad de procesamiento, atención, funciones ejecutivas, memoria episódica verbal y visual, memoria procedimental, funciones visoconstructivas, visoperceptivas y visoespaciales, y lenguaje. **Resultados:** se detectaron cambios cognitivos antes de los 50 años en tiempo de reacción cognitivo, control ejecutivo, adquisición inicial en memoria episódica verbal, funciones visoconstructivas y visoespaciales complejas, y acceso al léxico. Estos cambios precedieron un deterioro cognitivo más extenso evidenciado a la edad de 65 años. **Conclusiones:** existe una leve disfunción ejecutiva antes de los 50 años, junto con enlentecimiento cognitivo en la transición a la vejez. Este perfil de cambios podría explicarse por un deterioro en el lóbulo frontal y sus conexiones ya desde la adultez de mediana edad. Estos resultados, junto con investigación futura, podrían ser importantes para el diagnóstico, prognosis y prevención del envejecimiento patológico a nivel temprano.

Palabras clave: envejecimiento normal, envejecimiento patológico, adultez de mediana edad, pruebas neuropsicológicas, deterioro cognitivo temprano.

Cognitive aging has been extensively addressed both in cross-sectional and longitudinal studies. However, there is still a need for clinically useful measures of early cognitive decline. A reason for this is the scarce literature directly addressing this question in middle-aged adults (40-60 years) (Willis, Martin, & Rocke, 2010). Another reason is that cognitive studies are usually restricted to global cognition or few cognitive functions, which makes it difficult to identify sensitive measures of early cognitive decline. Therefore, studies covering a broad spectrum of cognitive functions in specific cohorts of middle-aged participants are mandatory. To define the age at which cognitive decline begins is extremely important to determine the most suitable window at which potential interventions can have greater benefits. Current evidence shows that different neurodegenerative processes begin 10-20 years before the diagnosis of dementia, probably overlapping the middle-age period (Sperling et al., 2011). Hence, research on middle-age is important, given that it is the critical point when the first pathophysiological changes take place.

Several studies have shown that cognitive decline is already evident in middle-age, with executive functioning (Singh-Manoux et al., 2012) and processing speed (Salthouse, 2009; Zimprich & Mascherek, 2010) being the most affected functions. Moreover, a previous study including 82 middle-aged adults showed that early cognitive decline was mediated by age-related changes in several gray matter regions (Ferreira et al., 2014). The first

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aim in the current study is to define the profile of early age-related differences in cognition in a larger sample and including a broader neuropsychological protocol. By covering a larger number of cognitive functions and components, we expect to identify the most sensitive measures for detecting early cognitive decline. Considering the recently reported needs about the better operationalization of the middle-age period in different sub-stages (Willis et al., 2010), we will divide this period in two equal stages: early-middle-age (40-50 years), and late-middle-age (50-60). Given that the aim is to study early cognitive decline, we will focus on early-middle-age. The second aim is to study whether those age-related cognitive differences described in early-middle-age precede cognitive decline in old age. To that end, we will analyze the transition from middle-age to old age by comparing individuals 50 years old (as the midpoint of middle-age), versus individuals 65 years old (as the starting point of old age).

Method

Participants

A total of 141 participants were included (101 middle-aged adults with ages between 40-50, ±2; and 40 older participants with age 65±2). Inclusion criteria were: (1) preserved cognitive and functional status; (2) clinically normal magnetic resonance exam; (3) no neurologic, psychiatric or systemic diseases; and (4) no history of substance abuse. Recruitment was done through primary care health centers, advertisements in local schools, and acquaintances of the research staff, covering a representative sample in terms of age, gender and education. Participation was completely voluntary and all subjects gave written informed consent approved by local ethics committee.

Middle-aged participants were classified into three age groups (40±2, 45±2, 50±2) (table 1), following the approach of narrow-age cohorts (Hofer & Sliwinski, 2001). WAIS Information subtest (Wechsler, 1997a) was used as indicator of education because it better represents benefits from educational experience as compared with other measurements of educational attainment (Correia, Nieto, Ferreira, Sabucedo, & Barroso, 2015). WAIS Information total score was significantly different between the initial 50±2 and 65±2 groups ($F_{(1,68)}$= 13.055; p = 0.001). Five participants with university level in the group of 50±2 were thus excluded in order to make both groups comparable in education and minimize possible cohort effects. The final 50±2 and 65±2 groups were comparable in demographics although the total score in the Mini-Mental State Examination (MMSE) was significantly lower in the older group (Table 1). Nonetheless, all subjects' scores were indicative of normality. Decline in MMSE has frequently been referred related to normal aging (Lezak, Howieson, & Loring, 2004).

Instruments

A comprehensive neuropsychological protocol was applied, covering processing speed, attention, executive functions, verbal and visual episodic memory, procedural memory, visuoconstructive, visuoperceptive and visuospatial functions, and language. The protocol is fully detailed in Table 2 and described elsewhere (Ferreira et al., 2014; Correia et al., 2015).

Procedure

Only nonstandard procedures are explained here. Tests' full name is displayed in Table 2. Regarding PASAT (Gronwall, 1977), calculation was changed by numbers comparison in order to discard dependence on working memory. The 8/30 SRT is an in-house modification of the 7/24 SRT (Rao, Hammeke, McQuillen, Khatri, & Lloyd, 1984). Administration and scoring procedure was the same as described by Rao et al., but an eight-dot pattern was displayed on a 5x6 grid instead of the original one. Finally, linguistic functions were assessed with two in-house computerized tests of lexical access. Briefly, TDAS is a visual confrontation naming task including pictures of 40 nouns and 20 actions. TGAAS is an auditory task where participants are given 30 nouns and semantically associated actions must be generated. Three 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 are more difficult. In both TDAS and TGAAS, stimuli were presented and responses recorded with milliseconds precision using the E-prime v1.1 Software (Psychology Software Tools, Inc, 2002).

Data analysis

Analyses of variance (univariate) were conducted to compare group performance across cognitive measures. The partial eta squared (η^2_{par}) is reported as a measure of the effect size. Bonferroni correction was applied for post-hoc comparisons. Chi-square test was used for categorical variables, and Pearson correlation and covariance analysis (ANCOVA) to study relationships among

Table 1
Demographic variables and global cognitive status

	Early-middle-age				Middle-age vs. old age		
	40±2 (n = 30)	**45±2 (n = 40)**	**50±2 (n = 31)**	**p**	**50±2 (n = 26)**	**65±2 (n = 30)**	**p**
Age (y)	40.33 (1.30)	45.33 (1.40)[c]	49.84 (1.29)[a, b]	**<0.001**	49.85 (1.26)	65.70 (0.99)	**<0.001**
Gender (F/M)	12/18	21/19	19/12	0.247	17/9	18/12	0.678
WAIS Information	14.35 (5.37)	16.41 (6.17)	16.55 (5.54)	0.157	14.77 (5.07)	12.14 (5.22)	0.064
MMSE	29.33 (1.06)	29.43 (0.84)	28.90 (1.04)	0.072	28.96 (1.04)	27.93 (1.60)	**0.006**

[a] p<0.05 between 50±2 and 40±2; [b] p<0.05 between 50±2 and 45±2; [c] p<0.05 between 45±2 and 40±2. MMSE = Mini-Mental State Examination; WAIS = Wechsler Adult Intelligence Scale

variables. Since education and gender may have significant effect on cognitive performance, they were entered as confounding variables when significantly correlated with cognitive performance. All statistical analyses were performed using SPSS 20.0 for Mac, with a p-value of <0.05 deemed significant.

Results

Age-related differences in cognition during early-middle-age (40-50, ±2)

Results showed worse performance with age in processing speed (PC-Vienna cognitive reaction time), attention/executive functions (CTT-2 and backward visuospatial span), episodic memory (TAVEC first learning trial), visuoconstructive functions (Block Design), visuospatial functions (JLOT), and language (lexical access by semantic associations) (Table 3).

Age-related differences between middle-age (50±2) and old age (65±2)

The 65±2 group performed worse in processing speed (PC-Vienna cognitive and motor reaction times), attention (TMT-A), executive functions (digit and visuospatial spans, Stroop test, verbal fluency for letters and actions, and Luria´s hand alternative movements and motor coordination), episodic memory (learning and delayed free recall in Logical Memory, TAVEC, and Visual Reproduction), procedural memory (errors and time in learning trials in Hanoi Tower), visuoconstructive functions (copy in Visual Reproduction and Block Design), and language (lexical access by visual confrontation) (Table 3).

Table 2
Neuropsychological protocol: Cognitive functions and components

Cognitive functions - Neuropsychological test	Reference	Cognitive component	Measure
Processing Speed and Attention			
PC-Vienna System (PCV)	Schuhfried (1992)	cognitive and motor Reaction Times	Choice Reaction Times (milliseconds)
Paced Auditory Serial Addition Test (PASAT)	Gronwall (1977)	maintenance of attention	Correct items, max. 60
Trail Making Test - Part A (TMT-A)	Reitan (1958)	focusing/visual tracking	Seconds
Color Trails Test - Part 1 (CTT-1)	D'Elia and Satz (1989)	focusing/visual tracking	Seconds
Executive Functions			
Digit Span (DS) / Visuospatial Span (VS)	Wechsler (1997b)	Working memory: amplitude (forward) and manipulation (backward)	Forward and Backward modalities (correct items)
Color Trails Test - Part 2 (CTT-2)	D'Elia and Satz (1989)	Mental flexibility/executive control	Seconds
Stroop Test (STROOP)	Golden (1978)	Cognitive inhibition	Sheet 1 Words, Sheet 2 Colours, and Sheet 3 Inhibition (correct items)
Verbal Fluency (VF)	Benton A, Hamsher K, & Sivan (1989) (letters and animals); Piatt, Fields, Paolo, Koller, & Tröster (1999) (actions)	Phonemic (letters), semantic (animals), and actions	Number of correct words
Luria's Premotor Functions (Luria's)	Christensen, 1979	Hand alternative movements, motor coordination and motor inhibition	Number of correct movements
Verbal and Visual Episodic Memory			
Logical Memory (LM)	Wechsler (1997b)	Immediate recall (or learning when several trials), delayed free recall (30 min), and recognition for every task	Number of correct elements
TAVEC	Benedet and Alejandre (1998)		Number of correct words
8/30 Spatial Recall Test (8/30)	Modification of the 7/24 SRT: Rao, Hammeke, McQuillen, Khatri, & Lloyd (1984)		Number of correct elements
Visual Reproduction (VR)	Wechsler (1997b)		Number of correct elements
Procedural Memory			
Hanoi Tower (HT)	Simon (1975)	Learning, delayed free recall (30 min), and recognition	Number of correct elements, time, errors
Visuoconstructive, Visuoperceptive and Visuospatial functions			
Visual Reproduction - Copy	Wechsler (1997b)	2-D visuoconstructive abilities	Number of correct elements
Block Design	Wechsler (1997a)	3-D visuoconstructive abilities	Total WAIS standard score
Facial Recognition Test (FRT)	Benton, Hamsher, Varney, & Spreen (1983)	Visuoperceptive abilities	Number of correct items
Judgment of Line Orientation Test (JLOT)	Benton et al. (1983)	Visuospatial abilities	Number of correct items in first half (JLOT1) and second half (JLOT2)
Language			
Nouns and Actions Naming Test (TDAS: *Test de Denominación de Acciones y Sustantivos*)	In-house task	Lexical access by visual confrontation	Nouns and Actions (number of correct items)
Generating Actions by Semantic Association (TGAAS: *Test de Generación de Acciones por Asociación Semántica*)	In-house task, described in Ferreira et al. (2014)	Lexical access by semantic association	Total, and nMA, MA and CMA conditions (number of correct items and errors)

nMA = nouns without a morphologic derived action; MA = nouns with a morphologic derived action; CMA = cognitive nouns with a morphologic derived action

Table 3
Age-related differences in cognition during early-middle-age and transition to old age

Cognitive Measures	Early-middle-age					Middle-age vs. old age			
	40±2 (n = 30) Mean (SD)	**45±2 (n = 40)** Mean (SD)	**50±2 (n = 31)** Mean (SD)	**p**	**ES**	**50±2 (n = 26)** Mean (SD)	**65±2 (n = 30)** Mean (SD)	**p**	**ES**
PCV-Cognitive	424.28 (8.87)	469.02 (7.61)[c]	451.69 (8.56)	0.001	0.14	453.31 (53.25)	548.41 (82.82)	<0.001	0.32
PCV-Motor	170.64 (37.67)	182.92 (48.35)	191.07 (47.59)	ns	–	196.49 (13.15)	272.80 (12.45)	<0.001	0.25
PASAT	58.86 (2.22)	59.35 (1.08)	59.34 (0.94)	ns	–	59.25 (0.99)	58.83 (1.60)	ns	–
TMT-A	29.03 (2.17)	33.54 (1.73)	34.27 (1.99)	ns	–	37.95 (3.74)	59.06 (2.64)	<0.001	0.33
CTT-1	36.59 (2.29)	40.45 (1.83)	42.51 (2.10)	ns	–	NA	NA	–	–
CTT-2	73.51 (5.10)	92.79 (4.16)[c]	95.03 (4.77)[a]	0.005	0.12	NA	NA	–	–
DS-forward	8.63 (2.53)	8.28 (1.75)	8.13 (2.11)	ns	–	7.49 (0.30)	6.42 (0.28)	0.014	0.11
DS-backward	6.32 (0.32)	5.98 (0.28)	5.81 (0.32)	ns	–	7.88 (1.48)	6.07 (1.41)	<0.001	0.14
VS-forward	8.40 (1.89)	8.03 (1.42)	8.13 (1.88)	ns	–	5.33 (0.25)	4.29 (0.24)	0.005	0.29
VS-backward	8.39 (0.26)	7.92 (0.22)	7.31 (0.25)[a]	0.014	0.09	5.33 (0.25)	4.29 (0.24)	0.005	0.31
STROOP-words	104.55 (2.53)	102.49 (2.19)	103.48 (2.48)	ns	–	100.09 (2.95)	83.10 (2.78)	<0.001	0.25
STROOP-colors	72.47 (12.20)	69.48 (11.59)	69.32 (10.72)	ns	–	68.53 (2.23)	52.49 (2.11)	<0.001	0.34
STROOP-inhibit.	43.39 (1.61)	41.79 (1.39)	39.99 (1.58)	ns	–	39.35 (1.61)	28.34 (1.52)	<0.001	0.32
VF-letters	35.63 (1.70)	34.98 (1.47)	34.70 (1.67)	ns	–	30.71 (1.79)	22.33 (1.69)	0.002	0.18
VF-animals	24.61 (0.86)	21.94 (0.74)	21.72 (0.84)	0.029[*]	0.07	20.31 (0.88)	17.89 (0.83)	ns	–
VF-actions	18.87 (1.03)	18.47 (0.89)	17.97 (1.01)	ns	–	15.53 (0.99)	9.46 (0.93)	<0.001	0.27
Luria's HAM	36.69 (1.50)	35.73 (1.28)	36.75 (1.47)	ns	–	35.15 (5.38)	12.48 (3.20)	<0.001	0.88
Luria´s MC	51.90 (2.92)	52.78 (2.47)	55.61 (2.82)	ns	–	53.43 (3.33)	27.74 (3.21)	<0.001	0.37
Luria's MI	19.70 (0.60)	19.75 (0.44)	19.76 (0.51)	ns	–	19.79 (0.42)	19.79 (0.41)	ns	–
LM-Imm.	40.35 (1.56)	41.49 (1.35)	39.94 (1.53)	ns	–	37.65 (1.54)	30.28 (1.45)	0.001	0.18
LM-Delay.	26.15 (1.11)	26.77 (0.97)	25.18 (1.10)	ns	–	21.51 (5.76)	18.53 (6.98)	0.010	0.28
LM Recog.	25.01 (0.54)	25.92 (0.47)	24.91 (0.53)	ns	–	23.38 (2.73)	23.64 (3.16)	ns	–
TAVEC-L1st trial	8.03 (1.99)	7.25 (1.71)	6.87 (1.48)[a]	0.031	0.07	6.92 (1.55)	6.17 (1.80)	ns	–
TAVEC-Learning	60.73 (8.03)	58.05 (7.61)	56.29 (7.29)	ns	–	56.59 (1.66)	49.36 (1.54)	0.002	0.16
TAVEC-Delay.	14.83 (1.66)	14.33 (1.93)	14.13 (1.86)	ns	–	13.12 (1.91)	11.79 (3.30)	0.019	0.24
TAVEC-Recog.	15.80 (0.48)	15.73 (0.55)	15.55 (0.62)	ns	–	15.27 (0.65)	14.94 (1.48)	ns	–
8/30-Learning	34.37 (5.51)	33.08 (6.21)	32.65 (5.64)	ns	–	31.85 (5.62)	28.90 (6.14)	ns	–
8/30-Delay.	6.69 (0.26)	7.03 (0.22)	6.74 (0.25)	ns	–	6.58 (1.60)	5.93 (1.49)	ns	–
8/30-Recog.	1.87 (0.51)	1.90 (0.38)	1.90 (0.30)	ns	–	1.81 (0.10)	1.75 (0.09)	ns	–
VR-Imm.	90.32 (1.66)	87.03 (1.44)	85.37 (1.63)	ns	–	82.80 (2.43)	60.08 (2.38)	<0.001	0.46
VR-Delay.	81.54 (2.87)	75.59 (2.48)	73.82 (2.81)	ns	–	58.78 (15.58)	48.66 (15.12)	0.020	0.53
VR-Recog.	45.37 (0.41)	45.11 (0.36)	44.69 (0.41)	ns	–	42.49 (2.78)	41.87 (2.93)	ns	–
VR-Copy	100.87 (2.36)	99.78 (2.82)	99.32 (2.43)	ns	–	98.96 (2.13)	96.69 (5.23)	0.038	0.07
HANOI-L-mov.	125.05 (5.64)	132.58 (5.00)	135.63 (5.52)	ns	–	135.73 (31.93)	126.33 (25.55)	ns	–
HANOI-L-time	376.74 (30.11)	374.32 (26.74)	407.02 (29.50)	ns	–	401.69 (181.95)	511.77 (276.05)	ns	–
HANOI-L-err.	0.13 (0.43)	0.24 (0.54)	0.13 (0.34)	ns	–	0.12 (0.33)	1.67 (3.58)	0.034	0.09
HANOI-D-mov.	22.60 (1.64)	26.01 (1.46)	24.48 (1.61)	ns	–	24.23 (7.22)	27.22 (9.51)	ns	–
HANOI D-time	54.70 (43.11)	56.05 (35.03)	56.23 (25.09)	ns	–	54.81 (21.57)	83.56 (46.40)	0.006	0.14
HANOI D-err.	0.00 (0.00)	0.00 (0.00)	0.03 (0.18)	ns	–	0.04 (0.20)	0.07 (0.27)	ns	–
Block Design	44.80 (1.64)	41.79 (1.42)	37.24 (1.61)[a]	0.005	0.10	34.06 (1.59)	25.41 (1.53)	<0.001	0.23
FRT	23.51 (0.35)	22.60 (0.31)	22.63 (0.35)	ns	–	22.50 (1.84)	20.79 (4.20)	ns	–
JLOT1	13.74 (0.24)	13.61 (0.21)	13.40 (0.24)	ns	–	12.91 (0.38)	12.39 (0.36)	ns	–
JLOT2	11.27 (0.48)	10.11 (0.41)	9.57 (0.47)[a]	0.042	0.06	9.17 (0.50)	8.32 (0.47)	ns	–
TDAS-Nouns-cor.	38.57 (0.18)	38.18 (0.15)	38.12 (0.17)	ns	–	96.63 (1.36)[†]	93.04 (1.28)[†]	ns	–
TDAS-Nouns-err.	0.27 (0.64)	0.38 (0.67)	0.23 (0.43)	ns	–	1.33 (1.15)[†]	2.48 (1.49)[†]	0.015	0.11
TDAS-Actions-cor.	18.83 (0.46)	18.55 (0.64)	18.53 (0.63)	ns	–	96.72 (1.73)[†]	88.89 (1.63)[†]	0.002	0.17
TDAS-Actions-err.	0.10 (0.40)	0.28 (0.51)	0.37 (0.56)	ns	–	5.43 (1.08)[†]	10.37 (1.41)[†]	<0.001	0.22
TGAAS-Total	25.89 (0.64)	24.95 (0.56)	23.43 (0.63)[a]	0.025	0.07	NA	NA	–	–
TGAAS-nMA	9.34 (0.23)	9.26 (0.20)	9.06 (0.23)	ns	–	NA	NA	–	–
TGAAS-MA	8.99 (0.24)	8.78 (0.21)	8.13 (0.24)[a]	0.032	0.07	NA	NA	–	–
TGAAS-CMA	7.57 (0.34)	6.91 (0.30)	6.25 (0.34)[a]	0.026	0.07	NA	NA	–	–

[a] p<0.05 between 50±2 and 40±2; [b] p<0.05 between 50±2 and 45±2; [c] p<0.05 between 45±2 and 40±2; [*] Non-significant differences in post-hoc analysis; [†] Number of correct items and number of errors were converted to percentages because two items had to be discarded in the 65±2 group due to technical reasons; Adjusted means (and standard errors) are presented when education and/or gender entered as covariates.
ES = effect size; NA = non-available; Complete names for cognitive measures are displayed in table 2

Discussion

The most relevant finding in this study is that although most of age-related differences in cognition were detected in the transition from middle-age (50) to old age (65), several age-related differences were evidenced before the age of 50.

A temporality of cognitive decline occurring between the ages of 40 and 65 can be described by integrating all the results. Regarding processing speed, decline in the cognitive component starts before the age of 50, with motor slowing occurring only in the transition to old age. This dissociation has not previously been shown, and supports the concept of cognitive slowing as early sign of normal aging (Salthouse, 2009), reported also in two middle-age studies (Gautam, Cherbuin, Sachdev, Wen, & Anstey, 2011; Zimprich & Mascherek, 2010). Regarding attentional functions, results showed decline in divided attention (i.e., CTT-2) before the age of 50. In addition, decline in TMT-A but not in PASAT was found in the transition to old age. This dissociation between TMT-A and PASAT suggests difficulties in tracing or visuomotor coordination rather than problems in maintenance of attention. Therefore, age had greater influence on those more complex attentional components, in agreement with previous studies (Zhou, Fan, Lee, Wang, & Wang, 2011). Regarding executive functions, decline in working memory was evident before the age of 50 in manipulation of visual information, also including manipulation of verbal information and the amplitude component in the transition to old age. Visual modality is known to be more demanding than verbal modality, and manipulation is more difficult than amplitude (Lezak et al., 2004; Luo & Craik, 2008). Our findings indicate that more complex components are more vulnerable to aging. Further age-related differences were found in the transition to old age in inhibitory processes (i.e. Stroop) and verbal fluency (i.e. letters and actions). These two fluency modalities have higher implication of the executive functions and/or cortical-subcortical frontal connections, in comparison with semantic fluency (Piatt, Fields, Paolo, Koller, & Tröster, 1999; Troyer, Moscovitch, Winocur, & Alexander, 1998). Decline in premotor functions was also evident in the transition to old age, both in alternations and mutual coordination.

Results in memory are of especial interest. In this study, we report for the first time a differentiation and temporalization of different verbal, visual, and procedural memory components during middle-age. The typical aging-related memory impairment defined by alterations in acquisition and/or free retrieval but not in consolidation (Luo & Craik, 2008) was present already before the age of 50 (i.e., TAVEC first learning trial). Difficulties in verbal learning during middle-age have also been reported in a recent study (Singh-Manoux et al., 2012). This memory decline is likely to be more associated with frontal lobe dysfunction than with the medial-temporal lobe (Davidson, Troyer, & Moscovitch, 2006). Similarly, results obtained in procedural memory showed an increase in errors and time of execution, which are more related to the frontal lobe (e.g., inhibitory control), as well as to processing speed (Lezak et al., 2004).

Regarding linguistic functions, results showed decline in lexical access by semantic associations before the age of 50, associated with inhibitory processes. In the transition to old age, differences were also found on a visual confrontation-naming task, in line with other studies (Mackay, Connor, Albert, & Obler, 2002). Finally, age-related differences were found in visuoconstructive and visuospatial functions, but not in visuoperceptive functions. Decline in three-dimensional visuoconstructive abilities and in line orientation (complex items) was evident already before the age of 50. Decline on two-dimensional abilities was also found in the transition to old age.

Different hypotheses of cognitive aging have been proposed. Some authors highlight the role of cognitive slowing (Salthouse, 1996), but others point to impairment in visual processing (Baltes & Lindenberger, 1997), or executive/prefrontal functioning (Tisserand & Jolles, 2003; West, 1996). This study suggests that the confluence of the three processes rather than one single factor is what seems to explain the findings. Moreover, the relevance of these factors may vary depending on the temporal stage. Our results suggest an early executive dysfunction during early-middle-age, with slowing in processing speed later in the transition to old age. The role of visual functioning may also explain some of the results (e.g. Visual Reproduction copy). This profile and temporality of age-related differences in cognition could be explained as the result of progressive changes in the frontal lobe and its connections starting before the age of 50. This observation is supported by previous results from a part of the cohort included in this study (Ferreira et al., 2014).

This study is one of the few including such a broad variety of cognitive measures in a specific cohort of middle-aged adults. By using a comprehensive neuropsychological protocol, a detailed analysis of the relationship between numerous cognitive functions and components was possible. Interestingly, this allowed the detection of very early cognitive decline occurring before the age of 50. Nonetheless, the use of numerous measures could lead to problems related to multiple comparisons. Only subtle cognitive decline was expected a-priori in this sample of normal middle-aged participants. Therefore, following previous middle-age studies (Debette et al., 2011; Ferreira et al., 2014), Bonferroni adjustments were only applied to post-hoc comparisons but not across variables, because some differences might be deemed non-significant due to increased Type II error (Perneger, 1998). Moreover, it must be noted that this study was explorative in nature, and the main aim was to identify sensitive measures of early cognitive decline. Future research is thus mandatory to further investigate the dynamics of these identified measures in normal and pathological aging. A second limitation is that, although cross-sectional comparisons allow studying age-related differences (Salthouse, 2009), our results should be complemented with longitudinal studies. Finally, a related drawback is that cross-sectional designs might be susceptible to cohort effects related to generational influences. Acknowledging this, we included narrow-age intervals, avoiding generational differences among groups as much as possible (Hofer & Sliwinski, 2001). Moreover, as cohort effects are mainly related to differences in social and environmental influences, we ensured group comparability on several key variables such as education and gender, and possible residual effects were statistically controlled.

Research on aging and measures to detect individuals at risk of developing dementia or cognitive impairment are of utmost importance. In this study, we defined the profile of age-related differences in cognition occurring in normal people before the age of 50. Moreover, we evaluated how these differences precede cognitive decline present at the age of 65. These findings, together with future research, may help to better characterize the early stages of the normal aging process. This knowledge will be important for the diagnosis, prognosis, and prevention of pathological aging at a very early level,

especially relevant when new disease-modifying treatments are available, in the near future. In conclusion, the following cognitive measures were found to be sensitive to early cognitive decline: PC-Vienna cognitive reaction time; CTT-2; backward visuospatial span (WMS-III); TAVEC first learning trial (i.e. CVLT); Block Design (WAIS-III); JLOT; and a task of lexical access. All these measures can be easily obtained in the clinical routine. If successfully validated in the future, these sensitive measures may be useful not only in clinics, but also in clinical trials and research on middle-aged people and/or individuals at the preclinical stage of neurodegenerative processes (Sperling et al., 2011).

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