ASSESSING PROCESSING SPEED AND EXECUTIVE FUNCTIONS IN LOW EDUCATED OLDER ADULTS: THE USE OF THE FIVE DIGIT TEST IN PATIENTS WITH ALZHEIMER'S DISEASE, MILD COGNITIVE IMPAIRMENT AND MAJOR DEPRESSIVE DISORDER

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Abstract

Objective: Many studies suggest that executive dysfunction is a common characteristic of Alzheimer´s disease (AD), mild cognitive impairment (MCI), and in elderly patients with major depressive disorder (MDD). The aim of this study is to evaluate the applicability of Five Digits Test (5D) in the assessment of executive functions in less educated older adults with pathological aging.

Method: We studied a total of 114 subjects divided in four groups: 30 patients with AD, 30 patients with MCI, 24 patients with MDD and 30 community-dwelling normal aged controls (NAC). All subjects were submitted to the 5D.

Results: The comparison of NAC and the mixed clinical group (AD + MCI + MDD) shows significant differences on the 5D both in speed and errors on 3rd (inhibition) and 4th (shifting) sections of the 5D. The ANOVA indicates significant differences for all measures, except for the total number of errors in the Decoding and Naming components of the 5D. The *Post Hoc* analysis indicates that in decoding (time), the NAC group performed better than AD and MDD but not MCI. MCI patients also performed better than AD. The analysis of components associated with executive functions of the 5D indicates that NAC outperformed AD and MDD in Inhibition (time) but only AD in Inhibition (errors) ($p<0.016$). The Shifting (time) of NAC was faster than MDD, but in the total errors of this component, NAC the group performed better than AD and MCI.

Conclusions: Our results point to the efficiency of 5D in identifying executive dysfunctions in pathological aging in comparison with the normal aging process. This task shows great potential for use both in research and in clinical practices in countries as Brazil, where a great amount of the population is illiterate.

Key words: Alzheimer´s disease, mild cognitive impairment, major depressive disorder, executive dysfunction, five digits test

Declaration of interest: none

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Introduction

Executive functions are *capacities that enable a person to engage successfully in independent, purposive, self-serving behavior* (Lezak et al. 2004). The development of executive functions occurs during the maturation of prefrontal networks (Fuster 2009). This development begins in early childhood and ends in adolescence and early adulthood, presenting a slow but consistent decay later in life in an inverted "U" shaped curve (Zelazo et al. 2004). The executive changes are mediated by a significant decrease in processing speed and reduced working memory capacity (Huntley and Howard 2010), a group of cognitive abilities named "cognitive mechanics" (Baltes 1997). Education is an important factor in the performance of the executive functions among the aging population. For instance, according to Lin et al. (2007), although the decline of some components of executive functions (i.e., attention allocation, planning and

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initiation) is correlated with the aging process, educational level is more significantly correlated with the decline of initiation, switching and flexibility, and online updating.

Many studies suggest that executive dysfunction is a common characteristic of Alzheimer´s Disease (AD), even in the early phase (Baudic et al. 2006), which is associated with episodic memory impairment. In mild cognitive impairment (MCI), the executive deficit is a diagnostic criteria for both single domain executive MCI and multiple domain MCI involving executive functions. Nonetheless, even in amnestic MCI, executive deficits may play an important role because the performance in executive tests may be affected by the atrophy of medial temporal structures (Nagata 2010). Executive function deficits are also observed in elderly patients with major depressive disorder (MDD), which is associated with gray and white matter signal abnormalities in the frontal and medial temporal regions of the brain (Sheline et al. 2006).

Executive function assessment is frequently performed using classical neuropsychological tools, such as the Stroop Color Word Test (SCWT) (Stroop 1935), the Trail Making Test (Hervey et al. 2004) or the Frontal Assessment Battery (Oguro et al. 2006). These tests are good measures of the executive functions in subjects with AD, MCI and MDD (Pachana et al. 1996). However, these tasks are influenced by reading abilities (Johnson et al. 2006) and formal education (Lucas et al. 2005, Steinberg et al. 2005).

In these situations, an alternative is the Mini-Verbal Test (MVT), which is designed to be as independent as possible from the previous experience, education, and culturally acquired routines of the subjects. In MVT, the verbal content is limited to a few familiar concepts, which are presented to the subject as series of visual images. The main value of this assessment framework is its use in conditions in which subjects lack the automatic reading routines that are absolutely necessary for its validity in the assessment of illiterate subjects or subjects with very low levels of education.

The Five Digit Test (5D), proposed by Sedó (2004), is an MVT adaptation of the SCWT. When performing this test, the subject must know only the first five numbers and their corresponding symbols. The test measures continuous verbal performance at different levels of the attentional network because it tests both a more "automatic" process (i.e., reading numbers and counting figures) and a more "controlled" process, in which the subject must inhibit an automatized routine of processing in favor of a secondary, non-intuitive mode of processing (i.e., speaking rather than reading the number of digits).

The aim of this study is to evaluate the applicability of 5D in the assessment of executive functions in less educated older adults with AD, MCI and MDD by evaluating the following hypothesis: (1) the 5D test will be a useful task in the assessment of executive functions in elderly population. Therefore, we expect that subjects affected by AD, MCI or MDD will perform poorly on the 5D compared to normal aged controls; (2) the performance in the 5D will be associated with a greater degree of general cognitive and functional impairment classified according Clinical Dementia Rating (CDR) (Morris 1993).

Methods

Participants

We studied a total of 114 subjects divided in four groups: 30 patients with AD, 30 patients with MCI, 24 patients with MDD and 30 community-dwelling normal aged controls. The participants were Brazilian older adults assessed in a secondary public healthcare center specializing in gerontology. In the city of Belo Horizonte, where this study was performed, a primary care physician who assesses older adults in his or her daily practice could request a specialized assessment if cognitive decline or dementia was suspected. In the secondary unit center, the patient was assessed by at least two gerontologists (ENM and MAB) and one clinical neuropsychologist (JJP). After the assessments and complementary exams were performed, clinical conferral confirms the diagnosis of each patient.

After the diagnosis, the patients were invited to participate in this study, and there was an interval of no more than one week between the diagnosis and research participation. Inclusion criteria were the following: at least 60 years old, no history of vascular or previous neurological disorders; no history of depressive disorder prior 60 years and no confusional status or psychotic illness. Diagnoses were determined by a consensus following a multidisciplinary assessment, according to the DSM-IV (American Psychiatric Association 1994), NINCDS-ADRDA (McKhann et al. 1984) and NINDS-AIREN (Román et al. 1993) criteria. For the MCI diagnosis, the Petersen et al. (2001) criteria were used. All MDD patients scored above the recommended cutoff for depression in the Brazilian version of the Geriatric Depression Scale (Paradela et al. 2005).

All MCI, MDD and AD participants followed their treatment plans, which included taking cholinesterase inhibitors, and they were free from typical or atypical antipsychotic drugs.

All subjects were classified according to the Clinical Dementia Ratting (0 (NAC), 0.5 (MCI and MDD) or 1 (mild AD). In the present study, only MDD patients with self-reported cognitive deficits and functional impairment were included (CDR=0.5). The MCI group was composed of 17 amnestic and 13 multiple domain (amnestic-executive) patients. Patients with MCI or AD who were also diagnosed with MDD according to the DSM-IV criteria or another mood disorder were excluded from the study. All subjects were assessed in accordance with the Declaration of Helsinki, and the Research Ethics Committee of the Federal University of Minas Gerais (334/06) gave written consent and approval. For AD patients, a relative (usually spouse) also gave written consent.

Procedures

All subjects performed a protocol composed of a cognitive and humor screening test and the 5D.

1) Cognitive and mood screening. Cognitive

screening was performed by the use of *Mini-Mental State Exam* (MMSE), a widely used screening test developed by Folstein, Folstein and McHugh (1975). Using 11 simple tasks, the MMSE evaluates temporal orientation, spatial memory, attention, language and praxia. The current study employed a Brazilian version with different cutoffs based on education (Brucki et al. 2003). The *Geriatric Depressive Scale (GDS)* was used for screening depressive symptoms in our sample. In this study, we used the Brazilian version of the GDS-15 (Paradela et al. 2005).

2) The five Digit Test: 5D is divided into four successive parts: 1) decoding, 2) describing, 3) inhibiting and 4) shifting. Each part involves the production of four identical verbal lists, using the activities of reading, describing, choosing, and switching. All parts of the test were preceded by a training session containing 10 items. After the instructions, the subject had four trials to correctly respond to the items. If the subject was unable to perform at the training session, these data are registered, and the test components that followed the interruption were excluded from the statistical analysis.

The items of each parts were presented in pages of 50 items (10 rows of five items), and each item was surrounded by a rectangular frame. On the first section, in the decoding section of the test, the subject is presented with a series of 50 boxes that require the automatic *reading* of the items inside each box, which are in groups of one to five congruous digits (one 1, two 2s, three 3s, etc.) that must be read. In the second section (the retrieving section), the subject is presented with a series of 50 boxes, in which one to five stars must be *counted*. In the third section (the inhibition section), digits are presented in incongruous forms (one 4, two 3s, five 1s, etc.), and the subject is asked to report the number of digits, and so must *inhibit* his or her immediate reaction (reading) and resolve to count the number of digits presented and continue counting them throughout the page. Finally, in the fourth section (the shifting section), of the test, the subject is presented with an additional difficulty: he or she must switch from counting to reading in 20% of the items of the page (the items marked by a much darker frame), demanding the more executive process of *shifting*. In each of the four sections of the 5D, we measured the subjects' speed of information processing (reading time in seconds) and the efficiency of their responses (number of errors). **Figure 1** shows the four test components.

Analyses

For the test of Hypothesis 1, the comparisons of the NAC group and the mixed clinical group (MCG) were carried out by independent-samples paired *t* tests, and a modified Cohen's d appropriated for unequal sample sizes (Hartung et al. 2008) was used as a measure of effect size. The statistical analyses of Hypothesis 2 consisted of a One-Way Analysis of Variance (ANOVA) for the group comparisons, using Sidak's Post Hoc to evaluate specific group differences because it offers a more conservative approach, minimizing the chance of type 1 errors in multiple comparisons (Ruxton and Beauchamp 2008). The squared eta was calculated as an estimate of effect size. We considered as statistically significant results where $p \leq 0.05$. The statistical analysis was conducted using the SPSS 17.0 software.

Results

We studied a total of 114 subjects divided in four groups: 30 patients with AD (12 males, age: 74.36 years ± 6.79, education: 3.85 years ± 3.0), 30 patients with MCI (13 males, age: 74.07 years ± 6.33, education: 4.57 years ± 3.00), 24 patients with MDD (5 males, age: 70.12 years ± 8.54, education 4.13 years ± 3.0) and 30 community-dwelling normal aged controls (10 males, age: 74.10 years ± 6.80, education: 4.27 years ± 2.25).

No significant differences were found between age ($p=0.093$), education ($p=0.793$), and sex ($p=0.335$) between the groups. The demographics and neuropsychological tests results are shown in **table 1**. **Table 1** shows the mean and standard deviations for the demographics, GDS, MMSE, the four components of 5D, and the significance of ANOVA and effect size for each group comparison.

The comparison of NAC and the mixed clinical group shows no differences in age ($p=0.481$), education ($p=0.889$) and gender ($p=0.815$). Significant differences ($p<0.001$) were found in MMSE and GDS-15 with large effect sizes (1.45, and 0.79, respectively). On the 5D, the Decoding ($p<0.001$; $d=0.73$) and Describing ($p<0.001$; $d=0.72$) times were different, but the number of errors was not different ($p=0.169$ and $p=0.109$). Considering both time and errors on 3rd (inhibition) and 4th (shifting) sections of the 5D, we also found statistically significant differences between groups with large effect sizes [Inhibition time ($p<0.001$ $d=0.62$) and errors ($p=0.001$ $d=056$); Shifting time ($p<0.003$ $d=0.52$) and errors ($p<0.001$ $d=0.66$)].

In the AD group, 1 patient was unable to execute the Inhibition component of the 5D, and 10 patients were unable to execute the Flexibility component ($\chi^2=22.5$ $p<0.001$), a pattern different from each of the other three groups, in which all the patients performed all of the 5D components. The ANOVA indicates significant differences for all of the neuropsychological measures, except for the total number of errors in the Decoding and Naming components of the 5D. The effect sizes of the comparisons were moderate to large, ranging from 0.081 (Inhibition Errors) to 0.190 (Describing Time). These results are shown in **table 1** and **figure 2**.

The *Post Hoc* analysis of the 5D indicates that in Decoding (time), the NAC group performed better than AD ($p<0.001$) and MDD ($p<0.018$) but not MCI ($p=0.687$). MCI patients also performed better than AD ($p=0.036$). In the Decoding (errors) analysis, no group differences were found. In Describing (time) the NAC group showed a similar pattern, with faster times than AD ($p=0.005$) and MDD ($p=0.027$) but not MCI ($p=0.920$). No differences were found between Describing (errors). The analysis of components associated with executive functions of the 5D indicates that NAC outperformed AD ($p=0.020$) and MDD ($p=0.014$) in Inhibition (time) but only AD in Inhibition (errors) ($p<0.016$). The Shifting (time) of NAC was faster than MDD ($p=0.005$), but in the total errors of

Figure 1. *Examples of 5d components*

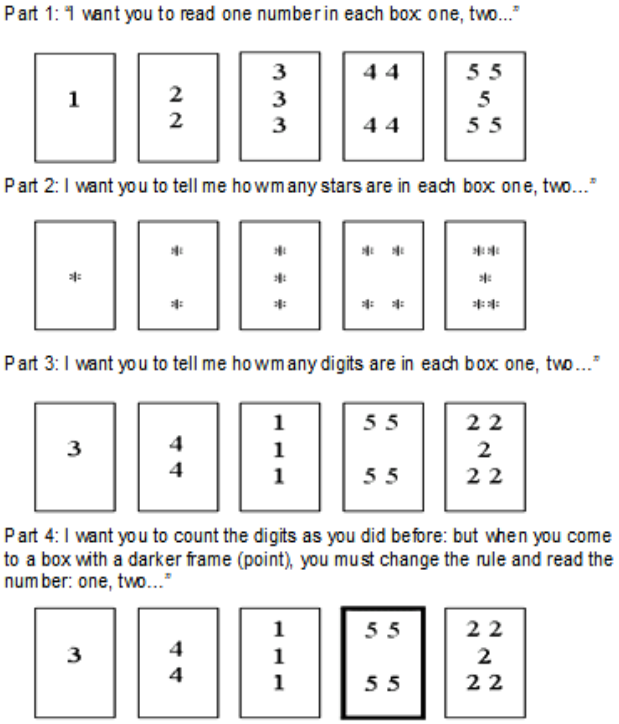

Figure 2. *Comparison among NAC, MCI, AD and MDD in 5D (time to complete Decoding, Retrieving, Inhibiting and Shifting parts)*

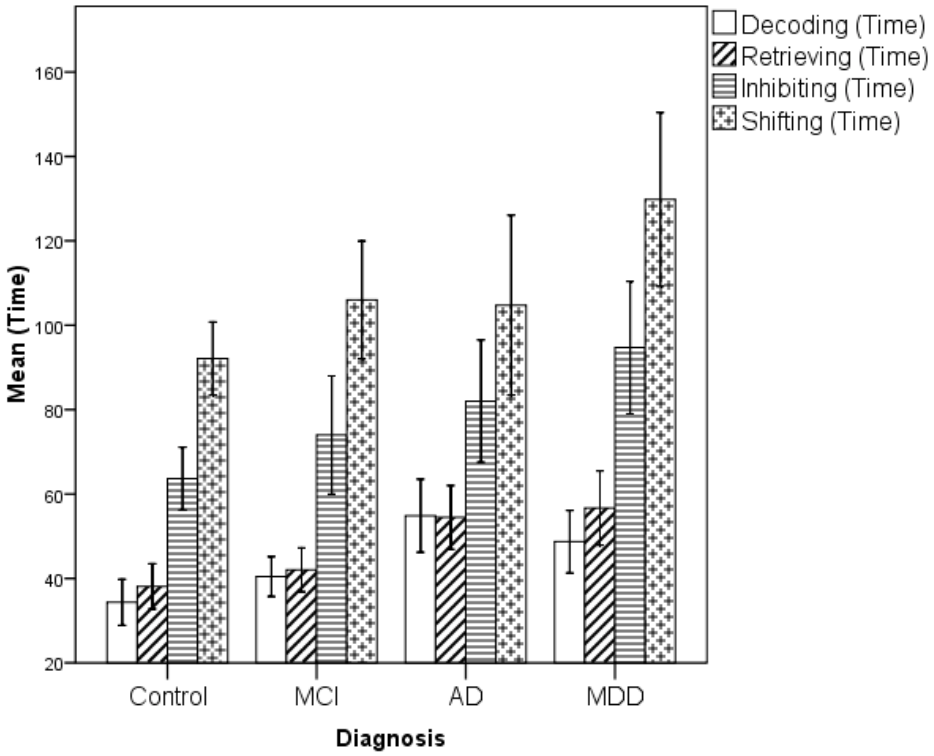

Table 1. *Demographics and neuropsychological tests results and comparisons among MCG, NAC, AD, MCI AND MDD*

	MCG		NAC		AD		MCI		MDD		Comparisons	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	ANOVA (Sig)	η2
Age	73.05	7.10	74.1	6.80	74.36	6.00	74.07	6.34	70.12	8.54	0.093	-
Education	4.18	2.93	4.27	2.26	3.85	2.92	4.57	2.94	4.00	2.97	0.793	-
GDS-15	5.13	3.86	2.30	2.77	4.02	2.69	2.31	1.77	10.50	1.85	0.000	0.47
MMSE	22.68	3.40	27.20	2.28	20.21	3.16	24.2	1.91	23.86	3.48	0.000	0.63
Decoding (Time)	47.27	18.71	34.33	14.88	52.97	22.12	40.43	12.97	48.71	18.15	0.000	0.15
Decoding (Errors)	0.11	0.38	0.03	0.18	0.17	0.46	0.10	0.40	0.04	0.20	0.420	-
Describing (Time)	52.01	21.01	38.10	14.66	58.27	23.11	42.03	14.19	56.67	21.51	0.000	0.19
Describing (Errors)	0.62	1.76	0.23	0.77	0.60	1.00	0.20	0.61	1.17	2.99	0.092	-
Inhibition (Time)	86.25	41.12	63.63	20.39	91.97	44.20	73.97	38.39	94.71	38.46	0.004	0.11
Inhibition (Errors)	6.26	8.80	1.97	2.28	8.11	9.81	5.53	8.39	5.00	8.05	0.027	0.08
Shifting (Time)	113.37	45.88	92.1	23.70	104.75	47.67	105.97	38.22	129.82	50.46	0.010	0.11
Shifting (Errors)	9.75	8.07	4.93	4.77	11.20	8.67	10.05	8.87	8.18	6.40	0.013	0.10

MCG: Mixed Clinical Group, NAC: Normal Aging Controls, AD: Alzheime's Disease, MCI: Mild Cognitive Impairment, MDD: Major Depressive Disorder.

this component, NAC the group performed better than AD (p=0.022) and MCI (p=0.046). No other group differences were found.

To further analyze the differences in executive functions among the groups, an interference score was computed subtracting the Decoding time from the Inhibition and Shifting time. The aim of this procedure was to minimize the influence of processing speed on executive performance, creating a more one-dimensional measure. No differences between the Interference-Inhibition (p=0.573) and Interference-Shifting (p=0.326) were found in the test of H1 or in Interference-Inhibition (p=0.096) and Interference-Shifting (p=0.201) in H2.

Discussion

This study evaluated the efficiency of 5D in the assessment of executive functions in less educated older adults with AD, MCI and MDD. Our findings show that the 5D may be a useful neuropsychological assessment tool for elderly patients with cognitive impairments. When a mixed clinical group is compared with the 5D, differences among the task components appear to be more related to processing speed (Decoding and Describing time), with large effect sizes, corroborating the discrepancy between the speed of performance of patients and controls. Processing speed declines with age (Salthouse 2000, Salthouse 2003, Brown et al. 2011), and older individuals tend to present a greater variability in performance (Salthouse 1998). Differences among clinical groups and healthy subjects are usually related (Wadley et al. 2011). As suggested by Boone et al. (1998), the performance results of multiple executive functions tend to show a moderate association, indicating a common structure and the presence of more specific components. In Boone's analysis, the SCWT had shared factorial loadings with the Digit Symbol task of the Wechsler Intelligence Scales, indicating that processing speed is related to the Inhibition process of the Stroop task.

The effect sizes of executive components were moderate to high, and differences in efficiency were found, suggesting that the executive process may also be compromised. Similar results were found using the SCWT in head-injury patients (Rios et al. 2004, Felmingham et al. 2004) and patients with Alzheimer's Disease (Spieler et al. 1996, Bondi et al. 2002); however, in MCI and MDD, recent studies have found no difference in the Inhibition time in Stroop Tasks (Zhang et al. 2007, Kertzman et al. 2010). It is important

to emphasize that interference scores from Stroop tasks may not be simple measures of inhibition. Salthouse and Meinz (1995) found that different measures of inhibition share most of their age-related variance with other measures of processing speed. Despite the proportion of shared age-related variance, they suggested that specific effects could be accurately estimated when the effects associated with the common influence are first controlled. As previously mentioned, the impairment of executive functions is not the core neuropsychological impairment found in MCI, AD and MDD, so a severe impairment was not expected in our sample, which may explain the more significant processing speed impairments.

Our data suggest that the processing speed impairments may be a more consistent finding in diffuse neurological damage, dementia or chronic mood disorders (Selnes and Vinters 2006, Duering et al. 2011, Brown et al. 2011, Burdick et al. 2010). As previously argued, the three clinical conditions examined in our study show white matter abnormalities (Alexopoulos et al. 2008, Douaud et al. 2011), which may mediate this cognitive deficit. According to this hypothesis, some evidence is provided by studies that show that processing speed may be secondary to a loss of integrity in white matter connection fibers (Fry and Hale 2000, Hansell et al. 2005, Rypma et al. 2005, Jung and Haier 2007, Turken et al. 2011). Penke et al. (2010) has shown that the general integrity factor of white matter is associated with a series of cognitive abilities, including processing speed, intelligence, and memory. Turken et al. (2011) also found a positive correlation between the structure of white matter pathways and processing speed in a healthy population and left hemisphere lesion patients. Although processing speed is not correlated with a specific brain region, the role of white matter in integrating information across spatially distinct brain regions suggests that cognitive slowing is related to neuronal efficiency. This hypothesis shows significant ecological validity because the impairments in processing speed are associated with greater functional deficits and may be used as estimates of MCI conversion to dementia (Tabert et al. 2002, Devanand et al. 2008).

When comparing the degrees of general cognitive and functional impairment, the performance in the 5D was not associated with a higher CDR score. Different clinical conditions can imply a marked slowness of performance in all test situations, especially controlled situations that require further use of voluntary self-direction, persistence and mental effort, and a greater resilience to the presence of stress and fatigability (Nathan et al. 2001). Normally, healthy older adults show declined performances in processing speed, inhibition and flexibility (Zelazo et al. 2004), three components of the 5D. This pattern may be influenced by general slowing difficulties associated with aging but tends to be more accentuated in clinical conditions, such as dementia. In AD patients, as suggested by Bondi et al. (2002), the slowness and magnitude of interference increases with the severity of dementia. The analysis of our second hypothesis revealed a discrepancy in performance of the four groups studied in all of the 5D components, excluding the total errors in Decoding and Describing, with moderate to high effect sizes. The *Post Hoc* analysis indicating that the CDR associated declines, however, was not supported by our data. In the Decoding and Describing Times, no differences were found between the NAC and MCI groups, but differences were present in NAC and MDD. MCI patients also performed better than AD. NAC patients were no faster than MCI in Inhibition and Shifting times but again had better performance than AD and MDD in Inhibition Time and better performance than MDD in Shifting Time. The efficiency of Inhibition of AD patients was inferior compared to the NAC group but not MCI and MDD, although in Flexibility, NAC outperformed MCI and AD patients. These results do not support our second hypothesis, but the Shifting differences encountered in terms of efficiency should be better evaluated in future studies. It must be considered that in the present study, the MCI sample is predominantly of the amnestic type, minimizing the degree of impairment expected in executive functions and processing speed. The small sample size may also be an important bias for these observations.

The poor performance of AD patients in Stroop Tasks is well documented in the neuropsychological literature (Bondi et al. 2002, Spieler et al. 1996, Perry and Hodges 1999, Perry et al. 2000). Our result, using an MVT task variation, corroborates this pattern, indicating convergence validity of the two tasks in a clinical sample. These results are consistent with those presented by Sedó and DeCristoforo (2001), where moderate to high correlations were found between the SCWT and the 5D in a healthy North American older adult sample, and those obtained by Hsieh et al. (1996) and Hsieh and Tori (2007) in a Chinese elderly population. In our sample, an important fact that may be used as a clinical guideline for older adults assessment is that NAC, MCI and MDD patients matched by age, education and gender to AD patients were able to complete all of the 5D components, although 10 of 30 AD patients were unable to perform the Shifting component and only one the Inhibition component. This cognitive shifting deficit may be a more specific feature of the AD neuropsychological deficits, which is also corroborated by the greater efficiency impairment with relative preservation of speed, in a fast but inaccurate performance, typical of executive impairments (Kogan 1971). Balota et al. (2010) showed, for example, that the errors on incongruent trials were the best discriminator of those who converted and those who did not convert to AD over a 14-year period.

Our results point to the efficiency of 5D in identifying executive dysfunctions in pathological aging in comparison with the normal aging process. Furthermore, the assessment of cognition in less educated elderly subjects needs to consist of appropriate stimuli (i.e., stimuli that do not require reading or writing abilities). This task shows great potential for use both in research and in clinical practices. Drawbacks in instruments, such as the chromatic (Lezak et al. 2004), visual (Dyer 1973, Spreen and Strauss 1998), and linguistic (Cox et al. 1997) properties of the SCWT, have limited their application in clinical special-needs contexts, where difficulties in color perception, visual impairments, specific reading problems, and language disorders are presented. This is the recurrent profile of

the elderly in Brazil, where 26% of the population is illiterate (IBGE 2009). In these contexts, the MVT tests appear to be an appropriate choice for the assessment of processing speed and executive functions.

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