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ARTICLE

White matter hyperintensities, executive function and global cognitive performance in vascular mild cognitive impairment

Hiper-intensidades de substância branca, função executiva e desempenho cognitivo global no comprometimento cognitivo leve vascular

Felipe Kenji Sudo[1], Carlos Eduardo Oliveira Alves[1], Gilberto Sousa Alves[1], Letice Ericeira-Valente[1], Chan Tiel[2], Denise Madeira Moreira[4], Jerson Laks[1,3], Eliasz Engelhardt[2]

ABSTRACT

Vascular mild cognitive impairment (VaMCI) represents an early symptomatic stage of vascular cognitive impairment and might be associated to fronto-executive dysfunction. **Methods:** Twenty-six individuals (age: 73.11±7.90 years; 65.4% female; schooling: 9.84±3.61 years) were selected through neuropsychological assessment and neuroimaging. Clinical and neuroimaging data of VaMCI individuals (n=15) were compared to normal controls (NC, n=11) and correlated with Fazekas scale. **Results:** VaMCI performed significantly worse than NC in Trail-Making Test (TMT) B, errors in TMT B, difference TMT B–A and Cambridge Cognitive Examination (CAMCOG) final scores. Correlations were found among scores in modified Fazekas scale and performances in TMT B (time to complete and errors), difference TMT B–A and CAMCOG total score. **Conclusion:** Extension of white matter hyperintensities might be correlated to poorer global cognition and impairments in a set of fronto-executive functions, such as cognitive speed, set shifting and inhibitory control in VaMCI.

Key words: mild cognitive impairment, dementia, vascular, executive function, neuropsychology, neuroimaging, cerebrovascular disorders.

RESUMO

Comprometimento cognitivo leve vascular (CCLV) representa um estágio sintomático precoce do comprometimento cognitivo vascular e associa-se à disfunção fronto-executiva. **Métodos:** Vinte e seis indivíduos (idade: 73,11±7,90 anos; 65,4% mulheres; escolaridade: 9,84±3,61 anos) foram selecionados por meio de avaliação cognitiva e neuroimagem. Os dados clínicos e de neuroimagem do grupo CCLV (n=15) foram comparados com controles normais (CN; n=11) e correlacionados com a escala de Fazekas. **Resultados:** CCLV apresentaram piores desempenhos que CN no *Trail-Making Test* (TMT) B, erros no TMT B, diferença TMT B–A e pontuação final do *Cambridge Cognitive Examination* (CAMCOG). Verificaram-se correlações entre escala de Fazekas e desempenhos no TMT B (tempo total e erros), diferença TMT B–A e a pontuação final do CAMCOG. **Conclusão:** A extensão das hiper-intensidades de substância branca, no grupo CCLV, correlacionou-se com pior desempenho cognitivo global e com comprometimento em um grupo de funções fronto-executivas, como velocidade e alternância cognitiva e controle inibitório.

Palavras-Chave: comprometimento cognitivo leve, demência vascular, função executiva, neuropsicologia, neuroimagem, transtornos cerebrovasculares.

Vascular mild cognitive impairment (VaMCI) is a term that may be used to refer to a clinical state that eventually converts to mild dementia in the continuum of vascular cognitive impairment (VCI)[1]. It represents a construct derived from mild cognitive impairment (MCI), operationally defined by Petersen[2], evolving from one of its subtypes, generally the non-amnesic single or multiple domain ones (executive function, visuospatial ability, and language), that was related to incipient forms of non-Alzheimer dementias, including vascular dementia (VaD). This subject was also addressed within the VCI concept, as Vascular Cognitive Impairment No-Dementia (VaCIND)[3].

[1]Instituto de Psiquiatria, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro RJ, Brazil;
[2]Instituto de Neurologia Deolindo Couto, Setor de Neurologia Cognitiva e do Comportamento, UFRJ, Rio de Janeiro RJ, Brazil;
[3]Universidade do Estado do Rio de Janeiro, Rio de Janeiro RJ, Brazil;
[4]Hospital Pró-Cardíaco, Rio de Janeiro RJ, Brazil.
Correspondence: Felipe Kenji Sudo; Rua Barata Ribeiro 383 / 1.004; 22040-001 Rio de Janeiro RJ - Brasil; E-mail: fksudo@gmail.com
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The American Heart Association and the American Stroke Association (AHA/ASA) workgroup approved VaMCI diagnostic criteria just as the clinical characteristics proposed in Petersen's criteria for MCI, based on cognitive testing of a minimum of 4 cognitive domains (executive/attention, memory, language, and visuospatial functions). The diagnostic criteria included probable, possible and unstable VaMCI. The diagnosis of probable VaMCI should be supported on (1) an assumption of decline in cognitive function from a prior baseline; (2) demonstration based on cognitive testing, of the presence of impairment in at least one cognitive domain, where the impairment is defined as a performance 1.5 standard deviation (SD) below the mean of normative values; (3) instrumental activities of daily living could be normal or mildly impaired, independently of the presence of motor/sensory symptoms; (4) history of clinical stroke or presence of subcortical cerebrovascular disease (CVD) by neuroimaging with a link between cognitive disorder and vascular lesions[4].

The importance of the necessary related vascular disease must be emphasized. The heterogeneity of vascular lesions underlying VCI is already known. One of the most prevalent subtypes (36–67%, according to different authors), the subcortical ischemic vascular disease (SIVD), is due to gradually progressive microvascular changes that might cause insidious and subtle cognitive impairments before diagnostic of VaD becomes established. Most (83.3%) subcortical small-vessel dementias might exhibit prodromal MCI, similar to what occurs in Alzheimer's disease (AD)[5]. On magnetic resonance imaging (MRI), SIVD usually appears as periventricular and deep white-matter signal hyperintensities (WMHs), visible on T2 and FLAIR images, and lesions in the prefrontal subcortical circuits are known to be involved in executive function, including control of working memory, organization, language, mood, regulation of attention, and constructional skills[3]. These lesions have been associated to aging, systemic arterial hypertension, dyslipidemia, smoking and diabetes mellitus[6]. The assumption that SIVD may induce cognitive changes by disrupting cortical-subcortical and cortical-cortical pathways is consensual, although correlations between extensions of WMH and cognitive measures could not be well established in some studies[6].

The definition of vascular-related cognitive disorders still needs to be refined. To date, diagnostic criteria developed to characterize cognitive syndromes associated with vascular disease require evidence of CVD or stroke previous to cognitive impairment, focal signs on physical examination, fluctuating stepwise course or dementia onset within three months of a stroke[4]. Although the need for a temporal association between stroke and cognitive changes may be relevant in cases of post-stroke dementia, it does not apply to cases of SIVD, in which cognitive decline may be slowly progressive rather than stepwise[5]. Therefore, diagnostic criteria for VCI due to SIVD should embrace cognitive impairments associated to deep white matter changes. Erkinjuntti et al. proposed a diagnostic approach of subcortical VaD, incorporating Binswanger disease and lacunar state. The neuroimaging criteria should cover both cases having predominantly white matter lesions (WML) (the "Binswanger type"), and those with predominantly lacunar infarcts (the "lacunar state type"). The "Binswanger type" cases corresponded to those with extending periventricular and deep WML, and the "lacunar state type" characterized by multiple lacunes and WML on brain images[7].

One important issue that awaits clarification is the threshold of vascular load required to produce cognitive impairment. Large longitudinal population-based studies found evidence that mild WMH might be highly prevalent in cognitively normal elderly individuals[6]. The difficulty in defining a non-demented pathological group with underlying small-vessel disease is to discriminate initial VCI cases, namely VaMCI individuals, from those with cognitive changes of normal aging, in neuropsychological evaluations. The need for harmonized cognitive testing for VCI is recognized by some investigators. Identification of clinical patterns of VCI, which could discern those patients from normal controls (NC) using non-standardized neuropsychological instruments, has proven challenging[3].

Such difficulties have been addressed in some studies. A cohort of post-stroke patients, classified as no-cognitive impairment (NCI), VaMCI, and VaD showed that VaMCI presented an intermediate load of WML compared to the other two classes (NCI=6.4±3.0 mm^3; VaMCI=8.2±4.1 mm^3; VaD=9.5±4.0 mm^3)[8]. A study that classified individuals with the modified Fazekas (mF) scale showed those as presenting mild (mF=1, corresponding to 6.49±4.7 mL of mean WMH volume), moderate (mF=2, equivalent to 18.83±7.7 mL of mean WMH volume) or severe (mF=3 or 51.35±26.1 mL of mean WMH volume) WMH9.

O'Brien[6] pointed out that patients with moderate to severe white matter changes might present high risk of lesion progression and consequently of clinical decline in VCI. Moreover, Schmidt et al.[10] showed that individuals presenting moderate and severe WMH did not significantly differ in performances on mini-mental state examination (MMSE) and executive function (EF) tasks.

Summing up the above findings, it seems to be possible to assume that a moderate to severe WML might be an adequate load to characterize VaMCI.

Although fronto-executive dysfunction has been related to VCI in studies[11], data suggested that some patients displayed dissociations in their performances on selected frontal tasks. For instance, some studies identified subtle declines in VCI subjects relative to NC on California Card Sorting test, whereas no significant differences were found in other executive tests[11]. Those aspects have led to the theory of a fragmentation of EF in a set of different skills related to the prefrontal lobe and its connections, comprising

abstract thinking, inhibition of overlearned patterns of behavior, inhibitory control, cognitive flexibility, set shifting, organizational ability, planning, regulation of working memory, and fluency of thought[11].

This cross-sectional study aimed to evaluate the overall cognitive performance and the EF of a sample of VaMCI patients. The contribution of the severity of WMH on cognitive deficits was also assessed. Our hypothesis is that some components of EF might show impairments in early VCI, which might be correlated to the degree of vascular lesions on MRI scans.

METHODS

Subjects

Twenty-six individuals (age: 73.11±7.90 years; 65.4% female; schooling: 9.84±3.61 years) were selected through neuropsychological assessment and neuroimaging. Clinical and neuroimaging data of VaMCI individuals (n=15) were compared to normal controls (NC, n=11) and correlated with Fazekas scale. They were consecutively evaluated at the Centre for Alzheimer Disease and Related Disorders (CDA), Federal University of Rio de Janeiro (UFRJ), Brazil, between October 2008 and August 2011. The detailed sample selection criteria for this study have previously been published[12].

Clinical, neuropsychological and neuroimaging assessment

Cognitive assessment, functional status and evaluation of depressive symptoms followed the procedure described in a previous paper from this group[12]. Working memory was assessed through Cambridge Cognitive Examination (CAMCOG), items 159–160, corresponding to ability to count backwards from 20 to 1 and ability to subtract serial sevens backwards from 100. Performance in clock-drawing task was assessed using CLOX scoring method[13].

In addition to the direct score, three variants of Trail-Making Test (TMT) scoring were calculated: difference score (TMT B–A), ratio score (TMT B:A) and logarithmic transformation (Log B:A). Derived TMT scores have been proposed by some authors to better describe cognitive skills required to complete the test. For instance, TMT B–A is meant to remove the speed component from the test evaluation. TMT B:A ratio might provide a sensitive index for task-switching ability[14]. The logarithmic transformation aimed to reduce dispersion in scores and may be useful for generalization of results across diagnostic groups[14].

All subjects underwent MRI scans of the brain on a 1.5T GE Signa Horizon machine. The modified version of the Fazekas scale was applied to visually measure periventricular and deep subcortical WMH on FLAIR images[9] and individuals were classified as presenting absent (mF=0), mild (mF=1), moderate (mF=2) or severe (mF=3) WMH. Hippocampal atrophy (HA) was estimated using de Leon's visual assessment score. For each hemisphere, the extent of HA is rated on a 4-point scale: (0-none, 1-questionable, 2-mild/moderate, and 3-severe). A cut-off score ≥2 on either hemisphere is considered evidence for qualitative HA[15]. Both Fazekas and de Leon were scored by a trained radiologist and a neurologist blind to the clinical and cognitive data.

Diagnosis

Subjects were diagnosed as VaMCI according the AHA/ASA criteria, in which cognitive impairment is defined as a performance 1.5 SD below the mean of normative values in neuropsychological assessment in at least one domain[4]. Normative data available in literature for each test for comparison to scores obtained by participants (patients and NC) in this study were used[16-19].

In order to characterize the lesion load to impair cognition at a VaMCI level, a cut-off score ≥2 on mF scale (moderate to severe degree of WMH) and HA ≤1 on de Leon score (none or questionable HA) were adopted, to ensure the inclusion of subjects with relevant white matter lesions, and with hippocampal size less compatible with neurodegenerative changes. Diagnostic criteria for probable VaMCI used in this study are summarized in Table 1.

The NC (n=11) did not present evidence of cognitive and functional impairment, and showed both Fazekas and de Leon scores ≤1. Individuals with significant depressive symptoms (Cornell Depression Scale ≥9), and functional deficiency (Pfeffer's Funcional Activities Questionnaire – FAQ≥5) were excluded from this research.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) – version 20 was used for data analysis. The Mann-Whitney test was used to assess statistically significant differences on neuropsychological tests, functional status and behavioral symptoms between VaMCI and NC. Pearson's χ^2 was applied to assess statistically differences when comparing categorical variables (gender, scores in de Leon and Fazekas scales)

Table 1. Diagnostic criteria for probable vascular mild cognitive impairment adopted in this study.

- Evidence, based on cognitive testing, of impairment of 1.5 SD below the mean on one or more cognitive tests in relation to normative values for age and schooling;
- Preserved or mildly impaired functional activities, as established with FAQ <5;
- Evidence of small-vessel disease, indicated by modified Fazekas scale ≥2;
- Absence of HA suggestive of neurodegenerative disease, as defined by de Leon score ≤1.

SD: standard deviation; FAQ: Pfeffer's Funcional Activities Questionnaire; HA: hippocampal atrophy.

between groups. Partial correlation was performed to verify the relationship between extension of WMH and cognitive tests elected after Mann-Whitney test, controlling for confounding effects of schooling and age. The level of significance was set at 0.05.

Ethics

This study is a branch of a project on vascular-related cognitive disorders, approved by the Ethics Committee of the Institute of Psychiatry, Federal University of Rio de Janeiro (IPUB-UFRJ). Informed consent was obtained from participants or from a family member responsible prior to enrolment.

RESULTS

Fifteen patients fulfilled previously described criteria for probable VaMCI. Table 2 illustrates socio-demographic variables, Fazekas and de Leon scores of the two groups of participants. There were no differences between NC and VaMCI in socio-demographic variables. As expected, groups differed significantly in Fazekas scale and Hachinski Ischemic Score (HIS), but not in de Leon scale.

Neuropsychological assessment showed significant mean differences between groups in TMT A and B, errors in TMT B, difference TMT B–A and CAMCOG total scores, for a significance level of 0.05. A trend for significance was identified in abstraction. These data are depicted in Table 3.

Based on significant results of the Mann-Whitney test, CAMCOG, TMT A and B, difference TMT B–A and errors in TMT B were selected to input to partial correlation test. Correlations were performed to determine whether extensions of WMH were associated with neuropsychological functions, with years of education and age included as control variables (Table 4). Albeit no significant differences were identified in years of schooling or age between groups, within-group variance in those variables might play a confounding effect on cognitive performances. Moderate negative correlations between scores in Fazekas scale and total score of CAMCOG (r=-0.533, p=0.006) were found, after controlling for schooling. Both time to complete and errors in TMT B presented positive correlations with scores in Fazekas scale. No correlation was found between TMT A and Fazekas scale, controlling for schooling (p=0.200). Moderate correlation was identified between difference TMT B–A and severity of WMH (r=0.502, p=0.015). Controlling for

Table 2. Demographic data, Hachinski Ischemic Score, Fazekas and de Leon scores.

	VaMCI (mean±SD)	NC (mean±SD)	p-value
Gender (M/F)	6/9	3/8	0.683[a]
Age (years)	74.13±8.06	69.36±7.11	0.148[b]
Schooling (years)	8.86±4.03	11.18±2.56	0.121[b]
MMSE	27.33±2.41	28.81±1.16	0.069[b]
HIS	5.50±4.03	1.50±1.50	0.011[b]
Fazekas scale (0/1/2/3)	0/0/7/8	3/8/0/0	<0.001[b]
de Leon scale (0/1/2/3)	7/8/0/0	6/5/0/0	0.691[a]

[a]Pearson's χ^2; [b]Mann-Whitney test; VaMCI: vascular mild cognitive impairment; NC: normal controls; M: male; F: female; MMSE: Mini-Mental State Examination; HIS: Hachinski Ischemic Score; SD: standard deviation.

Table 3. Cognitive and behavioral data from vascular mild cognitive impairment and normal control groups.

	VaMCI (mean±SD)	NC (mean±SD)	p-value[a]
FAQ	0.93±1.33	0.09±0.30	0.148
Cornell	2.66±2.69	1.27±2.28	0.164
Orientation	9.33±1.29	9.72±0.46	0.838
Language	25.86±2.16	27.18±1.07	0.097
Memory	19.60±3.43	22.0±2.96	0.097
Attention	4.73±1.79	5.54±1.75	0.305
Praxis	10.26±1.66	10.81±0.98	0.610
Perception	7.33±1.23	8.18±1.32	0.180
Calculation	2.00±0	1.90±0.30	0.721
Abstraction	4.66±2.35	6.27±1.61	0.061
CAMCOG	83.80±8.22	91.90±4.59	0.011
CLOX1	13.20±1.74	13.27±2.19	0.838
CLOX2	13.80±1.82	14.50±0.52	0.892
TMT A	87.53±35.73	60.54±17.24	0.041
Errors A	0.13±0.35	0.09±0.30	0.878
TMT B	265.84±136.49	127.45±46.76	0.004
Errors B	1.61±0.86	0.63±1.02	0.011
TMT B:A	3.28±1.54	2.19±0.83	-[b]
TMT B–A	180.07±118.50	66.90±43.75	0.006
Log TMT B:A	0.47±0.19	0.31±0.16	0.082
VF	15.71±4.56	16.63±3.38	0.809
Working	4.60±1.80	5.72±1.55	0.121

[a]Mann-Whitney test; [b]TMT B:A: quotient of mean values of TMT A and TMT B (>3: impairment of cognitive flexibility); VaMCI: vascular mild cognitive impairment; NC: normal controls; FAQ: Pfeffer's Funcional Activities Questionnaire; Cornell: Cornell Depression Scale; CAMCOG: Cambridge Cognitive Examination; CLOX 1: Clock Drawing Task part 1; CLOX 2: Clock Drawing Task part 2; TMT A: Trail-Making Test part A; Errors A: errors in Trail-Making Test part A; TMT B: Trail-Making Test part B; Errors B: errors in Trail-Making Test part B; TMT B:A: ratio TMT B/TMT A; TMT B–A: difference TMT B–TMT A; Log TMT B:A: logarithmic transformation of B:A; VF: verbal fluency; Working: working memory.

Table 4. Correlations among scores on Fazekas scale and neuropsychological tests.

	r[a]	p-value	r[b]	p-value
CAMCOG	-0.533	0.006	-0.609	<0.001
TMT A	0.265	0.200	0.497	0.011
TMT B	0.530	0.009	0.687	<0.001
Errors B	0.468	0.024	0.530	0.009
TMT B–A	0.502	0.015	0.669	<0.001

[a]Controlling for years of schooling; [b]controlling for age; CAMCOG: Cambridge Cognitive Examination; TMT A: Trail-Making Test part A; TMT B: Trail-Making Test part B; Errors B: errors in Trail-Making Test part B; TMT B–A: difference TMT B–TMT A.

age, difference TMT B–A (r=0.669, p<0.001), CAMCOG (r=-0.609, p<0.001), TMT A (r=0.497; p=0.011), TMT B (r=0.687, p<0.001) and errors in TMT B (r=0.495, p=0.019) presented moderate correlations with scores in Fazekas scale.

DISCUSSION

Our results suggest the occurrence of impairments in fronto-executive tasks associated with extension of periventricular and deep WMH in patients with probable VaMCI. Significant poorer results in TMT A and B, errors in TMT B, difference TMT B–A and CAMCOG total score were identified in VaMCI in relation to NC, and performances in those tests correlated with scores in Fazekas scale. A trend for significant difference was found in relation to mean scores in abstraction, compared to NC (p=0.061).

These data are in line with results from previous researches in which executive dysfunction was related to cerebrovascular disease[20]. A study using quantitative fractional anisotropy (DTI-FA) detected higher levels of interrupted fibers in anterior (frontal) brain regions in comparison to posterior regions-of-interest in patients with Binswanger disease, which might be compatible to disconnection of prefrontal-basal ganglia-thalamic circuits associated to executive function[21].

Both abstract thinking subtest in CAMCOG and TMT B require integrity of the prefrontal cortex and of its connections to basal ganglia. Dorsolateral and ventrolateral cortices were activated during tasks involving abstraction in studies using functional MRI (fMRI)[22]. Impairment in abstract thinking has distinguished VaMCI from NC in one study[12]. In addition, the Wechsler Adult Intelligence Scale-Revised (WAIS-R) similarities subtest, which evaluates abstract thinking, was selectively low in initial VCI patients compared to incident AD patients, in a large prospective study[23]. The present data showed a trend for significant differences in abstract reasoning between VaMCI and NC, which might provide evidence of the importance of extension of WMH on this cognitive function.

TMT B demands cognitive abilities such as inhibitory control, cognitive flexibility and processing speed. TMT B was related to activation in inferior dorsolateral prefrontal cortex, anterior cingulate, premotor cortex and intraparietal sulcus in fMRI studies[24]. Coherently, performance errors in TMT B have been reported as a feature with high positive predictive power for the presence of frontal lobe dysfunction[25]. Errors in TMT B were classified in 3 different types, which were consistent to dysfunction in prefrontal cortex and its subcortical connections, as follows: (1) sequential or tracking errors (proceeding to incorrect number or letter), (2) perseverative errors (failure to proceed from number to letter or vice versa) and (3) proximity errors (proceeding to an incorrect nearby number or letter)[26].

In addition, TMT B:A ratio in VaMCI patients achieved mean quotient above 3, which might be suggestive of impairment in task-switching. Corroborating this finding, the significant mean differences in TMT B–A might also represent impairment in cognitive flexibility in those patients. According to a previous study, this scoring method minimizes visuoperceptual and working memory demands, and might correspond to the most reliable index of task-switching ability among all TMT direct and derived scores[14]. A relatively high score in TMT B:A ratio observed in NC group, and the lack of significant differences in Log B:A between VaMCI and NC are consistent with the literature[27]. Previous researches that evaluated the validity of TMT derived indices indicated some issues concerning the sensitivity and specificity of those methods. For instance, the use of a cut-off score of 3 or greater for a TMT B:A ratio has been associated to high rate of false-positive results in studies[27]. The fact that NC presented a mean B:A ratio of 2.19±0.83 in our study indicates that some individuals in this group have surpassed the 3 cut-off, in spite of performing within normative values (i.e., total score less than 1.5 SD from the mean) for age and educational level in both TMT A and B direct scores. Further research is needed to validate its clinical utility as an index for dysexecutive syndrome.

Moreover, tests evaluating global cognitive function, mainly CAMCOG, were also correlated to severity of WMH in our study. Studies that analyzed CAMCOG as a screening tool for VCI showed excellent sensitivity and specificity[28].

Another aspect of our results also deserves to be addressed. Impairments in abstract thinking, TMT B, difference TMT B–A and errors in TMT B with preserved CAMCOG items for working memory and verbal fluency (VF) may load onto the idea of the multiple dimensions of EF, instead of an overarching executive construct. In fact, studies which performed factor analyses of putative EF measurements indicated discernible factors, such as "set shifting", "inhibitory control", "working memory" and "rule discovery"[29]. None of the tests usually applied to evaluate EF appears to assess all those traits comprehensively[13]. Oosterman et al.[30] noted significant associations between WMH and fronto-executive functions in a sample with risk factors for CVD, such as inhibitory control, planning and working memory. In the same study, HA was also associated to EF, showing a strong contribution to performance in working memory and set-shifting tasks. Diminished function of prefrontal-hippocampal circuits associated to HA was implied as a possible mechanism for these findings[30].

Strengths of the present investigation include a stricter diagnostic criterion for VaMCI, comprising clinical features and neuroimaging measurements. This might have provided better classification accuracy and a more homogeneous sample. Some limitations, nevertheless, should be commented. Firstly, our sample was recruited in a specialized memory

clinic, and our data cannot be generalized to other populations without further studies. Secondly, this study included a small sample of patients. It should also be noted that the absence of a golden-standard test for EF might cause divergence with results in different studies, according to the chosen neuropsychological battery.

Our findings support the importance of assessing fronto-executive functions in patients with probable initial VCI. The literature highlights the difficulties of evaluating those cognitive aspects and a set of neuropsychological tests recommended for extensively assessing executive dysfunction remains to be determined. It is possible to argue that TMT B (direct score and difference B–A), CAMCOG abstract thinking subtest and CAMCOG total score might specifically distinguish VaMCI from healthy controls.

In conclusion, the authors suggest that a comprehensive cognitive battery, including global cognitive assessment and executive function tasks, with emphasis in evaluation of abstract thinking, cognitive speed, set shifting and inhibitory control might be useful in the pursuit of a more specific identification of initial VCI.

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