



Cognitive evaluation in cerebral small vessel disease: towards an evidence-based identification of the reference standards. Part 1. A systematic review and qualitative data synthesis

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Abstract

Background Cerebral small vessel disease (cSVD) is a leading cause of cognitive impairment in the elderly. Despite cSVD cognitive profile is thought to be mainly characterized by attention and executive functions deficits, there is no definite agreement on the standards for its evaluation. This systematic review aims at identifying cognitive domains and neuropsychological tools specifically chosen in the assessment of cognitive impairment related to cSVD, and the temporal and geographic trends in their utilization.

Methods Following PRISMA guidelines, original articles focused on cSVD patient samples neuropsychologically evaluated were searched using PubMed, Scopus and PsycINFO databases without language or time restrictions (PROSPERO registration number CRD42018089882; date 27-02-2018).

Results We screened 13,688 studies and included 298 in the qualitative data synthesis. Global cognitive functioning and attention/executive functions were the most evaluated domains (87% and 69%, respectively). Mini Mental State Examination was the most used screening tool (73%), followed by MoCA (14%) whose utilization rapidly increased over the last years. The most frequently used second level tests were phonemic and semantic fluencies (39% and 30%, respectively), Trail Making Test (TMT) part A and B (31% and 32%, respectively), Stroop (31.5%), and Boston naming (30%). All tests resulted stably utilized over time, except for semantic fluency and Stroop whose use increased. Phonemic fluency and Boston naming were the most used in North America (51% and 45%, respectively), TMT in Europe (43%), and Stroop and semantic fluency in Asia (43% and 40%, respectively).

Conclusions This systematic review confirms that attention/executive functions domain is the most commonly evaluated in cSVD together with lexical retrieval abilities based on executive control processes. Temporal and geographic variability emerged in the choice of tests.

PROSPERO registration number CRD42018089882 (27-02-2018).

Keywords Cerebral small vessel disease · Cognitive domains · Neuropsychological tools · Attention and executive functions

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Introduction

Cerebral small vessel disease (cSVD) is a recognized and leading cause of stroke, disability and cognitive impairment in the elderly [1]. In patients with cSVD, cognitive impairment has usually a progressive course and is thought to be mainly characterized by deficits in attention and executive functions [2, 3]. However, this assumption might be biased by the selection of tools for the neuropsychological assessment.

There are various etiological types of cSVD. The most common forms of cSVD are the sporadic age- and

hypertension-related microangiopathy and cerebral amyloid angiopathy [3]. There are also genetic forms of cSVD of which CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is currently the most commonly studied. Of note, CADASIL is also considered a pure model of cSVD, because the age of onset is in young adulthood, when neurodegenerative changes are not present [4].

Neuropsychological assessment has the potential to better characterize the patient's cognitive and functional profile [5]. At present, despite the availability of several neuropsychological tools to assess the wide range of possible deficits, there is no definite agreement on which test should be considered specific for the pattern of cognitive deficits characteristic of patients with cSVD.

This systematic review represents the first part of a project [PROSPERO registration number: CRD42018089882] that applied an evidence-based clinical approach, with the final aim of identifying those neuropsychological tests which are better suited to detect the pattern of cognitive deficits that is possibly characteristic of cSVD.

More specifically, the present review was aimed to answer the following review questions:

1. Which cognitive domains have been evaluated in studies assessing the cognitive profile of patients with cSVD, either sporadic or genetic?
2. What are the neuropsychological protocols and tools specifically proposed or applied within each cognitive domain to evaluate cSVD patient samples?
3. Has there been a temporal variation and are there geographic differences in the utilization of neuropsychological tools in sporadic cSVD?

Methods

Study design

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) guidelines and has been registered in PROSPERO International Prospective Register of Systematic Reviews (<https://www.crd.york.ac.uk/prospero>, registration number: CRD42018089882; date 27-02-2018) [6]. The PRISMA-P 2015 checklist is provided in Online Appendix.

Search strategy

Original articles were searched using three comprehensive medical databases from their respective dates of inception up to February 2018. The databases searched were PubMed,

Scopus and PsycINFO. A targeted search based on pre-defined search terms and using various Boolean terms to build the various algorithms was conducted. The search identified the following key concept combinations which can be summarized as follows: ([Subcortical ischemic cerebrovascular disease] OR [Vascular cognitive impairment] OR [Small vessel disease] AND [neuropsychological evaluation] OR [neuropsychological tests] OR [perceptual disorders] OR [attention] OR [memory] OR [language] OR [executive function]). These key concepts were translated into searches adapting (controlled) terms, database specific search fields and syntaxes belonging to the different bibliographic databases. The complete search syntax is provided as Online Resource.

The search results were then exported to EndNote Web, and each search file individually saved. A master file including all the references was created, and duplicated citations were primarily identified using the EndNote function "find duplicates". Other duplicates were manually searched and then deleted.

Inclusion/exclusion criteria

All original reports, studies in press, and conference and meeting proceedings were included. The search was focused on human studies without restrictions on language or time period.

We included only original reports on patients with cSVD and their cognitive status that applied standardized neuropsychological tests. Cross-sectional, longitudinal, and case-control studies, as well as studies including a post-mortem verification of neuropathological diagnoses were included. Two types of population-based studies were eligible: those including patients with a clinical diagnosis of cSVD (either for the sporadic or genetic forms), and those in which cohorts of normal volunteers were recruited and followed prospectively with cSVD neuroimaging signs detected during follow-up. For many years, and before the more recent conceptualization of cSVD [3, 7], the only type of cSVD that was repetitively studied was white matter hyperintensities (WMHs). For this reason, also studies that defined the presence and extension of WMHs as one of the main outcomes were included. To be included, these studies had to report both grading methods and results concerning WMHs. We excluded studies reporting on patients with significant large vessel cerebrovascular disease, major stroke, multi-infarct dementia, and studies focused on other major non-vascular neurological diseases.

Selection of studies

After literature search completion, three authors (ES, MB, IC) screened titles and abstracts for potentially suitable

studies. The full texts of selected papers were reviewed, and those articles meeting the inclusion/exclusion criteria were included in the systematic review. In case of doubts about inclusion eligibility, the paper was reviewed by all three authors and included if two out of three were in agreement. The study selection process is detailed in a PRISMA flow diagram (Fig. 1).

Data extraction

Data were extracted from the studies selected for inclusion and reported in a dedicated database. The key data extracted included study details such as authors, year of the study start when available, year of publication, geographic area of the study defined as that one in which the patients were enrolled, patient population, and reported neuropsychological measures. In the case of more than one publication from the same study, the most informative paper was considered.

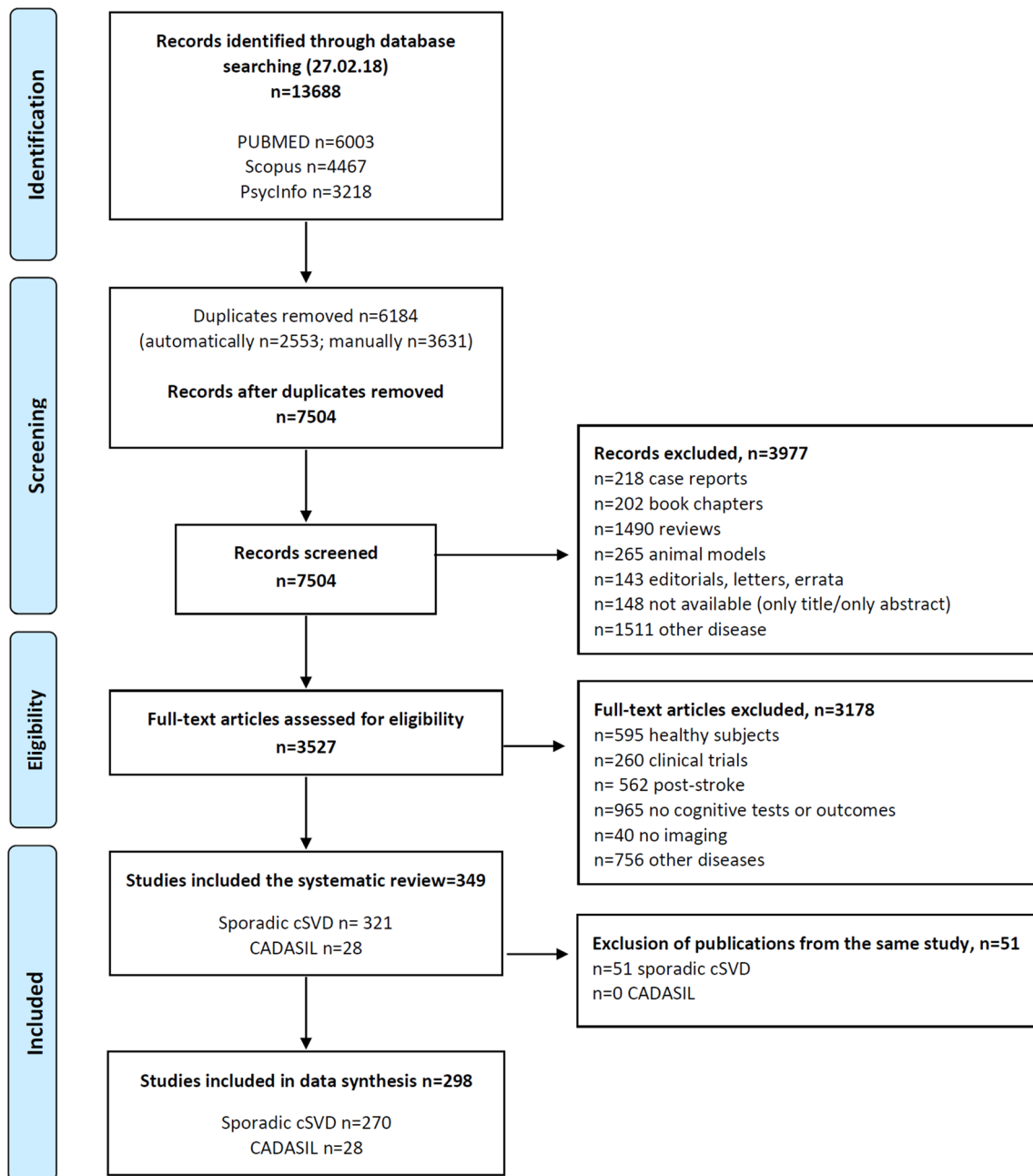


Fig. 1 PRISMA flow diagram

Data synthesis

Data were synthesized qualitatively, and descriptive analyses were performed to describe the frequency of evaluation of the cognitive domains among the included studies, the cognitive tests pertaining to each domain, and their frequency of utilization. Cognitive tools have been grouped into the following cognitive domains: global cognitive functioning (including either screening tests or batteries), attention/executive functions, memory, language, visuo-spatial, praxis and perceptual, intelligence, and social cognition. A cognitive domain was considered as evaluated when at least one test pertaining to that domain was included in that single study. Data deriving from studies on sporadic cSVD or CADASIL have been extracted and synthesized separately.

Descriptive data on temporal distributions of evaluation of cognitive domains, and temporal and geographic distributions of the selected tests were further extracted from the studies on sporadic cSVD. Percentages of utilization were computed considering the number of studies for each time period in temporal analyses and for each area in geographic analyses.

Results

Figure 1 shows the PRISMA flow diagram. Out of 13,688 articles identified through the electronic databases search, 6184 were removed as duplicates. Among the 7504 articles screened and assessed for eligibility, 349 fitted the inclusion criteria, but 51 publications deriving from the same study were further excluded. Thus, the final data synthesis included 298 studies (sporadic cSVD $n=270$, CADASIL $n=28$; for the list of included studies, see Online Resource Tables 1 and 2).

Taking into account the 270 studies on sporadic cSVD, global cognitive functioning was evaluated in 235 (87%) studies by the use of 30 different neuropsychological tools (either tests or batteries), attention/executive functions were assessed in 186 (69%) studies using 51 different tests, memory in 176 (65%) studies using 45 different tests, language in 173 (64%) studies using 21 different tests, visuo-spatial, praxis and perceptual abilities in 98 (36%) studies using 24 different tests, intelligence in 60 (22%) studies using two tests, and social cognition in 3 (1%) studies using two tests. Overall, 175 different neuropsychological tools were used in studies on the evaluation of cognitive profile in sporadic cSVD (for the list of tools, see Online Resource Table 3).

Year of the study start was available in 143 (53%) studies on sporadic cSVD and ranged from 1980 to 2015. For the data synthesis and description, studies were grouped according to the year of the study start and categorized in three periods (1980–1995, $n=17$ studies; 1996–2005,

$n=48$; 2006–2015, $n=78$). Figure 2 shows the frequency of evaluation of cognitive domains within each time period in respect of the overall number of studies in that period. The overall frequencies of evaluation of the attention/executive, memory, language and visuo-spatial, praxis and perceptual domains remained rather stable over time, while that of intelligence decreased. Figure 3 reports the frequency of utilization of tools in the three different time periods according to the type of cognitive tools utilized. In the last time period, a trend for a more frequent use of global cognitive functioning tools without any accompanying second level test emerged.

Taking into account the 28 studies on CADASIL patients, global cognitive functioning was explored in 19 (68%) studies by the use of 8 different screening tools (either tests or batteries), attention/executive functions in 25 (89%) studies using 11 different tests, memory in 19 (68%) studies using 17 different tests, language in 13 (46%) studies using 7 different tests, intelligence in 13 (46%) studies using 2 tests, and visuo-spatial, praxis and perceptual abilities in 7 (25%) studies using 7 different tests. Overall, among studies on CADASIL patients, 52 different neuropsychological tools were used (for the list of tools, see Online Resource Table 4).

The frequency of utilization of the cognitive tools among the included studies is presented in detail in Table 1. The Mini Mental State Examination (MMSE) was the most commonly used screening tool both in sporadic cSVD (73%) and in CADASIL (57%). The Montreal Cognitive Assessment (MoCA) was the second most commonly used screening test in sporadic cSVD (14%), while the Mattis Dementia Rating Scale and the Vascular Dementia Assessment Scale (VADAS) were well represented in CADASIL studies (18% and 14%, respectively).

Considering the frequency of utilization of the two most commonly utilized screening tools over time, MMSE had the highest percentages of use with a growing trend, ranging from 59 (1980–1995) to 71% (1996–2005) and 76% (2006–2015) of studies. The use of MoCA rapidly increased after its introduction in 2005. The frequency of utilization of MoCA has been particularly high in the years 2010–2015 reaching a frequency of 61% (Fig. 4).

Taking into account the attention/executive domain second level tests, the Trail Making Test (TMT) parts A and B and the Stroop Test resulted, by far, the most commonly used both in sporadic cSVD and in CADASIL. Among memory tests, the forward and backward digit span tests were the most frequently used in both populations (Table 1).

Considering the remaining cognitive domains, the most commonly used tests were: (1) phonemic and semantic fluencies, and the Boston naming test for the language domain; (2) the copy of the Rey-Osterrieth Complex Figure for the visuo-spatial, praxis and perceptual domain; (3) the following subtests of the Wechsler Adult Intelligence Scale

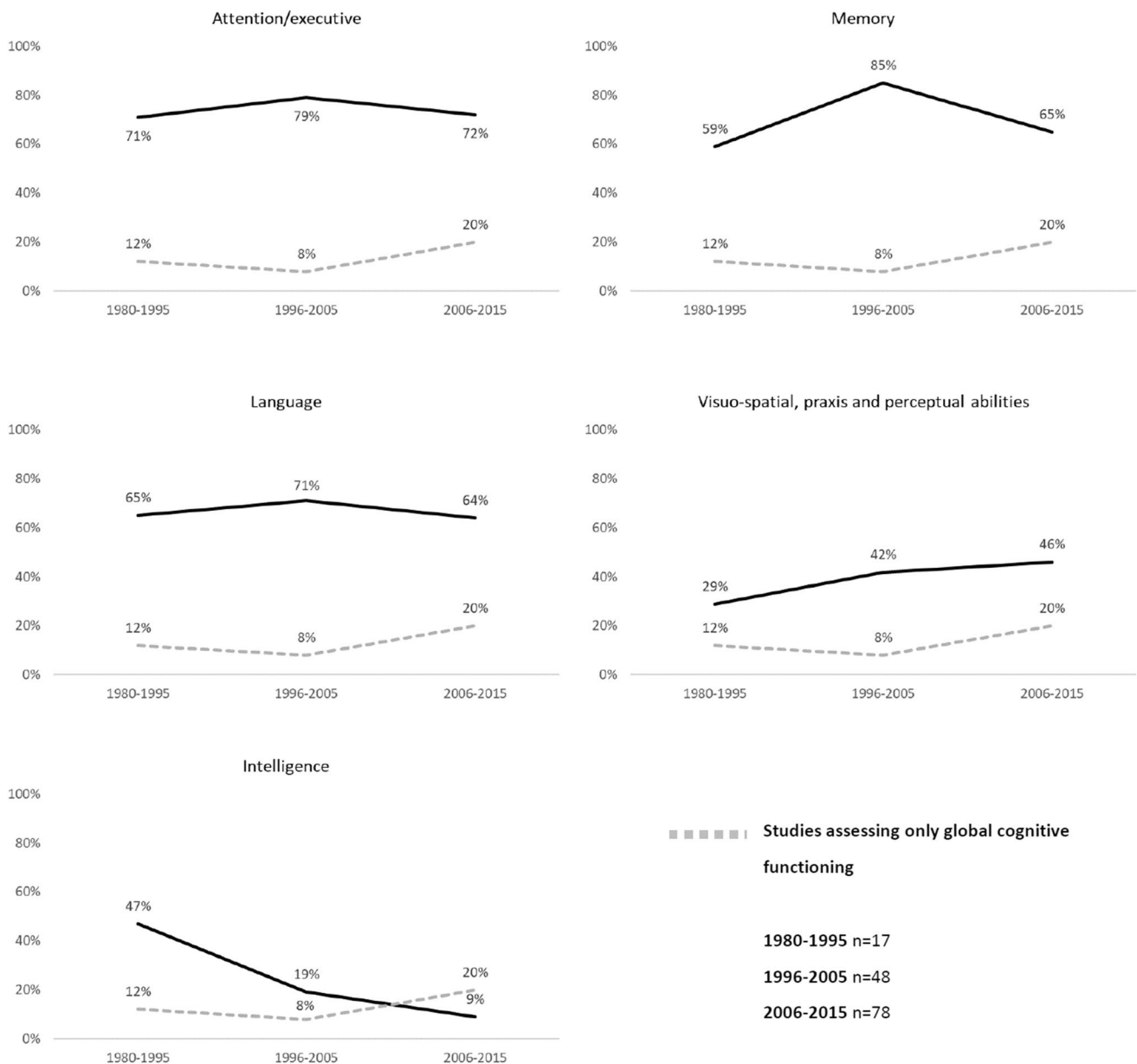


Fig. 2 Frequency of cognitive domains evaluation within each time period expressed as percentage in respect of the overall number of studies in that period (considering only sporadic cSVD). In each insert, the frequency of global cognitive functioning evaluation is reported for comparison

(WAIS) for the intelligence domain: Digit Symbol Substitution, Digit span, Similarities and Block design (Table 1).

Considering all the cognitive domains together, the most frequently used second level tests in studies on sporadic cSVD were: phonemic fluency (39%), TMT part B (32%), Stroop (31.5%), TMT part A (31%), semantic fluency (30%), and Boston naming (30%).

The frequencies of utilization remained stable over time for all tests, except for semantic fluency and Stroop tests that showed an increasing use over time (Fig. 5).

Geographic area where the study was carried out was available in all the 270 studies on sporadic cSVD. However,

two studies were conducted across different continents and, therefore, were excluded from the analysis. The frequency of utilization of the most commonly used tests in respect of the overall number of studies in each geographic area is shown in Fig. 6. Considering the screening tests, MoCA resulted more frequently used in Asia (31%), while the use of MMSE was high across areas (Asia 86%, Europe 71%, North America 61%) (Fig. 6). Taking into account the most frequently used second level tests, the frequencies of use of phonemic fluency are similarly distributed across Asia and Europe (34% and 36%, respectively), while the test is the most used second level test in North America (51%).

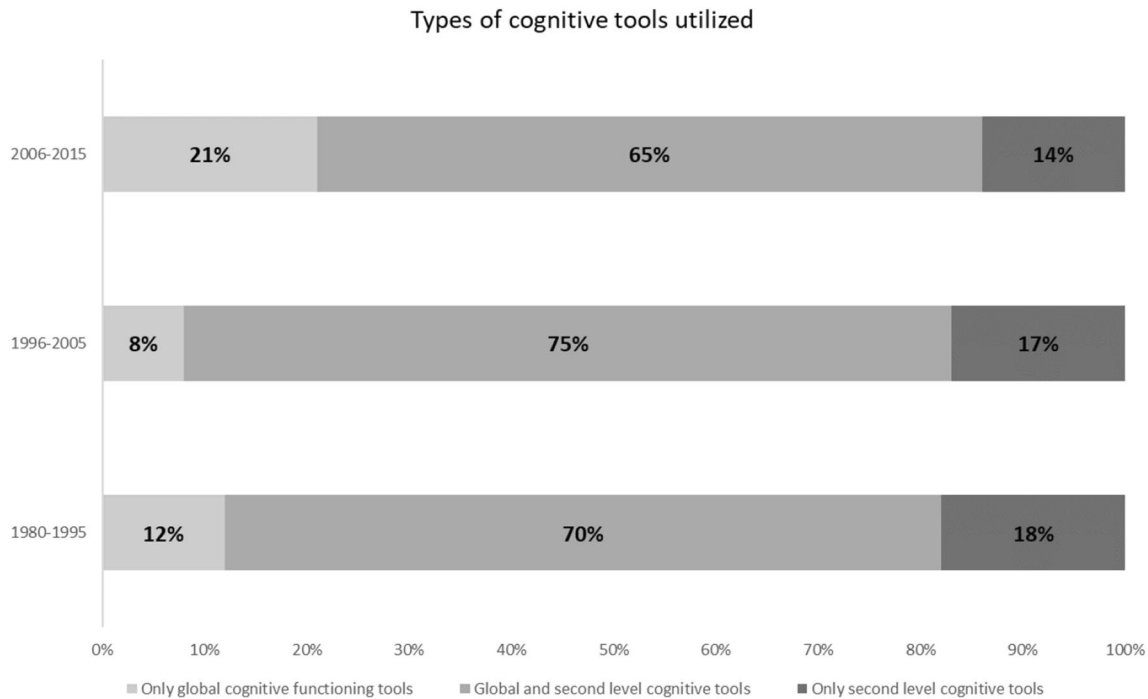


Fig. 3 Frequency of the types of cognitive tools utilized within each time period expressed as percentage in respect of the overall number of studies in that period (considering only sporadic cSVD)

Stroop Test and semantic fluency were more used in Asia (43% and 40%, respectively) and Europe (34% and 31%, respectively) than in North America (19% and 16%, respectively). Finally, TMT (both part A and B) resulted more frequently used in Europe (38% and 43%, respectively) and North America (35% and 33%, respectively) than in Asia (19% and 19%, respectively), and Boston naming was more used in North America (45%) and Asia (37%) than in Europe (15%) (Fig. 6).

Discussion

This systematic review shows that, indeed, in line with the construct that executive dysfunction is rather peculiar of cSVD-related cognitive decline, attention and executive functions domain resulted the most explored, and the neuropsychological tests related to this domain resulted the most utilized among all the applied tools in the literature.

Furthermore, except for the Boston naming, the most used second level tests in the other cognitive domains seemed to share the investigation of cognitive abilities somehow overlapped with the attention and executive functions domains: forward and backward digit span tests involve working memory processes and mental manipulation, phonemic and semantic fluency tests are widely known also as ‘executive’ tests due to their request of a ‘strategic’ search of

terms, and the copy of the Rey-Osterrieth Complex Figure requires planning and monitoring abilities. However, this does not directly imply that the administration of these tests to patients can provide relevant diagnostic information for the identification of the pattern of cognitive decline.

The results of this systematic review were partially expected and are in line with the selection of the second level cognitive tests in clinical practice reflecting the known dys-executive cognitive profile in patients with cSVD. Despite the fact that the attention and executive functions domain was the most frequently evaluated, also memory and language domains assessment was well represented in studies on sporadic cSVD, without an evident predominance of any domain. This evidence could be in line with the clinical need of a comprehensive and multidomain approach to cognitive evaluation, as a reference standard able to characterize the patients’ cognitive profile.

Overall, in studies on sporadic cSVD, the most used second level tests examined psychomotor speed, selective and divided attention, and lexical retrieval abilities based on executive control processes. The frequencies of use of these cognitive tools over time resulted quite stable.

The geographical distribution of utilization seemed to reveal some distinctive patterns among three main areas. In Asia, there was a trend toward a larger use of screening tests and of second level tests perhaps as an attempt to overcome difficulties related to linguistic translations.

Table 1 Frequency of utilization of cognitive tools in respect of all the studies assessing cognition in cSVD (tests used in < 10% of studies are not reported)

Test	Sporadic cSVD <i>n</i> = 270	CADASIL <i>n</i> = 28
Screening tests		
Mini Mental State Examination	197 (73%)	16 (57%)
Montreal Cognitive Assessment	37 (14%)	–
Clock drawing test	30 (11%)	–
Screening batteries		
Mattis Dementia Rating Scale	–	5 (18%)
Vascular Dementia Assessment Scale	–	4 (14%)
Attention/executive		
Trail making test—part B	86 (32%)	24 (86%)
Stroop test	85 (31.5%)	11 (39%)
Trail making test—part A	83 (31%)	19 (68%)
Wisconsin Card Sorting Test	–	4 (14%)
Symbol Digit Modalities Test (oral version)	–	5 (18%)
Memory*		
Digit span forward	70 (26%)	6 (21%)
Digit span backward	69 (25.5%)	6 (21%)
Rey Auditory Verbal Learning Test	38 (14%)	3 (11%)
Seoul Verbal Learning Test	26 (10%)	–
Logical memory	26 (10%)	5 (18%)
Word list	–	5 (18%)
Paired associated	–	3 (11%)
Visual memory	–	4 (14%)
Language		
Phonemic fluency	104 (39%)	6 (21%)
Semantic fluency	80 (30%)	5 (18%)
Boston naming test	80 (30%)	–
Animal fluency	34 (13%)	–
Verbal fluency	–	5 (18%)
Visuo-spatial, praxis and perceptual		
Rey-Osterrieth Complex Figure copy	60 (22%)	5 (18%)
Intelligence		
National Adult Reading Test	–	4 (14%)
Wechsler Adult Intelligence Scale		
Digit symbol substitution	26 (10%)	–
Digit span	–	6 (21%)
Similarities	–	8 (29%)
Block design	–	6 (21%)
Symbol search	–	4 (14%)

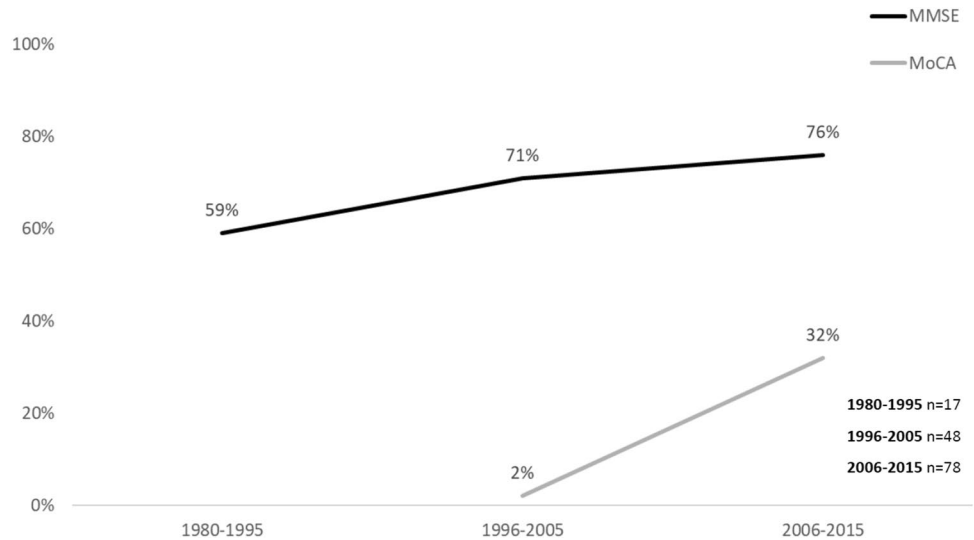
*Including WMS subtests

In Europe, there seems to be a higher utilization of the second level tests assessing attention and executive functions domain, while in North America, there is a larger use of phonemic fluency. It should be underlined that comparison across different continents has limitations due to the inherent geographic characteristics. For example, North America has homogeneous culture and language, while Europe has similar culture but different languages, and finally Asia is multi-cultural and multi-language and

studies from this continent mainly come from few countries, e.g. Japan, China and South Korea.

Considering the screening tools, MMSE was confirmed as the most widely used brief global cognitive functioning instrument, having a long-lasting tradition of use since 1980s and across all geographic areas. In 2005, the MoCA was proposed as a new screening test developed to detect Mild Cognitive Impairment, and in 2006, it was recommended from the harmonization standards for the study of vascular

Fig. 4 Frequency of utilization of Mini Mental State Examination and Montreal Cognitive Assessment within each time period in respect of the overall number of studies in that period (considering only sporadic cSVD)



cognitive impairment of the National Institute for Neurological Disorders and Stroke and the Canadian Stroke Network (NINDS-CSN) [8]. Differently from the MMSE, the MoCA covers most of the domains considered typically affected in cerebrovascular diseases (executive functions, attention, and concentration), and has been extensively applied in studies (particularly in Asia), thus reaching a frequency of use close to MMSE in approximately 5–10 years.

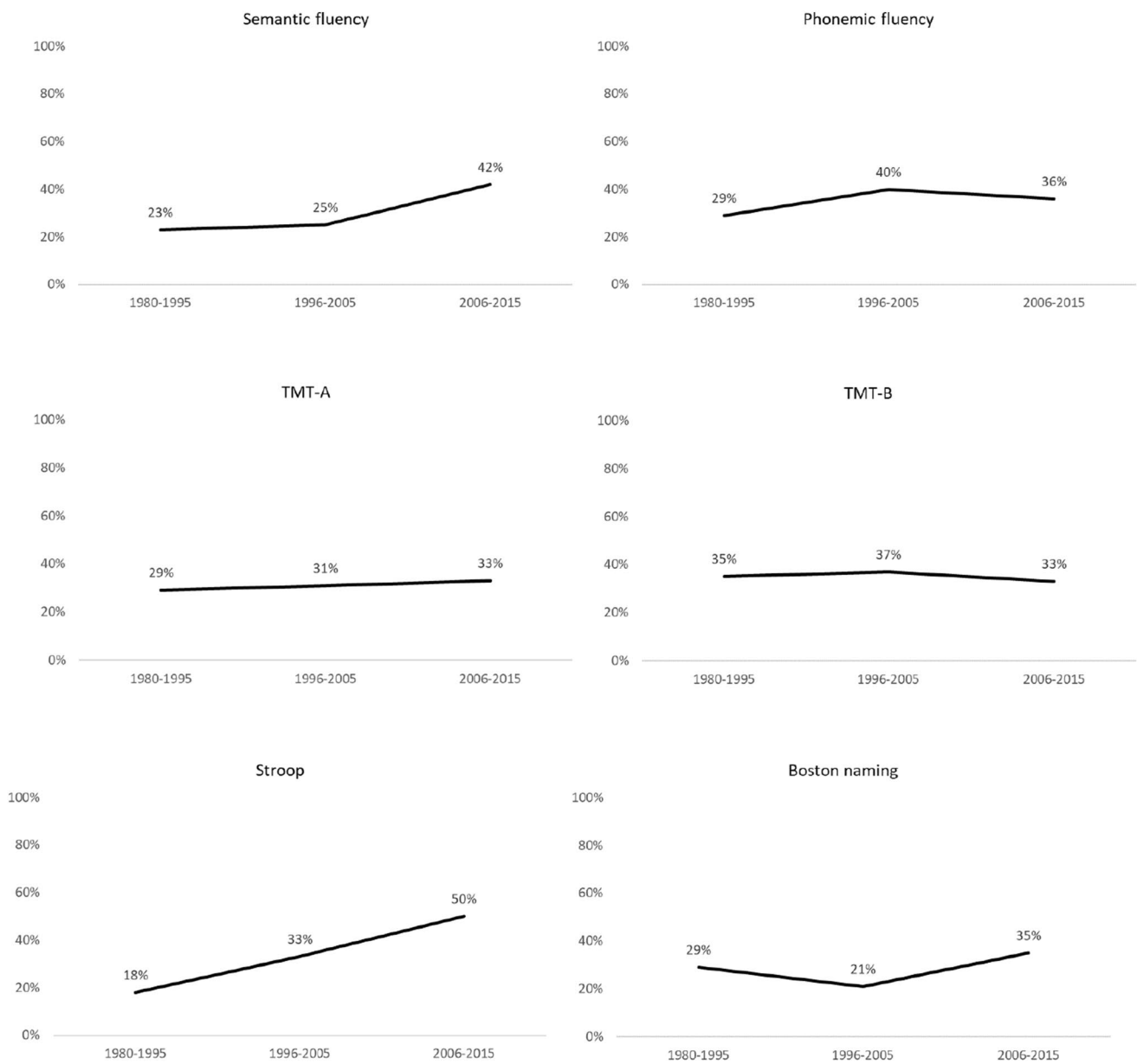
Considering the cognitive domains and tools used in CADASIL, the patterns of distributions were largely overlapped to what observed in sporadic cSVD, with a very high proportion of studies evaluating the attention and executive functions domain. Also this result was somehow expected considering that CADASIL is considered a pure model of vascular cognitive impairment.

The present review has some limitations that need to be addressed. First, it was focused on the frequency of utilization of cognitive tools in cSVD, and thus provides a picture of the most utilized tools in the field, without an evaluation of their diagnostic and prognostic values. This latter point will be the object of a following publication focused on the diagnostic accuracy of the selected cognitive tools and planned within the second part of our project [PROSPERO registration number: CRD42018089882]. A second limitation concerns the attribution of each test to a single cognitive domain. Despite the classification was done by two expert neuropsychologists (ES and MB), we are aware that overlaps still exist among the cognitive

constructs and domains. Another limitation concerns the definition of cognitive domains, particularly regarding the choice to include intelligence as a separated domain from global cognitive functioning. This was done to highlight that evaluation of intelligence was mainly related to the use of the Wechsler Adult Intelligence Scale between the end of the 80 s and the beginning of the 90 s, with a progressive decrease of use over time of this outdated construct. Third, within the genetic forms of cSVD, we limited our search to CADASIL, as it is the most studied. Few studies on CADASIL could be included in the qualitative analysis, and limited evidence is available. A last possible limitation was the choice to include studies focused on cSVD neuroimaging signs also in absence of a clinical diagnosis. Because stringent inclusion criteria could exclude some potentially relevant studies mainly in the older reports, we chose an inclusive strategy.

Strengths of this systematic review include a rigorous and comprehensive database search, covering over forty years of studies and a detailed quality appraisal process.

In conclusion, it is confirmed that the attention/executive domain is the most commonly explored in patients with cSVD but variability exists in the choice of the tools for this assessment. Further information about the role of cognitive evaluation in patients with cSVD will derive from the ongoing analysis about the prognostic and diagnostic value of these tools.



1980-1995 n=17

1996-2005 n=48

2006-2015 n=78

Fig. 5 Frequency of utilization of the most commonly used second level cognitive tests within each time period in respect of the overall number of studies in that period (considering only sporadic cSVD)

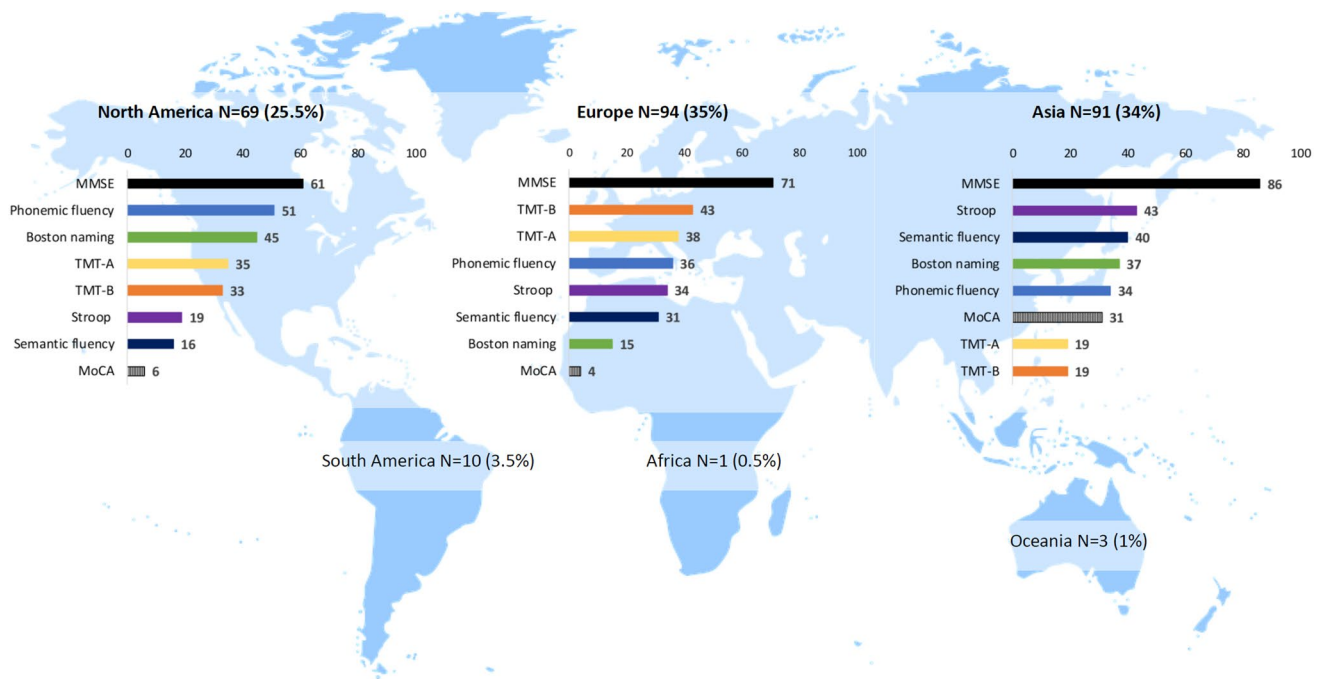


Fig. 6 Frequency of utilization of the most commonly used cognitive tests within each geographic area in respect of the overall number of studies in that area (considering only sporadic cSVD)

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by ES, MB and IC. The first draft of the manuscript was written by ES, MB and LP and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials The data that support the findings of this study are available on request from the corresponding author.

Compliance with ethical standards

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

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