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Cardiovascular & Cerebrovascular Correlates of Alzheimer's Disease

STROKOG (stroke and cognition consortium): An international consortium to examine the epidemiology, diagnosis, and treatment of neurocognitive disorders in relation to cerebrovascular disease

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Abstract

Introduction: The Stroke and Cognition consortium (STROKOG) aims to facilitate a better understanding of the determinants of vascular contributions to cognitive disorders and help improve the diagnosis and treatment of vascular cognitive disorders (VCD).

Methods: Longitudinal studies with ≥75 participants who had suffered or were at risk of stroke or TIA and which evaluated cognitive function were invited to join STROKOG. The consortium will facilitate projects investigating rates and patterns of cognitive decline, risk factors for VCD, and biomarkers of vascular dementia.

Results: Currently, STROKOG includes 25 (21 published) studies, with 12,092 participants from five continents. The duration of follow-up ranges from 3 months to 21 years.

Discussion: Although data harmonization will be a key challenge, STROKOG is in a unique position to reuse and combine international cohort data and fully explore patient level characteristics and outcomes. STROKOG could potentially transform our understanding of VCD and have a worldwide impact on promoting better vascular cognitive outcomes.

Keywords: Cohort studies; Vascular dementia; Post-stroke dementia; Vascular cognitive disorder; Small vessel disease; Data harmonization; International consortium

1. Introduction

Vascular cognitive disorders (VCDs) are a heterogeneous group of neurocognitive disorders with the salient feature being that cognitive decline is primarily attributable to cerebrovascular disease. The term VCD has a chequered history, and it includes not only vascular dementia (VaD; e.g., post-stroke and multi-infarct dementia), but also cognitive impairment of vascular origin that does not meet the criteria for dementia. VaD is common and is generally considered to be the second most common form of dementia, after Alzheimer's disease (AD) [1].

The prevalence and incidence of VCD varies depending on the diagnostic criteria applied and the populations studied. In 11 population-based European studies conducted in the 1990s, the age-standardized prevalence of VaD was estimated to be 1.6% compared to 4.4% for AD [2]; the prevalence of VaD was 0.3% in the age group 65–69 years and 5.2% in those aged 90 and above, and VaD accounted for 15.8% of all dementias in these studies [2]. The Canadian Study of Health and Aging used a broader concept termed vascular cognitive impairment (VCI) which consisted of three subgroups: VCI with no dementia, VaD, and AD with a vascular component. The authors estimated that approximately 5% of people over the age of 65 years had VCI, with 2.4% having VCI with no dementia, 0.9% having mixed (vascular and neurodegenerative) dementia and 1.5% having VaD [3]. Various clinical studies have shown that the prevalence of dementia is much greater in post-stroke patients, with 6 to 32% being reported as having dementia three months after stroke [3–8]. A systematic review reported that dementia is 3.5 to 5.6 fold more frequent in patients with stroke than in stroke-free controls [9]. Because risk factors for stroke are modifiable, and its incidence has been

shown to change with public health intervention, stroke may be regarded as a powerful and modifiable risk factor for dementia [10].

Poststroke dementia has emerged as an important subset of VCD primarily because of the large impact stroke has on the risk of VCD. The cognitive consequences of stroke as well as the associated burden of increased functional dependency, institutionalization, and mortality rates are increasingly being recognized [11]. However, many aspects of poststroke dementia are uncertain [5], and the precise impact of a stroke on preexisting cognitive impairment has been disputed. Patients with stroke usually have a complex combination of large and small vessel disease in the brain; in older patients in particular, nonvascular pathology such as AD may also be present [12]. Some studies found that up to 10% of stroke patients have cognitive impairment that could be classified as dementia before their first stroke [4,5,8], a finding that may be attributable to previous silent infarcts, noninfarct small vessel disease or AD pathology, or a combination of these. An American case-control longitudinal study reported that a stroke doubles the risk of dementia, that this excess risk diminishes with time, and that it does not apply to those >85 years [13]. According to a recent systematic review and meta-analysis, about one-tenth of patients develop new dementia soon after first stroke, and over one-third are demented after a recurrent stroke [8].

Although older age and low levels of education have consistently emerged as key predictors of worse cognitive outcome soon after stroke [8,14], studies have shown inconsistent findings in relation to other risk factors, which include cerebrovascular disease risk factors such as diabetes mellitus and atrial fibrillation, prior pathology, stroke features, and infarct characteristics [8,9,15].

Making better use of existing data to improve stroke and dementia prevention and treatment is a priority for many governments and funders. The Joint Program for Neurodegeneration (JPND) thus recently funded several initiatives to improve data usage. Metacohorts is one of these initiatives focused on vascular contributions to dementia and the group identified over 90 studies, including over 600,000 subjects worldwide that included data relevant to vascular effects on neurodegeneration including cognitive consequences of stroke [16].

Stroke and Cognition consortium (STROKOG) is a recently established consortium of prospective post-stroke/TIA studies from around the world, including, at the time of writing, 25 studies with up to 12,092 patients from 16 countries and 25 institutions worldwide. By harmonizing data and conducting individual participant data (IPD) meta-analyses on studies from around the world, STROKOG aims to better understand the longitudinal course of poststroke cognitive impairment and investigate differences in the prevalence of VCD as well as risk and protective factors between different countries and ethnic groups. In IPD meta-analysis, the original research data are sought directly from the researchers responsible for each study rather than extracting summary (aggregate) data from study publications or from investigators. The original data can then be re-analyzed centrally and combined, if appropriate, in meta-analyses. There are various advantages of conducting IPD meta-analyses over standard meta-analysis, such as the ability to investigate patient level characteristics, adjust for the same confounding factors across studies, address new research questions, and reduce publication bias [17,18]. By harmonizing and conducting analyses on a rich collection of individual participant data, STROKOG can examine risk factors on the patient level and apply standardized methods of statistical analyses and dementia diagnosis that could produce more accurate prevalence estimates and more detailed information on the risk factors for VCD and the impact stroke has on cognitive decline. It is anticipated that the findings of STROKOG will help guide and optimize preventative strategies and health policy worldwide. STROKOG was officially established at the VASCOG (Society for the Study of Vascular Cognitive and Behavioral Disorders) 2015 meeting in Tokyo, Japan.

2. Methods

2.1. Membership

Studies are eligible to participate in STROKOG if they meet the following membership criteria:

1. Prospectively recruited patients with stroke, TIA, or high-stroke risk (such as patients with atrial fibrillation, hypertension, genetic disorders such as CADASIL and so forth).
2. Are longitudinal, with a minimum of two waves of assessments conducted or planned.
3. Have a minimum sample size of 75.
4. The major outcome measures include dementia and/or cognitive impairment and/or cognitive decline.

Official enrollment requires the study lead investigator to sign a memorandum of understanding (MoU) which specifies a willingness to share nonidentifiable data for joint analyses. Studies that have restrictions on data use and data sharing may also participate in STROKOG by conducting in-house analyses using STROKOG protocols and providing summary data for pooling.

At the time of writing, there are 24 officially enrolled member studies of STROKOG and one unofficial member study which plan to obtain participants' permission to share data before signing the MoU. These studies and their key demographic characteristics are shown in Table 1. Supplementary Table S1 shows some salient findings from each member study. They represent 16 different countries, including one lower middle income country from across five continents (Africa, Asia, Australia, Europe, and North America). In total, there are 12,092 participants, and for most studies, patients were recruited consecutively as they were admitted to hospital with a recent stroke.

Approximately half of the studies admitted participants with a recent TIA, and those with a previous stroke were typically not excluded. The longest follow-up duration of the studies is 21 years and the median is 3 years. Table 2 shows the list of neuropsychological tests used in each study.

2.2. Organization

The STROKOG Research Steering Committee (RSC) consists of a representative from each of the contributing studies, generally the lead investigator or a delegate. The primary functions of the RSC are to

1. Develop guidelines for the inclusion and exclusion of studies.
2. Provide rules of participation and guidelines for the roles and responsibilities of the participating studies.
3. Approve Work Groups (see research projects below).
4. Select topics of interest.
5. Provide overall analytic strategies.
6. Develop rules for publication, including authorship.
7. Develop rules for the protection of intellectual property, when relevant.
8. Seek funds to support STROKOG.

2.3. Meetings

An initial meeting of many study leaders at the VASCOG 2015 conference in Tokyo on 16 September 2015 supported the official establishment of STROKOG. The proposed structure of the consortium, including the functions of the RSC and proposed projects were discussed. A second international meeting was held at VASCOG 2016 in Amsterdam on 14 October 2016. Preliminary findings from the first project were presented and potential projects were discussed.

2.4. Website

A website that contains a description of STROKOG and summaries of the member studies has been established (https://cheba.unsw.edu.au/group/strokog). The website is intended to serve as an avenue for presenting and preserving STROKOG project protocols and results.

2.5. Ethics

The overall STROKOG project has been approved by the Human Research Ethics Committee (HREC) of the University of New South Wales (UNSW), Sydney (reference number: HC14359). Member studies are responsible for obtaining approval (if necessary) from their local institutional review board for the sharing of data. Although de-identified data are not considered Protected Health Information by the National Institutes of Health of the United States, ethics review boards differ in their approach to this matter. A protocol for the de-identification of data has been developed. Additionally, each new project presented to STROKOG must be approved by an institutional review board and the HREC of UNSW informed about the project.

2.6. Research projects and data

The Sydney team will initiate the first project, collate study data and conduct the initial data harmonization and IPD meta-analyses across the different studies. STROKOG will follow guidelines for rigorous and effective harmonization [58] as well as for IPD meta-analyses and reporting [17,59]. Original data sets supplied by members and the harmonized data sets, which will include derived data, will be held by the Sydney team on a secure database at the University of New South Wales. A STROKOG RSC member can propose a research project, which need to undergo an approval process by the RSC. If the prospective proposer of a project is not a member of the RSC or affiliated with a member study, the proposal can still go ahead if it is sponsored by a member of the RSC. A student may similarly request data for a research project if sponsored by a member of the RSC. Once approved, the proposer will be advised to form a Work Group for the specific project, with a clearly identified project leader. Other members of the consortium may volunteer to be part of the Work Group if they have a clear interest and expertise in the research project. The Work Group will address and be responsible for the planning, analysis, and publication of the approved project. Data held by STROKOG will be released to the Work Group; newly joined and existing member studies will be requested to provide additional de-identified data. Each cohort can opt-in or opt-out of participation; opting-in represents a commitment to collaborate on the project. The central STROKOG data repository at UNSW, Sydney, will hold a copy of the data sets used for each project. The STROKOG data will not be used or accessed for any purpose other than contributing to an approved STROKOG project.

3. Discussion

3.1. Challenges

Large international consortia face general challenges that include efficient communication among personnel involved with studies across different countries and a need for additional funding to enable the further use of previously collected data. Such challenges have been previously described by other consortia (e.g., by CHARGE [60]).

Challenges more specific to STROKOG are those associated with data harmonization, many of which have also been previously described [61,62]. Neuropsychological test data are likely to be the most challenging set of data to be harmonized across studies due to heterogeneity in test instruments, administration, and criteria for defining impairment; however, the Sydney team has had experience harmonizing large data sets from diverse

Table 1
STROKOG member studies

Study	Country	Period	Sample size*	Follow-up schedule	Cognitive assessments	MRI assessments†	Dementia criteria	Key reference(s)
Action on Secondary Prevention Interventions and Rehabilitation in Stroke (ASPIRE-S)‡	Ireland	2011–2012	256	6m	6 mo	No	NA	Mellon et al. (2015) [19]
Bundang VCI cohort (Bundang-VCI)	Korea	2007–ongoing	918	3m, 1y, 2y, 3y; ongoing	3 mo, 1 y, 2 y, 3 y; ongoing	Initial, 1–3 y	DSM-IV	Lim et al. (2014) [20]
Clinical Biological and Pharmacological Factors Influencing Stroke Outcome (BIOSTROKE)	France	2005–2015	477	3m, 5y	5 y	Initial, 5 y	NA	Ducroquet et al. (2013) [21]
Cognition and Affect after Stroke: Prospective Evaluation of Risks (CASPER)	Netherlands	2013–2016	250	3m, 9m, 15m	3 mo, 9 mo, 15 mo	3 mo	DSM-V, NINCDS-ADRDA, NINDS-AIREN	Douven et al. (2016) [22]
Cognition and Neocortical Volume After Stroke (CANVAS)	Australia	2014–2018	135	1m, 3m, 1y, 3y	3 mo, 1 y, 3 y	Initial, 3 mo, 1 y, 3 y	DSM, NINDS-AIREN	Brodtmann et al. (2014) [23]
Cognitive Function After Stroke (CogFAST-UK)	UK	2002–2012	355	3m; 1–8y (annually)	3 mo; 1–8 y (annually)	3 mo, 2 y	Yes	Allan et al. (2011) [12]
Cognitive Function After Stroke Nigeria (CogFAST-Nigeria)	Nigeria	2010–ongoing	217	3m	3 mo	3 mo (small subset only)	DSM-IV, AHA/ASA	Akinyemi et al. (2014) [24]
Cognitive Outcome After Stroke (COAST)	Singapore	2009–2017	400 (planned)	3–6m, 1y, 3–4y, 5y, 6y, 7y	3–6 mo, 1 y, 3–4 y, 5 y, 6 y, 7 y	Initial (small subset only)	DSM-IV	Dong et al. (2012) [25]
Cracow Stroke Database (Cracow)	Poland	2000–2001	250	3m, 12m	3 mo, 12 mo	No	DSM-IV	Klimkowicz et al. (2004; 2006) [26,27]
Determinants of Dementia After Stroke (DEDEMAS)	Germany	2011–2019	600 (planned)	3m, 6m, 1y, 2y, 3y, 4y, 5y	6 mo, 1 y, 3 y, 5 y; (TICS only: 3 mo, 2 y, 4 y)	Initial, 6 mo; 3 y, 5 y	DSM-V	Wollenweber et al. (2013) [28]
Durban Stroke Data Bank (DSDB)	South Africa	1992–1998	1000	3m, 6m, 12m	Initial, 3, 6, 13 mo	Initial	DSM-IV	Hoffmann (1998; 2001) [29,30]
Epidemiologic study of the risk of dementia after stroke (Epi USA)	USA	1988–1999	585	Initial, 3m–10 y (annually)	3 mo–10 y (annually)	No	Modified DSM-III-R	Desmond et al. (2000, 2002) [7,31]
Göteborg 70 + Stroke Study (Göteborg Neuro70+)	Sweden	1993–1994	243	3m, 12m, 18m	18 mo	Subset	DSM-III-R	Linden et al. (2004; 2007) [32,33]
Groupe de Réflexion pour l'Evaluation COGnitive VASCulaire study (GRECOG-VASC)§	France	2010–2015	360	6m	6 mo	6 mo	VASCOG	Godefroy et al. (2012) [34]
Helsinki Stroke Aging Memory (SAM)	Finland	1993–2015	486	3m, 15m, 21y	3 mo	Initial	DSM	Jokinen et al. (2015) [35]; Oksala et al. (2009) [36]

(*Continued*)

Table 1
STROKOG member studies (*Continued*)

Study	Country	Period	Sample size*	Follow-up schedule	Cognitive assessments	MRI assessments†	Dementia criteria	Key reference(s)
Maastricht Cognitive Disorders After Stroke (CODAS)	Netherlands	2000–2003	194	1m, 6m, 1y, 2y	1 mo, 6 mo, 1 y, 2 y	No	DSM-III, DSM-III-R, DSM-IV, ICD-10, NINDS-AIREN, ADDTC	Rasquin et al. (2005) [37]
Mild Stroke Study II (MSS–II)	UK	2010–2015	264	1–3m, 1y, 3y	1–3 mo	Initial, 1–3 mo, 1 y	ACER; MoCA equivalent; NART	Heye et al. (2015; 2016) [38,39], Valdes Hernanadez et al. (2015) [40]
Korean-Vascular Cognitive Impairment Harmonization Standards Study (K-VCIHS)	Korea	2007–2008	620	3m	3 mo	Initial	DSM-IV	Yu et al. (2013) [41]
North East Melbourne Stroke Incidence Study (NEMESIS)	Australia	1998–2003	99	3m, 1y, 2y	3 mo, 1 y, 2 y	No	Yes	Srikanth et al. (2003; 2004; 2006) [42–44]
National Neuroscience Institute study (NNI Singapore)	Singapore	2011–2017	506	3–6m, 1y up to 5y	3–6 mo, 1 y up to 5 y	Initial	Yes	Kandiah et al. (2011; 2014, 2016) [45–47]
Prognosis of Intracerebral Hemorrhage (PITCH)	France	2004–ongoing	562	6 mo, 1 y, 2 y, 3 y, 4.5 y, 6 y, 8 y, 10 y	1 y, 2 y, 3 y, 4.5 y, 6 y, 8 y, 10 y	Initial, 6 mo; 1 y, 2 y, 3 y, 4.5 y, 6 y, 8 y, 10 y	Yes	Cordonnier et al. (2010) [48]; Moulin et al. (2016) [49]
Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)‖	Scotland, Ireland, Netherlands	1997–2001	649	9 mo, 1.5 y, 2.5 y, up to 3 y	Initial, 9 mo, 1.5 y, 2.5 y, study end	Initial, study end	NA	Shepherd et al. (2002) [50]
Stroke Registry Investigating Cognitive Decline (STRIDE)	Hong Kong	2009–2015	1013	3–6 mo, 1 y, 2 y, 3 y, 4 y, 5 y	3–6 mo	Initial	DSM-IV	Yang et al. (2015) [51]; Liu et al. (2015) [52]; Wang et al. (2015a, 2015b) [53,54]; Mok et al. (2016) [55]
Study of Factors Influencing Post-Stroke Dementia (STROKDEM)	France	2011–2018	1100 (planned)	6 mo, 1 y, 3 y, 5 y	6 mo, 1 y, 3 y, 5 y	Initial, 6 mo, 3 y, 5 y	Yes	NA
Sydney Stroke Study (SSS)	Australia	1997–2005	351	3–6 mo, 1 y, 3 y, 5 y	3–6 mo, 1 y, 3 y, 5 y	3–6 mo, 1 y, 3 y, 5 y	Consensus diagnosis	Sachdev et al. (2004; 2014) [56,57]

Abbreviations: m, month after index stroke; y, years after index stroke; ACER, Addenbrooke's Cognitive Examination; ADDTC, Alzheimer's Disease Diagnostic and Treatment Centers; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD-10, *International Statistical Classification of Diseases, 10th Revision*; MoCA, The Montreal Cognitive Assessment; NART, National Adult Reading Test performance in established dementia; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NINDS-AIREN, National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences; TICS, Telephone Interview for Cognitive Status; VASCOG, International Society for Vascular Behavioral and Cognitive Disorders.

*Sample size denotes enrollment number (not follow-up) and does not include healthy control subjects. The studies which recruited control subjects were: CANVAS (n = 40), CogFAST-Nigeria (n = 74), Epi USA (n = 249), NEMESIS (n = 99), PROSPER and SSS (n = 129).

†Some studies also obtained PET scans from a subgroup of their participants: GRECOG-VASC (amyloid for 100 patients with poststroke cognitive deficit), STROKDEM (at 1 year), DEDEMAS (amyloid/FDG for incident dementia cases), CANVAS (amyloid at 3 years), STRIDE (PiB, n = 50) and DSDB (SPECT, n = 36).

‡ASPIRE-S is an unofficial member that is planning to obtain participants' permission to share data outside of Ireland before signing the MoU.

§For the GRECOG-VASC study, only the 200 first patients from the Amiens center are included for STROKOG and the VASCOG criteria was used except for the threshold of cognitive impairment which was set at the 5th percentile.

‖PROSPER shares data at the summary level and not individual participant data.

Table 2
Cognitive measures used by the STROKOG member studies to diagnose dementia

Study	Cognitive domain				
	Attention/processing speed	Memory	Language	Construction (visuospatial)	Executive function/ abstract reasoning
ASPIRE-S*	NA	NA	NA	NA	NA
BIOSTROKE	- Trail Making Test A - Zazzo Test - Digit symbol coding - Bell's Test	- FCSRT	- Verbal fluency, category - Token Test	- VOSP - Rey Complex Figure Test: Copy - Praxis score	- Trail Making Test B - Verbal fluency, letter - Stroop Test
Bundang-VCI	- Trail Making Test A - Digit symbol coding	- Seoul Verbal Learning Test	- Boston Naming Test - Verbal fluency, category (animals)	- Rey Complex Figure Test: Copy	- Trail Making Test B - COWAT
CASPER	- Trail Making Test A - Digit Span Forward - Digit Symbol Coding - Start Cancellation Task	- RAVLT (15-Word, Dutch)	- Boston Naming Test - Verbal fluency, category (animals and professions)	- Clock-drawing	- Trail Making Test B - Digit Span backward - BADS Zoo map and key search
CANVAS	- Trail Making Test A - Digit Span Forward - Symbol Digit Modalities Test - Cogstate Detection Test and Identification Test - Star Cancellation Task	- Hopkins Verbal Learning Test - Rey Complex Figure Test: Recall	- Boston Naming Test - Verbal fluency, category (animals) - Token Test	- Clock-Drawing Test - Rey Complex Figure Test: Copy	- Trail Making Test B - Verbal fluency, letter (FAS) - Cogstate One-Back Test
CogFAST-UK	- Trail Making Test A - Simple Reaction Time - Choice Reaction Time - Number Vigilance task - Digit Span forward	- Word-List Memory - Rivermead Behavioral Memory Test	- Boston Naming Test - Verbal fluency, category (animals) - Token Test	- Clock-Drawing Test - Rey Complex Figure Test: Copy	- Verbal fluency, letter (FAS) - Verbal Reasoning - Visual Reasoning - Trail Making Test B - Digit Span backward - Stroop Test
CogFAST-Nigeria	- Choice Reaction Time	- Word-List Learning Test (10-item) - Delayed recall of stick design	- Boston Naming Test - Verbal fluency, category (animals) - Token Test	- Stick Design Test	- Verbal fluency, letter (FAS) - Verbal Reasoning - Visual Reasoning
COAST	- Digit Span Forward - Visual Memory Span Forward - Auditory Detection Test - Symbol Digit Modalities Test - Digit cancellation task	- Word-List Recall - Story Recall - Picture Recall (immediate and delayed recall, and recognition) - Visual Reproduction (immediate and delayed recall, and recognition)	- Boston Naming Test - Verbal fluency, category (animals, food)	- Clock-Drawing Test - Block Design - Visual reproduction copy	- Digit Span backward - Visual memory span backward - Frontal Assessment Battery - Maze task
Cracow†	NA	NA	NA	NA	NA
DEDEMAS	- Trail Making Test A - Digit Symbol Coding	- Word-List Memory and Recall - Discriminability - Constructional praxis (recall and savings) - FCSRT	- Boston Naming Test - Verbal fluency, category (animals)	- CERAD copy visual construction - Rey Complex Figure Test: Copy	- Trail Making Test B - Verbal fluency, letter (S-words) - Stroop Test
DSDB	- Trail Making Test A	- RAVLT	- Boston Naming Test	- Rey Complex Figure Test: Copy	- Trial Making Test B - Luria's tests - Wisconsin Card Sorting Test - Verbal fluency, letter (FAS)

(*Continued*)

Table 2
Cognitive measures used by the STROKOG member studies to diagnose dementia (*Continued*)

Study	Cognitive domain				
	Attention/processing speed	Memory	Language	Construction (visuospatial)	Executive function/ abstract reasoning
Epi USA	- Target finding for shapes and letters	- Selective Reminding Test - Benton Recognition Test	- Boston Naming Test - Verbal fluency, category - Complex Ideation and Repetition subtests of BDAE	- Copying geometric figures - Benton Matching Test	- Similarities subtest - Identities and oddities - Verbal fluency, letter
Göteborg Neuro70+*	NA	NA	NA	NA	NA
GRECOG-VASC	- Trail Making Test A - Digit Symbol Coding - Simple Reaction Time - Digit Tapping - Albert cancellation test	- FCSRT - Door Visual Recognition Test - Rey Complex Figure Test: Recall	- Boston Naming Test - Verbal fluency, category (animals)	- Rey Complex Figure Test: Copy	- Trail Making Test B - Verbal fluency, letter (PVR) - Strategic index (FCSRT) - Inventory of Behavioral Dysexecutive Disorders
SAM	- Trail Making Test A - Stroop color naming - Digit Span Forward - Bell's Test	- Logical memory - Visual Reproduction - Fuld Object Memory Evaluation	- Boston Naming Test - Verbal fluency, category (animals) - Token Test - Boston Diagnostic Aphasia Exam (overall speech evaluation) - Reading, writing, arithmetic operations	- Block Design - Figure copying test - Clock-Drawing Test - Poppelreuter	- Trail Making Test B - Digit Span backward - Verbal fluency, letter (K) - Stroop Test - Wisconsin Card Sorting Test - Similarities - Comprehension
CODAS	- Concept Shifting Test Parts A and B - Letter Digit Substitution Test - Stroop color naming and reading test	- RAVLT (15-Word, Dutch)	- Verbal fluency, category (animals, professions) - GIT Vocabulary	- Clock drawing, house drawing, pentagons, spiral (CAMCOG) - GIT Mental Rotation	- Concept Shifting Test Part C - GIT Analogies - Stroop Test
MSS–II*	NA	NA	NA	NA	NA
K-VCIHS	- Trail Making Test A - Digit Symbol Coding	- Seoul Verbal Learning Test	- Boston Naming Test - Verbal fluency, category (animals)	- Rey Complex Figure Test: Copy	- Trail Making Test B - COWAT
NEMESIS	- KSNAP Mental Status - Digit Span Forward - Digit Symbol Coding - KSNAP Number Recall	- Rivermead Behavioral Memory Test - RAVLT - Rey Complex Figure Test: Recall		- Rey Complex Figure Test: Copy - Picture Completion - Block Design - KSNAP Gestalt closure	- KSNAP 4 letter word test - Similarities - Digit Span backward - Verbal fluency, letter (FAS)
NNI Singapore	- Digit Span Forward	- Word Recall	- Verbal fluency, category (animals)	- Clock drawing (Sutherland)	- Digit span backward - Frontal assessment battery
PITCH	- Trail Making Test A - Digit Span Forward	- FCSRT - Rey Complex Figure Test: Recall	- Verbal fluency, category - Token Test	- Rey Complex Figure Test: Copy - Praxis score	- Trail Making Test B - Verbal fluency, letter - Card Sorting Test - Digit Span backward - Stroop Test
PROSPER	- Letter Digit Substitution Test	- Picture Learning test: immediate and delayed memory - Doors and People test			- Stroop Test
STRIDE*	NA	NA	NA	NA	NA

(*Continued*)

Table 2
Cognitive measures used by the STROKOG member studies to diagnose dementia (*Continued*)

Study	Cognitive domain				
	Attention/processing speed	Memory	Language	Construction (visuospatial)	Executive function/ abstract reasoning
STROKDEM	- Trail Making Test A - Zazzo Test - Digit Symbol Coding - Bell's Test	- FCSRT	- Verbal fluency, category - Token Test	- VOSP - Rey Complex Figure Test: Copy - Praxis score	- Trail Making Test B - Verbal fluency, letter - Stroop Test
SSS	- Trail Making Test A - Digit Span Forward - Mental Control - Symbol Digit Modalities Test - Choice Reaction Time	- Logical Memory I & II - Verbal memory recall - Visual Reproduction I & II - Visual memory recall	- Boston Naming Test - Sentence repetition - Verbal fluency, category (animals) - Token Test	- Block design - Simple copying - Picture completion	- Trail Making Test B - Digit Span backward - Similarities - Identities and oddities - COWAT

Abbreviations: BADS, behavioral assessment of the dysexecutive syndrome; BDAE, Boston Diagnostic Aphasia Examination; CAMCOG, Cambridge Cognitive Examination; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; COWAT, Controlled Oral Word Association Test; CSID, Community Screening Interview for Dementia; FCSRT, Free and Cued Selective Reminding Test; GIT, Groninger Intelligence Test; HCFD, higher cortical function deficits; KSNAP, Kaufman short neuropsychological assessment procedure; RAVLT, Rey Auditory Verbal Learning Test; VOSP, visual object and space perception battery.

NOTE. The assignment of a neuropsychological test to a particular cognitive domain is based on convention and previous work such as for COSMIC [17] and may not be how a study has assigned the test.

*ASPIRE-S, MSS-II, Göteborg Neuro70+ and STRIDE did not conduct detailed neuropsychological test batteries, instead, the following tests were used to diagnose dementia in each study: ASPIRE-S: MoCA (The Montreal Cognitive Assessment); Göteborg Neuro70+: Cognitive symptom ratings and items from ADAS-Cog (The Alzheimer's Disease Assessment Scale-Cognition); MSS-II: NART (National Adult Reading Test performance in established dementia) was conducted for pre-morbid cognitive ability; specific additional tests for current cognition were not performed outside of ACER (Addenbrooke's Cognitive Examination) and MOCA (equivalent); STRIDE: The Mini–Mental Status Examination (MMSE) and MoCA.

†Cracow study conducted neuropsychological tests under the five domains but these data were lost and not available.

studies, for example, for the COSMIC consortium [63]. There exists much heterogeneity in measurement instruments used by different studies. Even when studies have used similar tests, different versions of tests were used, and tests might have been administered in nonstandard ways. Owing to differences in culture and language, questions and responses may have been worded differently. There is no consensus on how each neuropsychological test should be allocated to a specific cognitive domain as such tests are generally multifactorial. Table 2 shows the list of tests used in the studies under five cognitive domains; each test was assigned to a cognitive domain based on convention and previous work such as for COSMIC [63]. Demographic effects such as age, gender, and education need to be accounted for. Furthermore, adequate normative data may or may not be available in all regions or for all ethnocultural groups; not all studies included nondemented stroke-free controls whose test scores may be used to derive adjusted scores and to define cognitive impairment.

3.2. Advantages

The benefits of being able to reuse, combine, and compare data from multiple cohorts are obvious, and this approach has been recommended by the Lancet REWARD Campaign [64]. Cohort studies focused on stroke and cognition are expensive, labor-intensive, and very demanding of researchers' and participants' time. Multiple factors may limit the study sample size and duration. There already exists a wealth of data from previous or current studies that are underutilized and can be put to further use. Standard meta-analysis is one way of analyzing the combined cohorts of existing studies, but it is limited to published results and specific research questions. STROKOG's approach in harmonizing individual participant data from various studies is an economical use of previously collected data to explore both existing and novel research questions. According to the Cochrane Methods group, IPD meta-analyses are considered the "gold standard" of systematic review [65]. In IPD meta-analyses, individual participant data from all studies can be modeled simultaneously while accounting for the clustering of participants within studies [17]. It allows detailed participant-level exploration of cognitive disorders in relation to the individuals' characteristics. Additionally, statistical analysis can be standardized across studies where more appropriate or advanced methods can be used; baseline and potential confounding factors can be adjusted for consistency across studies; results for missing or poorly acquired outcomes can be reported, thereby reducing bias within study reporting; results for specific subgroups of participants can be obtained across studies; unpublished data can be included, thereby addressing publication bias [17]. Having access to a rich collection of individual participant-level data from international studies, STROKOG is in a unique position to apply IPD meta-analyses techniques and fully explore and examine patient

level characteristics and outcomes, which in turn could lead to facilitating a better understanding of various aspects of post-stroke cognitive impairment.

A consortium such as STROKOG has the added benefit of informing new researchers of the need to standardize their measures and methods so that they are in step with other researchers in the same field. This is particularly important for stroke and dementia, as many researchers from low and middle income countries have recently become interested in this topic and are mounting studies that would benefit from comparability with existing studies. New studies therefore would have the benefit of validated measures and better comparability.

There is also the potential for the STROKOG database to be made available to nonconsortium researchers following consortium-based publications and with the approval of the RSC and the ethics review board. The scientific benefits of making large databases available to researchers worldwide have been demonstrated by the more than 250 publications that have resulted from the sharing of ADNI (Alzheimer's Disease Neuroimaging Initiative) data [66].

The research community that STROKOG proposes to create is likely to pay other dividends. It is expected that the productivity of the group will increase over time in quality and quantity; junior researchers will be supported, new ideas and lines of investigation will be generated and scientific interchange and collaboration will be facilitated. The benefits will therefore extend beyond the harmonizing and pooling of data.

3.3. Specific projects

The first project aims to describe the prevalence and profile of poststroke cognitive impairment, measured between 1 and 6 months after a stroke or TIA, in diverse geographical and ethnocultural settings as represented by the STROKOG member cohorts. The project is currently underway and is being coordinated by the Sydney team. A project proposal was approved by the RSC, and the following data are currently being requested:

1. Demographics.
2. Stroke-related variables.
3. Medical history/risk factors.
4. Functional assessments and screening tests.
5. Neuropsychological test data.
6. Neurological assessments and psychiatric examinations.
7. Cognitive disorder diagnosis.

A number of projects utilizing STROKOG data have been proposed for the future, and they aim to examine across STROKOG cohorts

1. Rates of cognitive decline in post-stroke patients.
2. Determinants of cognitive impairment.
3. Determinants of cognitive decline.
4. Effect of methodologic differences in the collection and interpretation of cognitive data on the estimation of prevalence of cognitive deficit.
5. Specific risk factors such as atrial fibrillation, congestive heart failure, diabetes, and homocysteine.
6. Depression and apathy in relation to cerebrovascular disease.
7. Relative contributions of Alzheimer's and vascular pathologies to dementia.
8. Precise and reliable quantitation and localization of white-matter hyperintensities, microbleeds, lacunes and micro-infarcts and examination of their relationship to cognition.

While many of the existing member studies have relevant data to contribute to the more general topics (such as 1 to 4 noted above), the more specific topics (5 to 8) will be best addressed by growing the STROKOG membership base. Therefore, we encourage any investigators with a study meeting the eligibility criteria to contact STROKOG and become a member of the consortium.

4. Conclusion

STROKOG is a truly international consortium of studies with a focus on cognitive disorders associated with cerebrovascular disease. It has the potential to transform our understanding of the epidemiology and natural course of VCD and have a worldwide impact on promoting better cognitive outcomes in the setting of cerebrovascular disease.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.dadm.2016.10.006.

RESEARCH IN CONTEXT

1. Systematic review: The authors performed a review of published studies of poststroke cognitive impairment and dementia using PubMed and invited all eligible studies to participate. Unpublished studies were identified through correspondence with members of the Society for Vascular Cognitive and Behavioral Disorders (VASCOG).
2. Interpretation: The STROKOG consortium brings together international longitudinal cohort studies of cognitive decline and dementia following stroke or TIA. By harmonizing data and conducting individual participant meta-analyses, STROKOG aims to better understand the determinants and manifestations of vascular contributions to cognitive disorders and help improve the diagnosis and treatment of vascular cognitive disorders.
3. Future directions: STROKOG will conduct individual projects investigating research topics such as the prevalence of VCD, rates of cognitive decline, determinants of cognitive impairment and the frequency of depression in relation to cerebrovascular disease. STROKOG invites other longitudinal studies on stroke/TIA patients and cognitive impairment to join, contribute to the database and participate in collaborative research.

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