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Neuroimaging

The Meta VCI Map consortium for meta-analyses on strategic lesion locations for vascular cognitive impairment using lesion-symptom mapping: Design and multicenter pilot study

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Abstract

Introduction: The Meta VCI Map consortium performs meta-analyses on strategic lesion locations for vascular cognitive impairment using lesion-symptom mapping. Integration of data from different cohorts will increase sample sizes, to improve brain lesion coverage and support comprehensive lesion-symptom mapping studies.

Methods: Cohorts with available imaging on white matter hyperintensities or infarcts and cognitive testing were invited. We performed a pilot study to test the feasibility of multicenter data processing and analysis and determine the benefits to lesion coverage.

The authors report no conflicts of interest.

¹Authors contributed equally. ²Representatives of each member group and consortium are listed in the Acknowledgments section.

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Results: Forty-seven groups have joined Meta VCI Map (stroke $n = 7800$ patients; memory clinic $n = 4900$; population-based $n = 14,400$). The pilot study (six ischemic stroke cohorts, $n = 878$) demonstrated feasibility of multicenter data integration (computed tomography/magnetic resonance imaging) and achieved marked improvement of lesion coverage.

Discussion: Meta VCI Map will provide new insights into the relevance of vascular lesion location for cognitive dysfunction. After the successful pilot study, further projects are being prepared. Other investigators are welcome to join.

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Keywords: Cerebrovascular disease; Vascular cognitive impairment; Stroke; Small vessel disease; Consortium; Data harmonization; Support vector regression; Lesion-symptom mapping; Lesion location

1. Introduction

Cerebrovascular disease is a major cause of cognitive impairment and dementia, either alone or in combination with Alzheimer's disease. This vascular contribution to cognitive decline is collectively referred to as vascular cognitive impairment (VCI) [1]. VCI is a heterogeneous construct, both in terms of cognitive phenotypes and nature and severity of underlying vascular etiologies and comorbid conditions. Despite this heterogeneity, lesion location is likely to be an important determinant of cognitive impact of different manifestations of vascular brain injury. Based on early observations, certain lesion locations are considered to be "strategic," including the left angular gyrus, thalamus, and basal ganglia. However, a recent statement on VCI from the American Heart Association/American Stroke Association emphasized that current concepts of strategic infarction are largely based on small case series and warrant reexamination in larger imaging studies [1]. For white matter hyperintensities (WMHs), there are also indications that lesion location is related to cognitive impact, but this relationship is less clear [2,3].

Lesion-symptom mapping (LSM) is an increasingly utilized method in the VCI research field [4,5]. The concept of LSM is that it examines relationships between the location of brain injury—usually at the level of individual voxels or regions of interest—and behavioral measures such as cognition. This is commonly done through statistical comparisons of patients with and without a lesion for individual voxels or by associating regional lesion volumes with cognition. LSM studies have identified strategic lesion locations for acute infarcts [6] and small vessel disease [3]. A growing number of scientific publications and lesion analysis methods have emerged over the past decades [7]. Yet, most LSM studies are hampered by incomplete lesion coverage of the brain. This is important because the cognitive impact of damage to a particular brain region can only be addressed in the statistical analyses if this region is damaged in a sufficient number of patients. Because vascular lesions are not distributed randomly across the brain, some regions are commonly affected, but others that may be relevant for cognition—such as the orbitofrontal lobes in anterior cerebral artery territory infarction [8,9]—are rarely affected. As a consequence, previous studies (e.g., [5,10,11]) found that

even with several hundred subjects, large regions of the brain were not affected by vascular lesions and could therefore not be considered in LSM analyses. Thus, it remains difficult to obtain a comprehensive picture of strategic lesion locations for cognitive dysfunction.

Meta VCI Map is a recently established consortium that aims to perform **Meta**-analyses on strategic lesion locations for **VCI** using lesion-symptom **Mapping**. This consortium provides an international collaborative platform for multicenter LSM projects. By integrating existing data sets with imaging data on vascular lesions and cognitive data, LSM studies can be performed on larger study samples to improve brain lesion coverage.

Meta VCI Map has two key objectives. The first objective is to create vulnerability maps of the brain that show where vascular lesions have the most impact on cognition. Such vulnerability maps would be of diagnostic and prognostic value and could help explain why some patients with vascular lesions develop VCI while others do not. The second objective is to further establish strategic lesion locations that lead to impairment of specific cognitive functions.

In this study, we provide an overview of the design and objectives of this consortium. In addition, we present the methods and results of the pilot study, which aimed to determine the feasibility and potential benefits of multicenter LSM studies.

2. Methods

2.1. Consortium design

2.1.1. Membership and data index

Membership is open to all research groups and consortia willing to share suitable data. Data sets are eligible for inclusion if both brain imaging and data on cognitive performance are available. Study populations typically involve patients with ischemic stroke, memory clinic patients, or population-based subjects. Study design may be cross-sectional or longitudinal. Lesions of interest are infarcts (on computed tomography [CT]/magnetic resonance imaging [MRI]) or WMH (on MRI). Availability of lesion maps is preferred, but not a prerequisite. Meta VCI Map image processing and analysis pipelines allow for inclusion and

combination of different types of imaging data (see 2.1.4). Standardized measures of cognitive performance or decline should have been collected, for example, cognitive screening tests (e.g., Montreal Cognitive Assessment [MoCA]), neuropsychological tests (e.g., Trail Making Test), clinical diagnoses (e.g., mild cognitive impairment or dementia), or norm-based scores for individual tests or cognitive domains. Other clinical parameters, such as gait or depressive symptoms, may also be suitable for LSM analyses.

Data sets available from members are listed in the Meta VCI Map data index. This data index is used to select cohorts with comparable study populations and cognitive outcomes that can be used in meta-analyses. These analyses are performed on a project-by-project basis. Membership as such does not require the actual submission of data. Data are only shared in the context of specific projects (see 2.1.2).

Potential members were identified and invited through other collaborative networks in the VCI research field, including STRIVE [12], METACOHORTS [13], and HARNESS (www.harness-neuroimaging.org) and asked to fill in a survey to explore their interest in participating and support creation of the data index. As of November 2018, 47 groups have joined Meta VCI Map, and the data index includes approximately 7800 patients with ischemic stroke, 4900 memory clinic patients, and 14,400 population-based subjects. An overview of cohorts is presented in Table 1. Recruitment of members is an open and ongoing process. Interested parties are invited to sign up through e-mail or the Meta VCI Map website.

The website is active at www.metavcimap.org. It provides a public platform for information on the consortium. This includes the data index of member cohorts and consortia. The website also has a section for technical support (see 2.1.4/2.1.5).

2.1.2. Organization

Meta VCI Map is governed by a Steering Committee, which consists of representatives from study groups who have participated in Meta VCI Map projects. The Steering Committee is responsible for the governance of the consortium and oversees research projects performed within the consortium framework. To support individual projects in various areas of expertise, Working Groups for data analysis, data management, cognitive assessment, and ethics and regulations have been established.

Data will be shared on a project-by-project basis. This enables each consortium member to opt-in or opt-out on sharing data for specific projects, which allows individual investigators to prioritize projects of their interest accordingly. Each project involves individual data sharing agreements between participating centers, defining data use and access for that particular project. This ensures that local requirements for privacy, ownership, and traceability of the data are fulfilled. To accelerate workflow, a data sharing agreement template is provided, which has been optimized for international use (available at <https://metavcimap.org/features/downloads>).

2.1.3. Ethics

Meta VCI Map supports and encourages sharing of data, while strictly adhering to ethical and legal institutional review board regulations to ensure protection of (data from) human subjects, including the European Union General Data Protection Regulation. Consortium members are responsible for adhering to their local regulations and for proper deidentification of data before sharing. Requirements will differ for each institution and particular research project and therefore must be reviewed on a project-by-project basis.

2.1.4. Image processing

Lesion segmentation and image processing tools are available for determining the location of brain lesions, including infarcts (on CT, fluid-attenuated inversion recovery [FLAIR], or diffusion-weighted imaging [DWI]) or WMH (on FLAIR). An overview of typical image processing steps is shown in Fig. 1. Meta VCI Map provides technical support for each step, thereby allowing interested parties to contribute imaging data at different stages of processing.

For image and lesion data processing, Meta VCI Map promotes the use of the RegLSM image processing pipeline, which was recently developed in a collaborative LSM project between Utrecht and Hong Kong [10]. RegLSM can transform lesion maps to fit onto a standardized brain template. For the present pilot study, the Montreal Neurological Institute (MNI)-152 template [63] was used, but this can be substituted by other brain templates depending on individual preference [64]. RegLSM provides custom-fit settings for CT [65], MRI T1 and FLAIR [11], and DWI [10] (Fig. 1). It can also process scans from different vendors and field strengths. Furthermore, it can correct for anatomical variation (e.g., ethnicity-based morphometric differences or brain atrophy) by performing intermediate transformation steps using population-adjusted templates. The output is the same for each setting, that is, lesion maps in standardized brain space, which allows lesion data from different imaging modalities (e.g., CT/MRI) and sequences (e.g., T1/FLAIR/DWI) to be combined into one data set.

RegLSM and other downloadable software packages, protocols, and tutorials will be provided on the Meta VCI Map website (see 2.1.1) to facilitate and harmonize data processing. Although we strive to implement standard pipelines across projects, ultimately the selection of particular (or combinations of) pipelines will be decided on a project-by-project basis, but always with rigorous quality controls. Our processing pipelines are in constant development; therefore, we encourage our members to share their tools and knowledge.

2.1.5. Data analysis

Meta-analysis of multicenter data can be challenging due to heterogeneity of data. For imaging data, the ability to detect and localize lesions depends, for example, on the imaging

Table 1
Overview of Meta VCI Map member studies

Study	Country	Sample size	Imaging data	Cognitive screening tests	Cognitive domain-specific assessment	Lesion maps*	Key reference(s)
Ischemic stroke cohorts							
Bundang VCI cohort	Republic of Korea	2233	T1, FLAIR, DWI	MMSE, IQCODE	Mem, AEF, Vis, Lan	No	Lim et al., 2014 [14]
Center of Excellence in Rehabilitation Medicine, UMC Utrecht—De Hoogstraat Rehabilitation cohort	Netherlands	150	CT, T1, FLAIR, DWI	MoCA, MMSE, neglect screening	Mem, AEF, PS, Vis, Lan	Yes	Ten Brink et al., 2016 [15] Ten Brink et al., 2019 [16]
Clinical Biological and Pharmacological Factors Influencing Stroke Outcome (BIOSTROKE)	France	395	T1, T2, FLAIR, T2-star, DWI	MoCA, MMSE, CDR	N/A	N/A	Ducroquet et al., 2013 [17]
Cognition and Affect after Stroke: Prospective Evaluation of Risks (CASPER)	Netherlands	250	T1, T2, FLAIR, SWI	MMSE, neglect screening	Mem, AEF, PS, Vis, Lan	Yes	Douven et al., 2016 [18]
Cognitive Outcome After Stroke (COAST)	Singapore	117	CT, FLAIR, DWI	MoCA, MMSE	Mem, AEF, Vis, Lan	Yes	Dong et al., 2012 [19]
Cognitive Deficits in Cerebellar Stroke (CODECS)	Netherlands	40	CT, T1, T2, FLAIR, DWI	MoCA, FAB	Mem, AEF, PS, Vis, Lan	Yes	N/A
Cognitive function after lacunar stroke MUMC study	Netherlands	77	T2, FLAIR, T2-star, DWI	R-CAMCOG	Mem, AEF, PS	No	Huijts et al., 2013 [20]
Cognitive Function After Stroke (CogFAST-UK)	United Kingdom	100	CT, T1, FLAIR	MMSE, CDR, CAMCOG IQCODE	N/A	N/A	Allan et al., 2011 [21]
Clinical Relevance of Microbleeds in Stroke (CROMIS-2)	United Kingdom	1000	T1, T2, FLAIR, T2-star, DWI, SWI	MoCA	Mem, AEF, PS, Vis, Lan	N/A	Charidimou et al., 2015 [22] Wilson et al., 2018 [23]
Chinese University of Hong Kong—Stroke Registry Investigating Cognitive Decline (CU-STRIDE)	Hong Kong	410	CT, T1, T2, FLAIR, DWI	MoCA, MMSE, CDR, IQCODE	None	Yes	Yang et al., 2015 [24] Mok et al., 2016 [25]; Zhao et al., 2017 [10]
Determinants of Dementia After Stroke (DEDEMAS)	Germany	131	T1, FLAIR, DTI	MoCA, MMSE	Mem, AEF, PS, Vis, Lan	Yes	Wollenweber et al., 2013 [26]
Hallym VCI cohort	Republic of Korea	994	T1, FLAIR, DWI	MoCA, MMSE, IQCODE	Mem, AEF, Vis, Lan	No	Yu et al., 2013 [27]
Kaohsiung Chang Gung Memorial Hospital stroke cohort	Taiwan	500	T1, FLAIR, DWI, DTI	MMSE, CASI	None	No	N/A
Linkou Chang Gung Memorial Hospital stroke cohort	Taiwan	100	T1, FLAIR, DWI, DTI	MoCA, MMSE	Mem, AEF, Lan	No	N/A
Mild Stroke Study II (MSS-II)	United Kingdom	200	T1, T2, FLAIR, T2-star, DWI, DTI	MoCA, MMSE, ACE-R	None	Yes	Wardlaw et al., 2017 [28]
Neurovascular Underpinnings of Exercise post-Stroke (RISE3)	Canada	15	T1, T2, FLAIR	MoCA	Mem, AEF, PS	Yes	Robertson et al., 2015 [29]
Prediction of Cognitive Recovery After Stroke (PROCRAS)	Netherlands	242	CT, T1, T2, FLAIR, DWI, DTI	MoCA, IQCODE	Mem, AEF, PS, Vis, Lan, emotion recognition	Yes	Aben et al., 2018 [30]
Recovery Improved post-Stroke with Exercise (RISE1)	Canada	13	T1, T2, FLAIR	MoCA	Mem, AEF, PS	Yes	Robertson et al., 2017 [31]

(Continued)

Table 1
Overview of Meta VCI Map member studies (Continued)

Study	Country	Sample size	Imaging data	Cognitive screening tests	Cognitive domain-specific assessment	Lesion maps*	Key reference(s)
Study of Factors Influencing Post-Stroke Dementia (STROKDEM)	France	300	T1, FLAIR, T2-star, DTI	MoCA, MMSE, IQCODE, CDR	N/A	N/A	Bournonville et al., 2018 [32] Delattre et al., 2017 [33]
Tel Aviv Brain Acute Stroke Cohort (TABASCO)	Israel	421	T1, T2, FLAIR, DWI, DTI	MoCA	Mem, AEF, Vis, Lan	Yes	Ben Assayag et al., 2012 [34]
Utrecht Stroke and COgnition (USCOG)	Netherlands	121	CT, T1, FLAIR	N/A	Mem, AEF, PS, Vis, Lan	Yes	Biesbroek et al., 2014 [35]
Memory clinic cohorts							
ADNI-1/2/GO (WMH segmentations by University of California, Davis) [†]	United States of America	1231	T1, T2, FLAIR	MMSE, CDR	Mem, AEF, PS, Vis, Lan	Yes	Jack et al., 2015 [36] http://adni.loni.usc.edu/
ADNI-2/GO (WMH segmentations by University College London) [†]	United Kingdom	929	T1, FLAIR	MoCA, MMSE	Mem, AEF, PS, Vis, Lan	Yes	http://adni.loni.usc.edu/
Alzheimer Center Erasmus MC [‡]	Netherlands	130	T1, T2, FLAIR	MMSE, FAB	Mem, AEF, PS, Vis, Lan	No	N/A
Cognition and Aging Center—Kaohsiung Chang Gung Memorial Hospital (CAC-KCGMH)	Taiwan	100	T1, FLAIR	MMSE, FAB, CASI	Mem, AEF, PS, Vis, Lan	No	Huang et al., 2017, 2018 [37,38]
The Dutch Parelinoer Institute—neurodegenerative diseases [‡]	Netherlands	1200	T1, T2, FLAIR, DWI	MMSE	Mem, AEF, PS, Vis, Lan	Yes	Aalten et al., 2014 [39]
Functional Assessment of Vascular Reactivity (FAVR) and Brain IMPACT	Canada	150	T1, T2, FLAIR, DTI	MMSE	Mem, AEF, PS, Vis	Yes	Case et al., 2016 [40]
Harmonization PRE-MCI	Singapore	167	T1, T2, FLAIR	MoCA, MMSE	Mem, AEF, PS, Vis, Lan	Yes	Biesbroek et al., 2016 [41]
Prospective Dementia Registry Austria (PRODEM-Austria)	United Kingdom	91	FLAIR	MMSE	Mem, AEF, PS, Vis	No	Archer et al., 2006 [42]
Recovery Improved in Covert Stroke With Exercise (RISE2)	Austria	819	T1, T2, FLAIR	MMSE	Mem, AEF, PS, Vis, Lan	Yes	Pusswald et al., 2015 [43]
Utrecht-Amsterdam Clinical Features and Prognosis in Vascular Cognitive Impairment (TRACE-VCI) [‡]	Canada	47	T1, T2, FLAIR	MoCA	Mem, AEF, PS	Yes	https://clinicaltrials.gov/ct2/show/NCT02068391
Young Onset Alzheimer's disease (YOAD) cohort	Netherlands	860	T1, T2, FLAIR, SWI	CDR, MMSE, CAMCOG	Mem, AEF, PS, Vis, Lan	Yes	Boomsma et al., 2017 [44]
Population-based cohorts							
Austrian Stroke Prevention Study (ASPS), Graz Study	United Kingdom	69	T1, T2	MMSE	Mem, AEF, PS, Vis, Lan	Yes	Slattery et al., 2017 [45]
Calgary Normative Study	Austria	1188	T1, T2, FLAIR	MMSE	Mem, AEF, PS, Vis, Lan	Yes	Seiler et al., 2014 [46]; Schmidt et al., 1994, 1999 [47,48]
Chinese University of Hong Kong – Risk Index for Subclinical brain lesions in Hong Kong (CU-RISK)	Canada	200	T1, FLAIR, DTI	MoCA	N/A	Yes	Tsang et al., 2017 [49]
Epidemiology of Dementia in Singapore (EDIS)	Hong Kong	851	T1, T2, FLAIR, DTI	MoCA, MMSE	Mem, AEF, PS, Vis, Lan	Yes	Wong et al., 2015 [50]
	Singapore	1500	CT, T1, T2, FLAIR, T2-star, DWI	MoCA, MMSE, IQCODE	Mem, AEF, PS, Vis, Lan	Yes	Hilal et al., 2013 [51]

Framingham Heart Study	United States	1820	T1, T2	N/A	Mem, AEF, PS, Vis, Lan	Yes	Au et al., 2006 [52]
Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)	Netherlands	550	T1, T2, FLAIR, T2-star, DWI	MMSE	Mem, AEF, PS	Yes	Shepherd et al., 2014 [53]
Rotterdam Study	Netherlands	5400	T1, T2, FLAIR, T2-star, DTI	MMSE	Mem, AEF, PS, Vis, Lan	Yes	Ikram et al., 2015, 2017 [54,55]
Southall And Brent Revisited (SABRE)	United Kingdom	1306	T1, T2, FLAIR, T2-star, DTI	N/A	Mem, AEF, PS, Lan	Yes	Shibata et al., 2013 [56] Sudre et al., 2018 [57]
Sydney Memory and Ageing Study (MAS)	Australia	540	T1, FLAIR	MMSE	Mem, AEF, PS, Vis, Lan	Yes	Sachdev et al., 2010 [58]
UC Davis ADC Diversity Cohort	United States	1063	T1, FLAIR	N/A	Mem, AEF, Vis	Yes	Hinton et al., 2010 [59]
Other cohort types							
Blood-brain barrier in cerebral small vessel disease cohort	Netherlands	75	T1, FLAIR	N/A	Mem, AEF, PS	Yes	Zhang et al., 2017 [60]
Discontinuation of Antihypertensive Treatment in Elderly People (DANTE)	Netherlands	219	T1, T2, FLAIR, T2-star	MMSE	Mem, AEF, PS	N/A	Moonen et al., 2015 [61]
Munich CADASIL cohort	Germany	125	T1, FLAIR, T2-star, DTI	MMSE	Mem, PS, Vis	Yes	Dueling et al., 2011 [5]
Radboud University Nijmegen Diffusion tensor and Magnetic resonance imaging Cohort (RUN DMC)	Netherlands	503	T1, T2, FLAIR, T2-star, DWI, DTI	MMSE	Mem, AEF, PS, Vis	Yes	Van Norden et al., 2011 [62]

Abbreviations: ACE, Addenbrooke's Cognitive Examination; AEF, attention and/or executive functions; CAMCOG, Cambridge Cognitive Examination; CDR, clinical dementia rating; CASI, Cognitive Abilities Screening Instrument; CT, computed tomography; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; FAB, frontal assessment battery; FLAIR, fluid-attenuated inversion recovery; IQCODE, Informant Questionnaire for Cognitive Decline in the Elderly; Lan, language; Mem, memory; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; N/A, (information on data) not available; PS, processing speed; SWI, susceptibility-weighted imaging; Vis, visuospatial functions (e.g., perception, construction); VCI, vascular cognitive impairment; WMH, white matter hyperintensity.

*Lesion maps: infarcts for stroke cohorts; white matter hyperintensities for cohorts with memory clinic patients, population-based subjects, and other cohort types.

[†]Lesion segmentations of ADNI data have been provided by different centers (i.e., University of California at Davis and University College London). Therefore, a large degree of overlap in subjects between these data sets must be noted.

[‡]The Dutch Parelinoer Institute—Neurodegenerative diseases cohort is a collaboration between the eight Dutch University Medical Centres (www.parelsnoer.org). This includes subjects from the TRACE-VCI and Alzheimer Center Erasmus MC cohorts; thus, partial overlap between these cohorts must be noted.

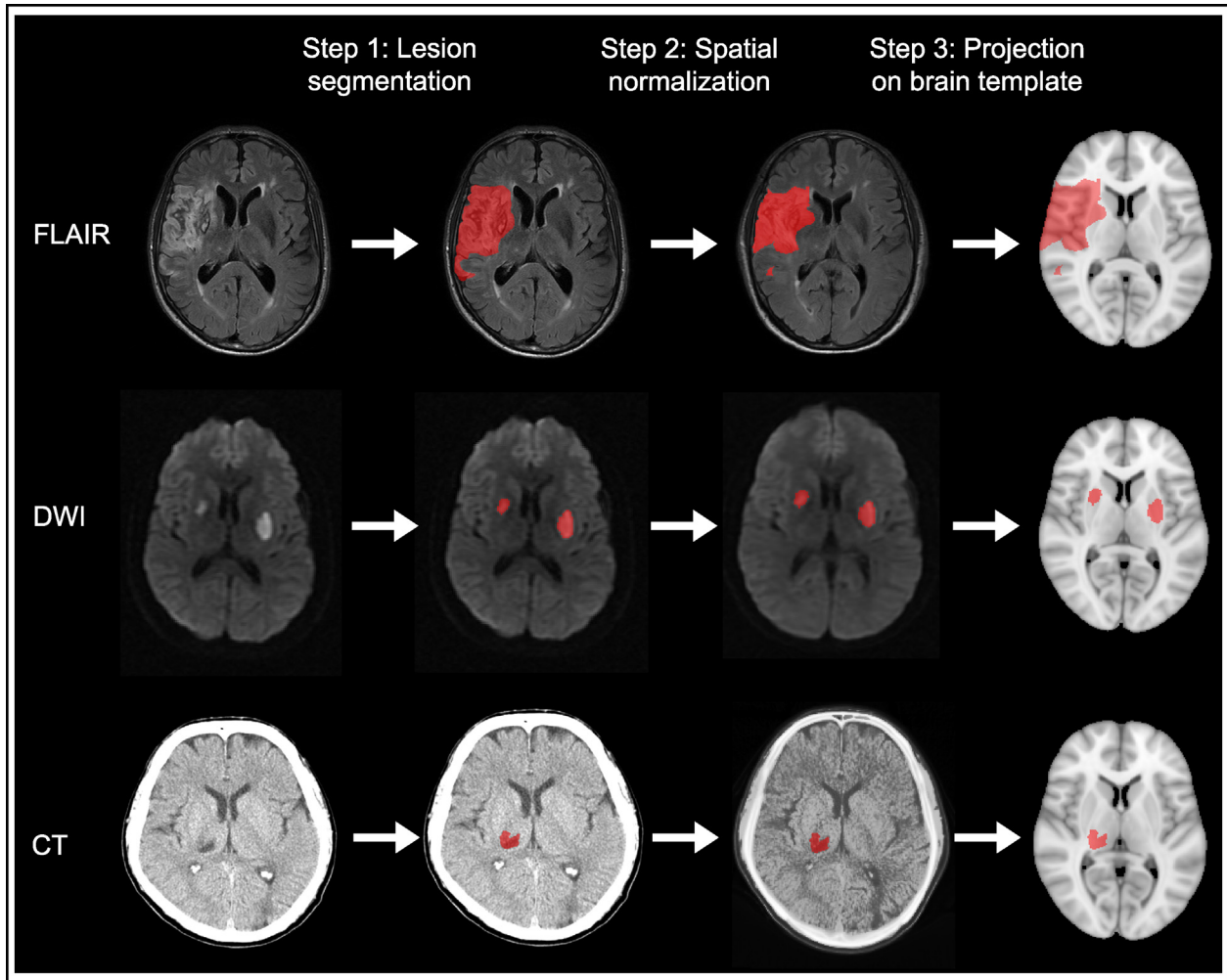


Fig. 1. Typical image and lesion processing pipeline for lesion-symptom mapping studies. Lesion-symptom mapping studies essentially require three image and lesion processing steps to prepare lesion maps. Examples are shown for three common imaging sequences: FLAIR, DWI, and CT. First, the lesion must be delineated on the original scan data (lesion segmentation). This can be done manually, or (semi-)automatically using computer algorithms. Next, the scan and corresponding lesion map are transformed to fit the size and shape of a brain template (spatial normalization). An intermediate registration step to an age-specific template is often used to improve registration accuracy. Finally, the resulting lesion map is projected onto the brain template. This result is compared to the original scan, to determine whether lesion registration was successful. Main criteria are that the key anatomical landmarks of the transformed scan and template should correspond and that the registered lesion map accurately represents the original lesion regarding location, size, and shape. The final lesion map can be used for group comparisons, unrestricted by type and format of the raw imaging data. Abbreviations: CT, computed tomography; DWI, diffusion-weighted imaging; FLAIR, fluid attenuated inversion recovery.

modality and sequence, and timing of assessment. For cognitive data, the wide variety of available neuropsychological test batteries and diagnostic criteria make this challenging to harmonize across cohorts. Meta VCI Map projects will account for heterogeneity by pooling data from cohorts that use internationally validated, commonly used cognitive tests (e.g., MoCA, Trail Making Test), or by recoding data into standardized cognitive outcomes (e.g., dementia yes/no). The data index will allow cohorts to be selected based on the availability of comparable data.

Meta VCI Map will implement state-of-the-art multivariate LSM analysis techniques, which show a higher sensitivity and better spatial accuracy than the original

mass-univariate approach [66]. The consortium will facilitate the utilization of multivariate LSM methods by providing software and manuals on its website and offer hands-on support through the Data Analysis Working Group.

2.2. Pilot study

2.2.1. Objectives

As a pilot, we performed a multicenter LSM study in which we integrated data from different cohorts, to test the feasibility of data exchange, image processing, and

analysis procedures. A second objective was to determine whether an integrated data set would improve brain lesion coverage.

2.2.2. Cohort and patient selection

The target population for the pilot was based on the responses to the initial survey. We aimed to include at least five different cohorts, to test our processing and analysis pipelines on different types of imaging data from different sources. The initial survey identified patients with ischemic stroke, with symptomatic infarcts as the lesion of interest and MoCA as cognitive outcome, as a suitable target population. This was operationalized in the following inclusion criteria: (1) patients admitted with acute ischemic stroke; (2) availability of brain imaging (CT/MRI) showing acute infarct(s); and (3) MoCA performed within 1 year after stroke. All eligible cohorts (per December 2017) were invited to participate.

2.2.3. Generation of lesion maps

Processing of imaging and lesion data was performed by the project team in Utrecht. Imaging data could be submitted in different formats and at different stages of processing, ranging from raw imaging data to fully prepared lesion maps.

For cohorts that provided raw imaging data, lesion segmentation was performed manually with in-house developed software using MeVisLab (MeVis Medical Solutions AG, Bremen, Germany) [67]. Infarcts were delineated on MRI DWI (<2 weeks after stroke) or FLAIR (≥ 2 weeks after stroke), or on CT (≥ 1 day after stroke) if no MRI was available. The acute (symptomatic) lesion was identified based on imaging features, which needed to be compatible with the poststroke interval. In cases of uncertainty based on imaging alone, the reported neurological deficit or the clinician's localization of the infarct was used to help localize the lesion. One trained rater performed lesion segmentation for all scans (E.M.H.), which was reviewed by a second rater (N.A.W.). In case of uncertainty regarding lesion location or classification, a third rater performed a consensus rating (J.M.B.). All raters were blinded to the neuropsychological data. Intraobserver and interobserver agreement were determined using the Dice Similarity Coefficient, which expresses the degree of overlap between the segmented regions on a scale from 0 to 1, on a random subset of 15 scans (5 for CT/FLAIR/DWI each) [68,69]. Both interobserver (0.81 ± 0.08) and intraobserver (0.83 ± 0.07) agreement were excellent.

Next, segmented lesions were registered to the MNI-152 template using the RegLSM software package (see 2.1.4). Each registered lesion map underwent visual quality control. Lesion maps in MNI-152 space were compared to the original scan, to determine whether key anatomical landmarks corresponded, and whether the registered lesion map accurately represented the infarct regarding

location, size, and shape. In case of minor errors, manual adjustments were made using ITK-SNAP v3.6.0 (www.itksnap.org) [70].

2.2.4. Neuropsychological assessment

Cognitive performance was assessed using the MoCA total score as measure of global cognition. In addition, a domain score for language was calculated by combining the scores for the animal picture naming and sentence repetition tasks [71]. This language domain score was included for comparative purposes, to determine whether our LSM analyses would identify different strategic infarct locations for distinct cognitive processes (i.e., global cognition vs. language).

2.2.5. Statistical analyses

Support vector regression (SVR)-based lesion-symptom mapping was performed using a previously published method [10]. Two independent SVR-based analyses were performed: voxel-based LSM (SVR-LSM) and region of interest-based analyses (SVR-ROI). The methodology of SVR-LSM and SVR-ROI is described extensively in the original study [10]. Further details are provided in the [Supplementary Material](#). To allow for optimal comparison with the original study, we applied the same correction factors (i.e., age, sex, years of education, clinical history of stroke and/or TIA, and total infarct volume) and statistical analyses.

3. Results

3.1. Cohort selection and data transfer

In December 2017, nine cohorts of acute ischemic stroke patients with available MoCA scores were invited to participate in the pilot study. Within the time frame of 6 weeks, investigators from six cohorts responded and agreed to participate [10,19,26,28,30]. Data transfer was straightforward and completed within 2 months, though some regulatory challenges were encountered, mainly due to differences in the required documentation regarding ownership and traceability of data. This has led to further streamlining of data sharing procedures for future projects (see 2.1.2).

3.2. Patient selection and data processing

A flowchart of patient selection is shown in [Fig. 2](#). Three cohorts provided raw imaging data ($n = 330$), two cohorts provided imaging data and lesion maps in native brain space ($n = 211$), and one cohort provided lesion data in MNI-152 space ($n = 410$). From the 330 patients with raw imaging data, 73 were excluded because the quality of imaging data was insufficient ($n = 26$), or if no acute infarct was visible ($n = 47$).

Lesion segmentation was performed manually for 257 patients (35 DWI; 177 FLAIR; 45 CT). Spatial

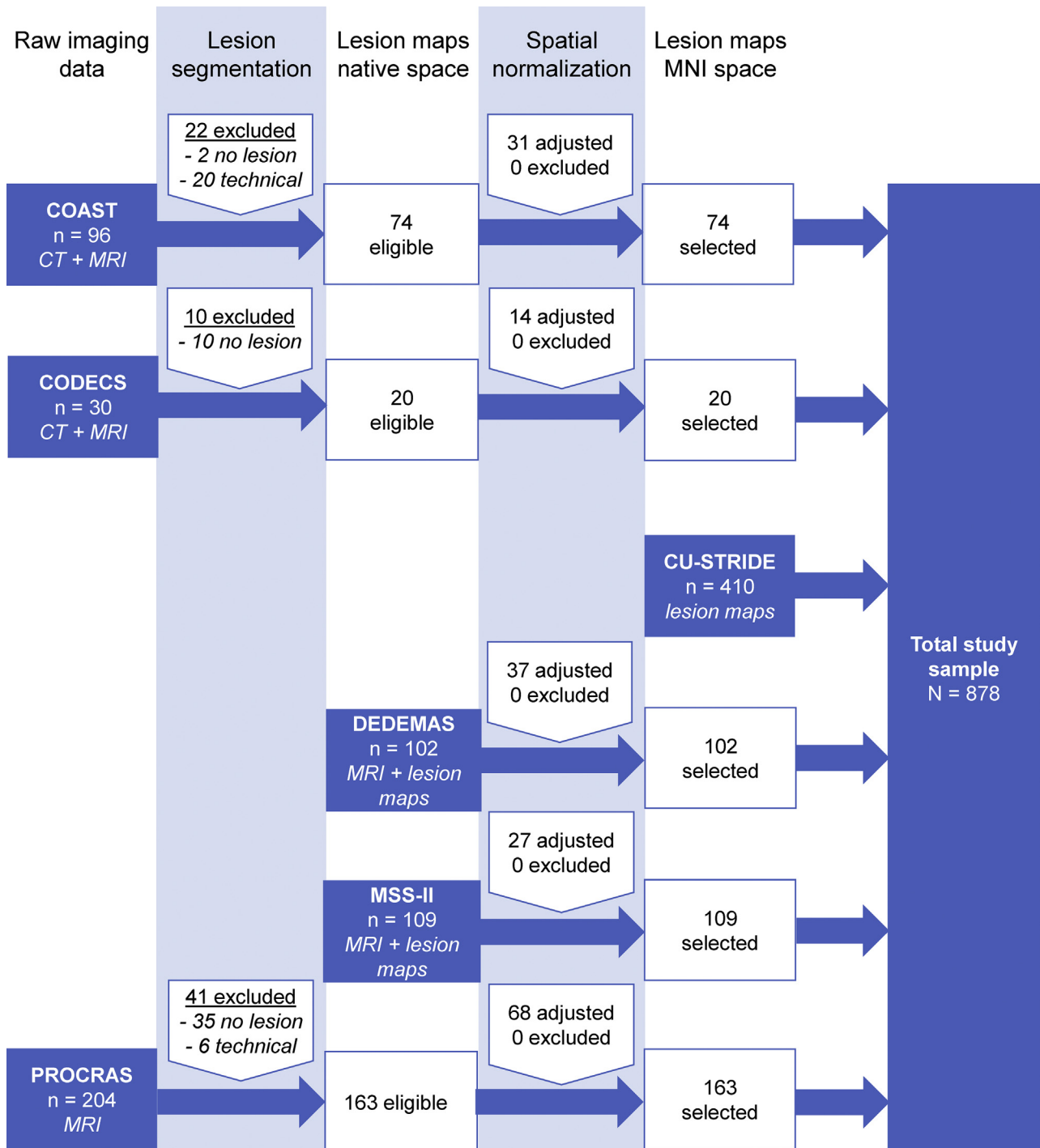


Fig. 2. Flowchart of patient selection for the Meta VCI Map pilot study. Patient selection is shown for each cohort separately. Cohorts could join at any given step of image processing. The processing steps—congruent with the pipeline shown in Fig. 1—are shown at the top. Availability of clinical data was a prerequisite to be considered. The blue boxes indicate at what stage the cohort entered the pipeline, and what kind of imaging data was provided. Note that spatial normalization passed visual quality control in all cases, though (minor) manual adjustments were made in 177 (38%) cases.

normalization was performed for 468 patients, which was successful in all cases. Manual adjustments were made in 177 cases, which was comparable for each cohort and type of imaging data. This resulted in a final study sample of 878 subjects. Characteristics of the total and individual study samples are shown in Table 2.

3.3. Brain lesion coverage

Lesion prevalence maps of individual cohorts and the collective study sample are shown in Fig. 3. Compared with CU-STRIDE, the largest of the six included cohorts (n = 410), lesion coverage in the merged data set

Table 2
Patient characteristics of pilot study sample

Characteristics	COAST (n = 74)	CODECS (n = 20)	CU-STRIDE (n = 410)	DEDEMAs (n = 102)	MSS-II (n = 109)	PROCRAS (n = 163)	Total sample (n = 878)
Relevant inclusion criteria	Acute ischemic stroke (within 14 days), age ≥ 21 years	Cerebellar stroke, age ≥ 18 years	Ischemic stroke, Chinese ethnicity, language: Cantonese	Acute ischemic stroke (within 3 days), age ≥ 18 years, language: German	Lacunar or mild cortical ischemic stroke (within 4 weeks), age ≥ 18 years, visible infarct	Acute ischemic stroke, age ≥ 50 years, language: Dutch	-
Relevant exclusion criteria	Significant aphasia or dysarthria, prior dementia, psychiatric comorbidity	Significant aphasia or severe dysarthria, prior cognitive impairment	Significant aphasia, prior dementia, psychiatric comorbidity	Prior dementia	None	Prior dementia, severe stroke requiring long-term care	-
Demographic characteristics							
Age in years, mean \pm SD	58.4 \pm 10.5	60.3 \pm 16.7	68.6 \pm 10.4	71.0 \pm 8.7	65.6 \pm 11.4	69.5 \pm 0.76	67.6 \pm 10.9
Female, n (%)	21 (28.4)	10 (50.0)	163 (39.8)	35 (34.3)	41 (37.6)	53 (32.5)	323 (36.8)
Education in years, mean \pm SD	6.8 \pm 3.7	13.6 \pm 4.6	5.9 \pm 4.7	10.6 \pm 2.1	12.1 \pm 3.2	11.4 \pm 2.5	8.5 \pm 4.7
Handedness, left/right/ambidext., n	N/A	13/4/0 (n = 17)*	396/7/7	95/6/1	97/12/0	153/6/4	754/35/12 (n = 801)*
Clinical history of stroke or TIA	10 (13.5)	0 (0.0)	56 (13.7)	17 (16.7)	16 (14.7)	34 (20.9)	133 (15.1)
Cognitive assessment							
MoCA total (max. 30), mean \pm SD	21.0 \pm 5.0	24.9 \pm 3.4	19.9 \pm 5.9	25.0 \pm 3.3	25.3 \pm 3.5	22.0 \pm 4.3	21.8 \pm 5.4
MoCA language (max. 5), mean \pm SD	3.9 \pm 0.9	4.4 \pm 0.8	4.3 \pm 0.9	4.7 \pm 0.6	4.8 \pm 0.6	4.3 \pm 0.9	4.4 \pm 0.9
Time point of MoCA assessment, n days after stroke onset, median (IQR)	121 (47)	3 months [†]	154 (47) [‡]	2 (2)	389 (43) (n = 107)*	3 (3)	134 (172) (n = 856)*
Brain imaging							
Scan used for lesion segmentation, DWI/FLAIR/CT, n	30/4/40	5/10/5	307/0/103	102/0/0	0/109/0	0/163/0	444/286/148
Normalized acute infarct volume in milliliters, median (IQR)	6.82 (30.59)	16.59 (48.95)	2.31 (11.99)	2.52 (11.15)	2.59 (8.74)	4.30 (18.88)	2.88 (13.19)
Time point of imaging, n days after stroke onset, median (IQR)	2 (3)	5 (24) (n = 18)*	1 (2) [‡]	3 (3)	4 (6)	33 (14)	3 (7) (n = 856)*

Abbreviations: CT, computed tomography; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; IQR, interquartile range; MoCA, Montreal Cognitive Assessment; SD, standard deviation; TIA, transient ischemic attack.

*Missing data; available sample size (n) is noted behind the respective variable.

[†]3 months is protocol for this study; no exact numbers available, therefore counted as missing data in total sample.

[‡]Days after admission to clinical ward (i.e., 0 to 3 days after stroke onset or presentation at emergency department), instead of days after stroke onset.

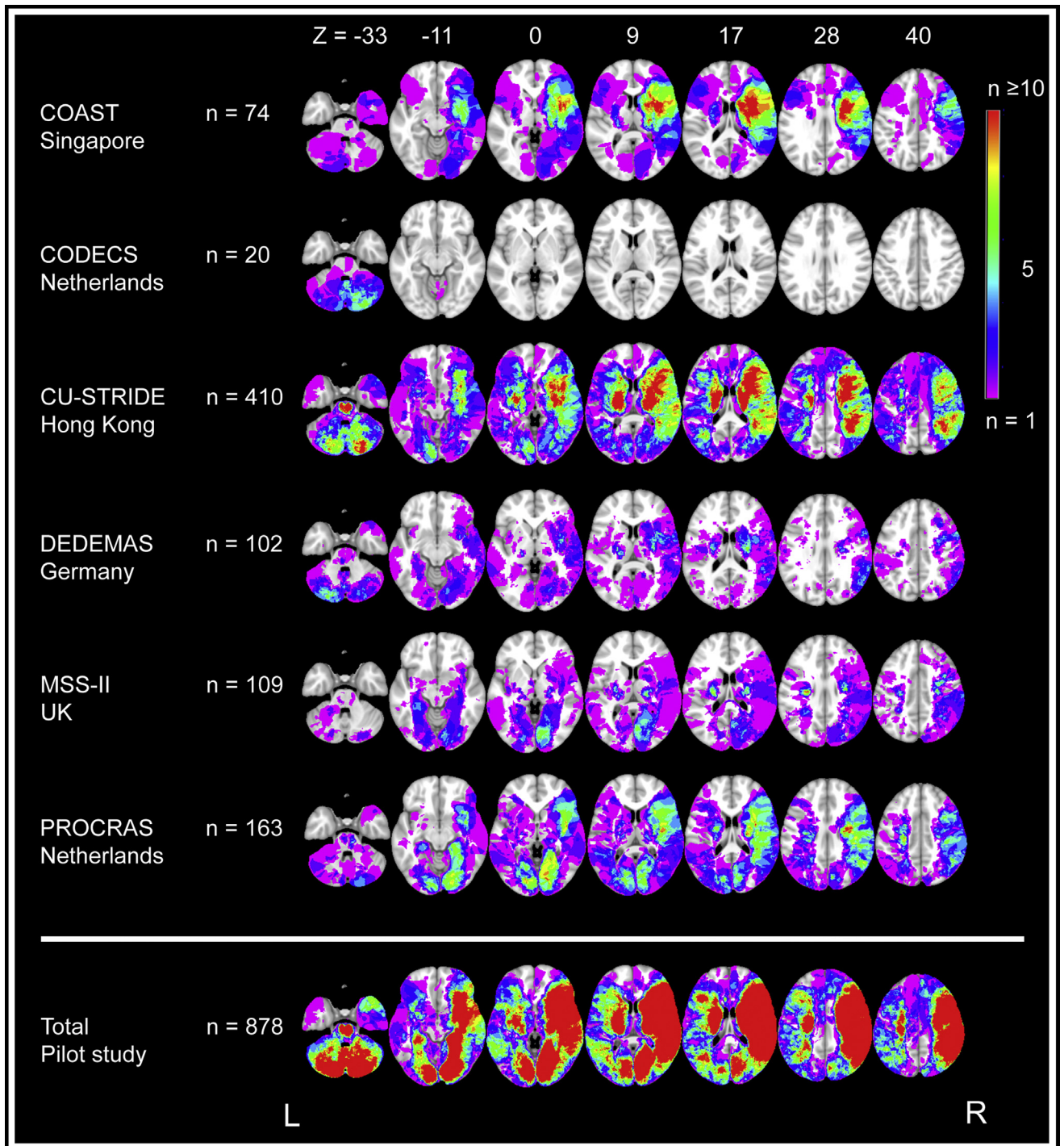


Fig. 3. Lesion prevalence map for individual cohorts and the collective data set of the Meta VCI Map pilot study. Voxel-based lesion prevalence map of infarcts for individual cohorts and collective data set, shown on the Montreal Neurological Institute 152 T1 template [63]. Every voxel that is damaged in one or more subjects in the cohort is shown in colors ranging from purple ($n = 1$) to red ($n \geq 10$). The right hemisphere is depicted on the right, which is conventional in lesion-symptom mapping studies. To prevent that lesion-symptom mapping analyses are biased by voxels that are only rarely affected, a minimum number of patients with a lesion in a particular voxel is commonly set. Although there is no general rule on where to set this threshold, it is typically set in the range of $5 \leq n \leq 10$ [66]. In this figure, blue- and purple-colored voxels are damaged in less than five subjects and thus would normally be excluded from lesion-symptom mapping studies. The bottom lesion map was created by merging lesion maps from all the cohorts, which shows a considerably increased number of included voxels after integrating the data from all six cohorts. Note that the left hemisphere is relatively underrepresented; most cohorts used aphasia as an exclusion criterion because it precluded reliable cognitive assessment. Thus, subjects with (large) left hemispheric lesions were often excluded during initial inclusion of stroke patients.

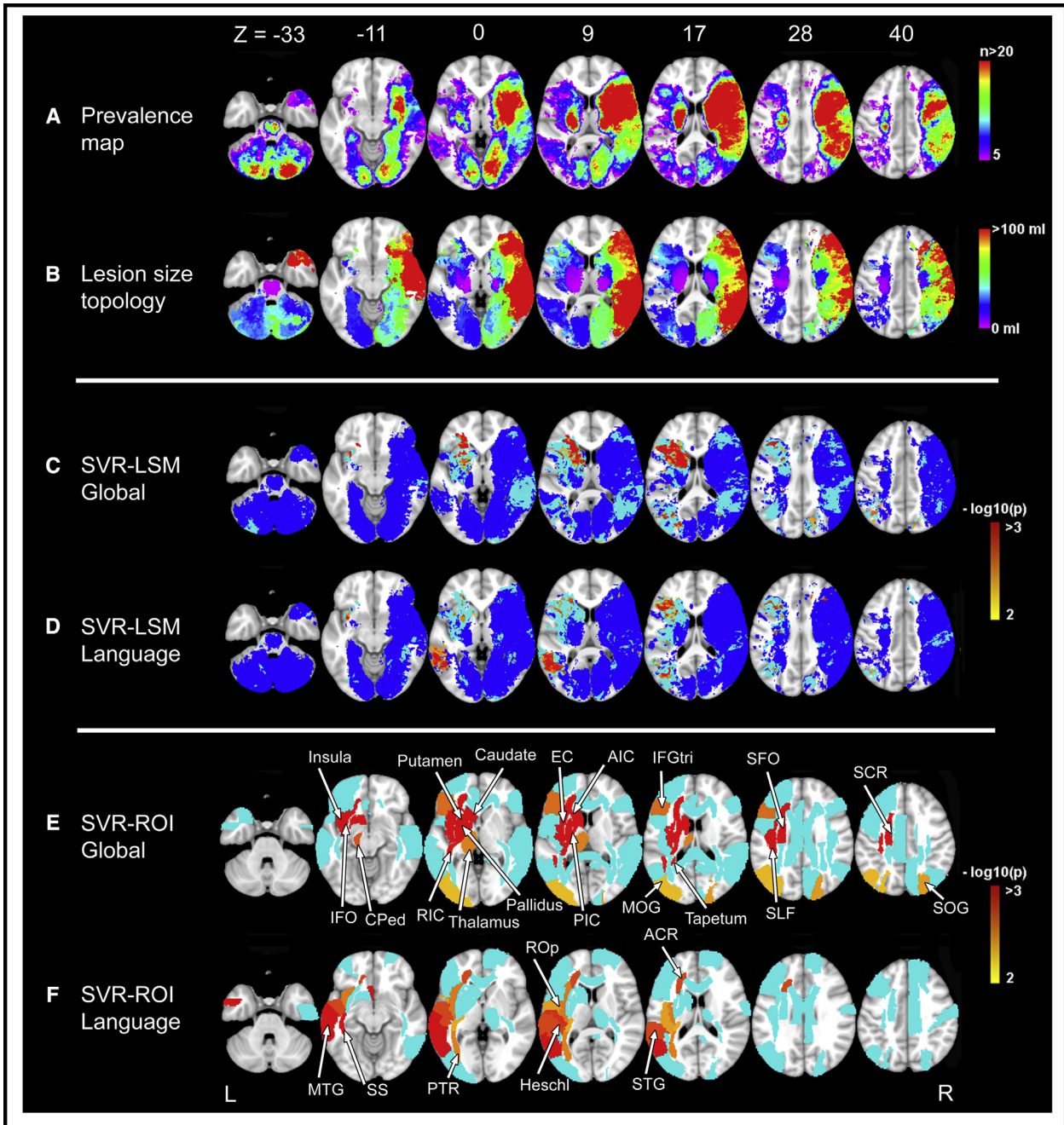


Fig. 4. Lesion prevalence map and lesion-symptom mapping results. Lesion prevalence map (A), lesion size topographies (B), and SVR-LSM and SVR-ROI results (C–F). The right hemisphere is depicted on the right. (A) Lesion prevalence map showing voxels that are damaged in at least five patients is projected on the 1 mm MNI-152 template [63]. The bar indicates the number of patients with a lesion for each voxel. (B) Lesion size topographies for each voxel lesioned in at least five patients. The bar indicates the median lesion volume (in milliliters) per patient, given that the specific voxel is lesioned. This illustrates whether a particular voxel is more often damaged by relatively large infarcts (red) or small infarcts (purple). In the present study, right hemispheric infarcts were often larger and commonly included cortical areas, while infarcts in the thalamus, brain stem, and internal capsule were often small. (C–D) Results of multivariate lesion-symptom mapping. Voxelwise associations between the presence of a lesion and Montreal Cognitive Assessment (MoCA) total score (C) or language domain score (D) were determined using support vector regression (SVR-LSM). This multivariate approach assesses the intervoxel correlations and identifies which voxels have an independent contribution to the outcome measure. These associations are corrected for age, gender, and education. Significant clusters are shown in colors ranging from yellow ($P = .01$) to red ($P < .001$). To visualize the voxels that were included in each step of the analyses, voxels associated with cognition in the univariate analyses (without correction for multiple testing), but not in the multivariate analyses, are shown in light blue. Voxels with no univariate association with cognition are shown in dark blue and were not included in the multivariate analysis. Uncolored voxels were not included in any step of the analyses because these were damaged in less than five individuals. (E–F) Results of multivariate region of interest-based analyses using support vector regression (SVR-ROI). The ROIs where the regional infarct volume was statistically associated with the cognitive functions are colored from yellow ($P = .01$) to red ($P < .001$). ROIs that were associated with cognition in the univariate analyses but not in the multivariate analyses are shown in light blue.

($n = 878$) showed an absolute increase of 26% (374,100–840,300 voxels; 20%–46% of the MNI-152 template, respectively). This increase was most prominent in the left hemisphere, right occipital lobe, and cerebellum. Meanwhile, coverage of the left hemisphere and orbitofrontal lobes was relatively limited. For the left hemisphere, this was likely due to aphasia being an exclusion criterion in most cohorts, because this would preclude reliable cognitive assessment. This is also reflected in the finding that left hemispheric infarcts were often smaller and did not cover cortical regions in the frontal and temporal lobes (Fig. 4A, B). For the orbitofrontal lobes, coverage was likely limited because anterior cerebral artery infarcts are relatively rare [9].

Lesion distributions differed between cohorts, reflective of differences in inclusion criteria and recruitment strategies (Table 2). For example, CODECS only included patients with cerebellar infarcts. Meanwhile, DEDEMAS and MSS-II included subjects with milder stroke symptoms, who generally had smaller infarcts that showed less overlap (Fig. 3).

3.4. Lesion-symptom mapping results

SVR-LSM and SVR-ROI results are shown in Fig. 4 and Supplementary Tables 1 and 2. Both methods identified significant associations between total MoCA scores and infarcts located in the left inferior frontal gyrus, left basal ganglia and their surrounding white matter tracts, left insula, and bilateral occipital lobes. Language domain scores were associated with infarcts located in the left middle and superior temporal gyri, left insula, left posterior thalamic radiation, and left anterior corona radiata.

4. Discussion

The Meta VCI Map consortium will provide new insights into the relevance of vascular lesion location for cognitive dysfunction, by creating a research framework that facilitates collaborative LSM projects. The pilot demonstrates that this novel multicenter LSM approach is feasible and substantially improves brain lesion coverage. Our image processing and LSM analysis pipelines showed that integration of multicenter patient data is feasible, allowing for inclusion of both CT and MRI scans from different data sets.

This pilot study demonstrates the benefits of multicenter LSM. First, we achieved a marked improvement of brain

lesion coverage by integrating individual data sets. Compared with the CU-STRIDE study, one of the largest (monocenter) LSM studies to date ($n = 410$) [8], the increased coverage in our merged data set ($n = 878$) allowed us to identify strategic infarct locations in previously excluded brain areas. Furthermore, we provided a proof-of-concept that multicenter LSM can identify strategic lesion locations for distinct cognitive processes. For example, infarcts in the basal ganglia and internal capsule were associated with impairment of global cognition, which agrees with the known critical role of these structures [1], whereas infarcts in the left superior temporal lobe and frontal white matter were associated with language impairment, which agrees with well-established neural correlates for language [72,73].

Several challenges for future multicenter LSM studies were also identified. First, achieving better brain lesion coverage of rarely affected brain regions, such as orbitofrontal regions for infarcts and temporal lobes for WMH, will require even larger study samples. However, although larger multicenter data sets will lead to an increase of statistical power by including more patients with a lesion in each voxel, it must be taken into account that regions with higher lesion frequency will be more likely to be found in the LSM analysis than voxels with a lower lesion frequency [74]. This spatial bias persists in larger data sets because vascular lesion distribution typically follows the vascular tree. Further improvement of LSM methods is therefore an ongoing endeavor of the Data Analysis Working Group. Second, preparation and processing of lesion data is labor intensive, particularly for infarcts because these require manual lesion segmentation and frequent manual adjustments after registration (approximately 25% of cases). In our experience, this issue is less prominent for WMH, where automated segmentation tools are available (e.g., at <https://software.harness-neuroimaging.org>) and adaptations are generally needed in <5% of subjects (e.g., [41,75]). Nevertheless, efforts to reduce requirements for manual editing are a key priority of the Data Analysis Working Group. Third, although integration of different types of imaging data at different processing stages is technically feasible, this could introduce variability that must be taken into account, preferably through implementation of standardized protocols for each processing step. Fourth, our pilot study cohort had heterogeneous characteristics in terms of time point of cognitive assessment and inclusion criteria, which might impact our LSM results. Notably, the cognitive impact of acute versus chronic stroke is known to differ due to network reorganization and

◀ The names of the significant ROIs are labeled in the figure. Abbreviations: ACR, anterior corona radiata; AIC, anterior limb of internal capsule; CPed, cerebral peduncle; EC, external capsule; IFGtri, inferior frontal gyrus (triangular); IFO, inferior fronto-occipital fasciculus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; PIC, posterior limb of internal capsule; PTR, posterior thalamic radiation; RIC, retrolenticular part of internal capsule; ROP, rolandic operculum; SCR, superior corona radiata; SFO, superior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus; SOG, superior occipital gyrus; SS, sagittal striatum; STG, superior temporal gyrus.

significantly influences lesion-symptom correlations [6,7]. Finally, other contributing factors to cognitive decline, such as the presence and burden of other vascular lesions and premorbid cognitive status, should be taken into account in future projects. This should also include markers of neurodegeneration, which often accompany vascular lesions, particularly in older individuals. Of note, LSM techniques are well equipped to deal with such factors, for example, by including biomarkers for amyloid or tau in the analyses.

Future Meta VCI Map projects aim to include thousands of subjects to achieve even better brain lesion coverage. Several Meta VCI Map projects are in preparation. First, for patients with acute ischemic stroke, we aim to create a comprehensive vulnerability map of the brain that shows which infarct locations predict poststroke cognitive impairment, with particular focus on differences between early and late poststroke phases. Second, for infarcts and WMH, we aim to establish strategic lesion locations for domain-specific cognitive functions. Third, multidimensional LSM models will be implemented to study the interplay between MRI manifestations of vascular injury and other contributing factors to cognitive decline, such as risk factors and biomarkers for neurodegeneration.

Current members and other interested parties already show a great willingness to contribute data. Future projects will benefit from a growing Meta VCI Map membership base. Therefore, we invite all investigators who are interested and can contribute data to join Meta VCI Map.

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N.A.W. was the study coordinator, contributed to the design of the consortium and the pilot study, analyzed the data, and wrote the manuscript. L.Z. was a coinvestigator, analyzed the data, and contributed to the writing of the manuscript. J.M.B. and H.J.K. were coinvestigators, contributed to the design of the consortium and the pilot study, and contributed to the writing of the manuscript. G.J.B. was the leading investigator and chairman of the consortium, conceived and designed the consortium and the pilot study, and wrote the manuscript. H.J.B., C.P.L.H.C., M.D., R.S.G., O.K.L.H., S.H., P.L.M.K., B.Y.K.L., J.S.L., V.C.T.M., and J.M.W. were members of the Meta VCI Map Steering Committee, who contributed to the design of the consortium and pilot study, and reviewed the content of the draft and final manuscript. Other listed authors contributed to the pilot study and/or were involved in data acquisition and analysis of the cohorts included in the pilot study. Authors included under the banner of “Meta VCI Map consortium” are representatives from the Meta VCI Map member groups, who provided information on their respective cohorts for presentation in

the overview table, and reviewed and approved the final version of the article.

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Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.dadm.2019.02.007>.

RESEARCH IN CONTEXT

1. Systematic review: We reviewed published literature on lesion-symptom mapping in vascular cognitive impairment (VCI) using PubMed. Potential members for the consortium were identified and invited through existing collaborative networks in the VCI research field.
2. Interpretation: Published lesion-symptom mapping studies proved to have limited lesion coverage. The Meta VCI Map consortium brings international researchers together to perform multicenter lesion-symptom mapping studies. Our initial inventory revealed a great willingness of investigators to share data. The pilot study demonstrates that multicenter data integration is feasible and markedly improves brain lesion coverage. This allows us to study the cognitive impact of vascular lesions in more brain regions.
3. Future directions: Subsequent Meta VCI Map projects will include thousands of subjects to achieve even better brain lesion coverage, to comprehensively establish strategic lesion locations for cognitive dysfunction. Procedural challenges, also identified through the pilot, are being addressed to allow further upscaling of multicenter study samples.

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