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RESEARCH ARTICLE

Cortical microinfarcts in adults with Down syndrome assessed with 3T-MRI

Mateus Rozalem Aranha[1,2,3,4] | Victor Montal[1,2,5] | Hilde van den Brink[6] | Jordi Pegueroles[1,2] | Maria Carmona-Iragui[1,2,7] | Laura Videla[1,2,7] | Lucia Maure Blesa[1,2] | Bessy Benejam[1,2,7] | Javier Arranz[1] | Sílvia Valldeneu[1,2] | Isabel Barroeta[1,2] | Susana Fernández[7] | Laia Ribas[1,2] | Daniel Alcolea[1,2] | Sofía González-Ortiz[8,9] | Núria Bargalló[9,10] | Geert Jan Biessels[6] | Rafael Blesa[1,2] | Alberto Lleó[1,2] | Artur Martins Coutinho[3] | Cláudia Costa Leite[4] | Alexandre Bejanin[1,2] | Juan Fortea[1,2,7]

[1]Sant Pau Memory Unit, Institut d'Investigació Biomèdica Sant Pau (IIB SANT PAU), Barcelona, Spain

[2]Center of Biomedical Investigation Network for Neurodegenerative Diseases (CIBERNED), Barcelona, Spain

[3]Laboratory of Nuclear Medicine (LIM 43), Department of Radiology and Oncology, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, São Paulo, Brasil

[4]Laboratory of Magnetic Resonance in Neuroradiology (LIM 44), Department of Radiology and Oncology, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, São Paulo, Brasil

[5]Barcelona Supercomputing Center, Plaça d'Eusebi Güell, Barcelona, Spain

[6]Department of Neurology and Neurosurgery, University Medical Center Utrecht Brain Center, University Medical Center Utrecht, Utrecht, the Netherlands

[7]Barcelona Down Medical Center, Fundació Catalana de Síndrome de Down, Barcelona, Spain

[8]Hospital del Mar - Parc de Salut Mar, Barcelona, Spain

[9]Neuroradiology Section, Radiology Department, Diagnostic Image Center, Hospital Clínic de Barcelona, Universitat de Barcelona, Barcelona, Spain

[10]Magnetic Resonance Image Facility, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain

Correspondence
Juan Fortea, Neurology Department, Hospital de la Santa Creu i Sant Pau, Sant Antoni Mª Claret 167, Barcelona 08025, Spain.
Email: jfortea@santpau.cat

Abstract

BACKGROUND: Cortical microinfarcts (CMI) were attributed to cerebrovascular disease and cerebral amyloid angiopathy (CAA). CAA is frequent in Down syndrome (DS) while hypertension is rare, yet no studies have assessed CMI in DS.

METHODS: We included 195 adults with DS, 63 with symptomatic sporadic Alzheimer's disease (AD), and 106 controls with 3T magnetic resonance imaging. We assessed CMI prevalence in each group and CMI association with age,

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AD clinical continuum, vascular risk factors, vascular neuroimaging findings, amyloid/tau/neurodegeneration biomarkers, and cognition in DS.

RESULTS: CMI prevalence was 11.8% in DS, 4.7% in controls, and 17.5% in sporadic AD. In DS, CMI increased in prevalence with age and the AD clinical continuum, was clustered in the parietal lobes, and was associated with lacunes and cortico-subcortical infarcts, but not hemorrhagic lesions.

DISCUSSION: In DS, CMI are posteriorly distributed and related to ischemic but not hemorrhagic findings suggesting they might be associated with a specific ischemic CAA phenotype.

KEYWORDS

Alzheimer's disease, cerebral amyloid angiopathy, cerebral microbleeds, cortical microinfarcts, Down syndrome, magnetic resonance imaging, neuroimaging, small vessel diseases

Highlights

- This is the first study to assess cortical microinfarcts (assessed with 3T magnetic resonance imaging) in adults with Down syndrome (DS).
- We studied the prevalence of cortical microinfarcts in DS and its relationship with age, the Alzheimer's disease (AD) clinical continuum, vascular risk factors, vascular neuroimaging findings, amyloid/tau/neurodegeneration biomarkers, and cognition.
- The prevalence of cortical microinfarcts was 11.8% in DS and increased with age and along the AD clinical continuum. Cortical microinfarcts were clustered in the parietal lobes, and were associated with lacunes and cortico-subcortical infarcts, but not hemorrhagic lesions.
- In DS, cortical microinfarcts are posteriorly distributed and related to ischemic but not hemorrhagic findings suggesting they might be associated with a specific ischemic phenotype of cerebral amyloid angiopathy.

1 | BACKGROUND

Cerebral cortical microinfarcts (CMI) are ischemic lesions that were until recently invisible on magnetic resonance imaging (MRI) and only detected in *post mortem* studies.[1] However, the development of 7T-MRI allowed their detection in vivo with ex vivo validation.[2] More recently, guidelines for visual detection of CMI on 3T-MRI[3] enabled their detection in large cohorts, linking CMI to vascular risk factors,[4] cardiac dysfunctions,[5,6] cerebral hypoperfusion,[7,8] stroke, and vascular cognitive impairment.[9] A few studies have also suggested that CMI is a common feature of cerebral amyloid angiopathy (CAA), together with cerebral microbleeds and superficial siderosis.[10–12]

In Down syndrome (DS), there is a triplication of chromosome 21, resulting in an overproduction of the amyloid precursor protein (APP), which is coded in this chromosome, and increased amyloid beta (Aβ) deposition in the brain parenchyma and capillaries.[13] DS is a genetic form of Alzheimer's disease (AD) and is associated with a higher CAA prevalence than the general population,[14,15] but with a lower prevalence of arterial hypertension, ischemic heart disease, atherosclerosis, and dyslipidemia.[16–20] These features make DS a great model for studying Aβ pathology as a possible cause of CMI, with a lesser influence of vascular risk factors.

We hypothesize that, given the ubiquitous brain amyloidosis and low prevalence of vascular risk factors in DS, CMI are related to CAA pathology in this population. Our aim was to characterize CMI in DS by studying their prevalence, number, and spatial distribution of CMI in this population, and their association with demographics, biomarkers, and vascular risk factors, as well as the changes along the AD clinical continuum in adults with DS.

2 | METHODS

2.1 | Study design and setting

This was a single-center cross-sectional study performed at Hospital Sant Pau (Barcelona, Spain) and approved by the local ethics committee, following the Declaration of Helsinki. All participants and/or their legally authorized representatives gave written informed consent. MRI

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data were acquired at Hospital del Mar and Hospital Clínic (Barcelona, Spain), in the same period.

2.2 | Participants

Participants were recruited between January 2011 and July 2021. We included adults with DS of both sexes (+18 years), with available volumetric T1-weighted (T1w) and T2*-weighted (T2*w: susceptibility-weighted [SWI] or gradient-echo [GRE]) magnetic resonance images. As comparative references we also included sporadic symptomatic AD patients and cognitively unimpaired euploid controls with available T1w and T2*w MRI sequences.

All participants were recruited from the Sant Pau Initiative on Neurodegeneration (SPIN) and Down Alzheimer Barcelona Neuroimaging Initiative (DABNI) cohort, established in 2011 and 2014 respectively, for multimodal biomarker discovery and validation in different neurodegenerative diseases that cause dementia.[21] The DABNI cohort is built on a population-based health plan to screen symptomatic AD in adults with DS and aims to investigate the natural history of AD in DS with multimodal biomarkers.[22]

2.3 | Clinical and neuropsychological evaluations and study subgroups

To be included in the DABNI cohort, participants with DS underwent intellectual disability (ID) assessment according to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V), based on caregivers' reports and the Intelligence Quotient score of the Kaufman Brief Intelligence Test Spanish version.[23] ID was categorized as mild, moderate, severe, or profound. Cognitive assessment in participants with DS was performed with the Cambridge Cognitive Examination for Older Adults With Down Syndrome (CAMCOG-DS) Spanish version,[24,25] and the modified Cued Recall Test (mCRT).[26] In the present study, the total CAMCOG-DS score (ranging 0–109) and the mCRT's total immediate recall score (ranging 0–36), were used as proxies of global cognition and episodic memory performance, respectively. In both tests, higher scores indicate better cognition. Euploid participants underwent the comprehensive neuropsychological battery included in the SPIN cohort,[27] and in the current study the Mini-Mental State Examination (MMSE) was used as a measure of global cognition. MMSE ranges from 0 to 30, with higher scores indicating better cognitive performance. Also, at the enrollment in SPIN or DABNI cohorts, each subject (with a caregiver, when appropriate) undergoes a structured questionnaire about previously diagnosed medical conditions, among them arterial hypertension, diabetes mellitus type 2, and dyslipidemia.

After independent neurological and neuropsychological evaluations blinded to the biomarker data, each participant with DS was clinically classified according to the presence of AD symptoms as asymptomatic (aDS; absence of cognitive or functional impairment), prodromal AD (pDS; when there was cognitive, but not functional, impairment), and AD dementia (dDS; when there was cognitive and functional impairment). The classification was based on a consensus meeting.[28] The assessment of functional status for differentiating pDS and dDS was based on anamnesis, the Dementia Questionnaire for People with Learning Disabilities, and the Comprehensive Assessment for Dementia in People with Down Syndrome and Others with Intellectual Disabilities (CAMDEX-DS).[29] Similarly, participants with sporadic AD were also clinically divided into prodromal AD (pAD; cognitive, but not functional, impairment) and AD dementia (dAD; cognitive impairment impacting daily activities).[21] Controls were divided into young (age < 60 years) and old (age ≥ 60 years) to serve as control groups for participants with DS and sporadic AD, respectively.

RESEARCH IN CONTEXT

1. **Systematic review**: Cerebral cortical microinfarcts (CMI) have been attributed to cerebrovascular disease and cerebral amyloid angiopathy (CAA). CAA's prevalence is increased in Down syndrome (DS) while hypertension is rare, but no studies have assessed CMI in this population. Relevant publications are appropriately cited.
2. **Interpretation**: CMI prevalence was 11.8% in DS and increased with age and along the Alzheimer's disease clinical continuum. CMI were predominantly located in the parietal lobes, and were significantly related to ischemic neuroimaging findings (lacunes and cortico-subcortical infarcts), but not with vascular risk factors or hemorrhagic lesions, suggesting that CMI might be associated with a specific ischemic phenotype of CAA in DS.
3. **Future directions**: From a neuroimaging perspective, CAA has been largely recognized by its hemorrhagic manifestations. Identifying new ischemic markers potentially related to CAA helps characterize the spectrum of neuroimaging findings associated with this entity.

2.4 | Image acquisition, preprocessing, and automated quality control

3T-MRI data were acquired with a Philips Achieva scanner (Philips Healthcare) at Hospital del Mar or a Siemens Prisma scanner (Siemens Healthcare) at Hospital Clínic. Both imaging protocols included T1w with 1.0 mm isotropic resolution, T2*w, and fluid-attenuated inversion recovery (FLAIR) images. The acquisition parameters for each scanner are provided in Table S1 in supporting information.

We used the quality assurance report provided by the Computational Anatomy Toolbox (CAT12; Christian Gaser and Robert Dahnke; http://dbm.neuro.uni-jena.de/cat/) for Statistical Parametric Mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) to exclude participants with low T1w image quality that could impair

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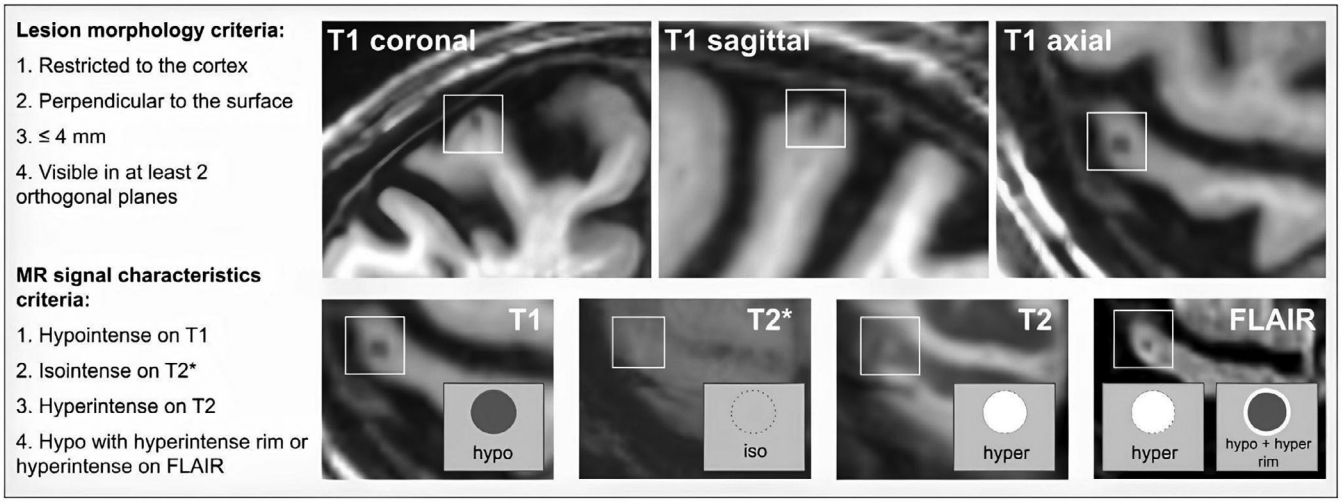

FIGURE 1 Criteria for visual detection of cortical microinfarcts in 3T magnetic resonance imaging. FLAIR, fluid-attenuated inversion recovery; MR, magnetic resonance

CMI's visual detection (image quality rating ≤ 80%). Figure S1 in supporting information shows the flowchart and the reasons for the exclusion of participants. We also conducted a sensitivity analysis of basic demographic and clinical characteristics between included and excluded subjects with DS, and we found no statistically significant differences between these samples (Table S2 in supporting information).

Artifacts of magnetic field inhomogeneity were corrected in all images using an N4 bias field correction pipeline[30] available in the Advanced Neuroimaging Tools software (ANTs, http://stnava.github.io/ANTs/) to minimize the influence of manual windowing during visual analysis. Within each subject, T2*w and FLAIR images were coregistered to the T1w images using a rigid registration implemented in ANTs to ensure anatomical correspondence between all analyzed images.

2.5 | MRI visual analysis

MRI visual analysis was performed by a board-certified neuroradiologist (MRA), blind to the participant's group, between March 2022 and March 2023. The rater was trained for CMI visual detection in 3T-MRI on an official training program available at the University Medical Center (UMC) Utrecht. The program consists of a theoretical background, training sessions on 7T and 3T-MRI, and a practical exam on 3T-MRI. After each training case, an official score based on autopsy-validated criteria[9] was provided by UMC Utrecht and the case was discussed with an assigned supervisor. After completion of the exam, the rater's scores were compared to the provided official scores and the Dice similarity index was calculated by the assigned supervisor. After training, good reliability results were obtained (Dice similarity index = 0.83).

Images were analyzed using MeVisLab (MeVis Medical Solutions AG; version 3.4.1). This study focuses on chronic CMI visual detection following autopsy-validated criteria[9] (as in the training program) that define chronic CMI as lesions restricted to the cortex and perpendicular to the cortical surface, ≤ 4.0 mm, visible in at least two orthogonal planes, and distinct from microbleeds or enlarged perivascular spaces (Figure 1). Chronic CMI candidates identified on T1w images were simultaneously evaluated on T2*w to be differentiated from microbleeds. When available, FLAIR images were also used to aid chronic CMI identification. While the original criteria[9] describe acute CMI's MRI signal characteristics for T2-weighted (T2w), FLAIR, and diffusion-weighted imaging (DWI), the absence of these sequences for all subjects in our dataset limited our ability to reliably analyze acute CMI.

Other vascular neuroimaging findings, namely cerebral microbleeds, superficial siderosis, lacunar infarcts (chronic infarct [3 to 15.0 mm] in the territory of perforating arterioles), large cortico-subcortical infarcts (≥5.0 mm), and white matter FLAIR hyperintensities (WMH) were rated as defined by the STRIVE guideline (Standards for Reporting Vascular Changes on Neuroimaging).[31] The interobserver agreement for detection of these vascular neuroimaging findings was assessed in a subset of subjects, with high reliability results (Dice similarity index of 0.83, 1.00, 0.85, 1.00, and 1.00 for cerebral microbleeds, superficial siderosis, lacunar infarcts, cortico-subcortical infarcts, and WMH, respectively).

Those participants with cerebral microbleeds and superficial siderosis on MRI were further classified as having Probable CAA or Possible CAA, according to the modified Boston criteria,[32] regardless of the age criterion included in the criteria set (> 55 years), as adults with DS present CAA pathology before this age.[14]

2.6 | Cerebrospinal fluid and plasma amyloid/tau/neurodegeneration biomarkers acquisition and analyses

A subset of participants underwent a cerebrospinal fluid (CSF) and/or blood sampling (Table S3 in supporting information). Samples were

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TABLE 1 Demographic data, CMI prevalence, fluid AT(N) biomarkers, and cognitive performance in each study group.

	YC (*N* = 76)	All DS (*N* = 195)	*P* value	aDS (*N* = 126)	pDS (*N* = 29)	dDS (*N* = 40)	*P* value
Demographics							
Age (years)	52.6 [46.9; 56.2]	44.4 [35.0; 50.9]	<0.001[a]	39.0 [30.0; 44.4]	49.6 [47.7; 52.3]	54.2 [49.0; 56.6]	<0.001[c]
Sex (female)	69.7%	42.6%	<0.001[b]	42.1%	44.8%	42.5%	0.964[b]
APOE ε4 +	34.7%	19.2%	0.013[b]	19.0%	26.9%	15.0%	0.483[b]
APOE ε2 +	5.3%	10.4%	0.288[b]	9.5%	23.1%	5.0%	0.061[b]
Hypertension	13.2%	2.1%	0.002[b]	0.8%	0.0%	7.9%	0.041[b]
Dyslipidemia	34.0%	19.2%	0.035[b]	15.1%	31.0%	23.7%	0.106[b]
D. mellitus 2	0.0%	3.1%	0.345[b]	3.2%	3.4%	2.6%	1.000[b]
CMI prevalence							
Overall	2.6%	11.8%	0.031[d]	8.7%	6.9%	25.0%	0.012[d]
CSF and plasma biomarkers							
CSF Aβ40	11.3 [9.8; 13.7]	11.2 [8.3; 14.4]	0.724[a]	11.6 [9.3; 15.1]	10.1 [7.2; 12.5]	11.1 [8.6; 13.2]	0.242[c]
CSF Aβ42	1.1 [1.0; 1.4]	0.7 [0.5; 0.9]	<0.001[a]	0.9 [0.7; 1.3]	0.5 [0.4; 0.6]	0.5 [0.4; 0.6]	<0.001[c]
CSF Aβ42/40	0.1 [0.1; 0.1]	0.1 [< 0.1; 0.1]	<0.001[a]	0.1 [0.1; 0.1]	<0.1 [< 0.1; 0.1]	<0.1 [< 0.1; < 0.1]	<0.001[c]
CSF p-tau	3.2 [2.6; 4.1]	4.4 [2.1; 10.7]	0.038[a]	2.6 [1.6; 4.2]	9.1 [5.0; 14.3]	14.3 [9.3; 18.2]	<0.001[c]
Plasma p-tau	1.3 [1.0; 1.8]	1.5 [0.9; 2.4]	0.459[a]	1.1 [0.8; 1.6]	2.0 [1.3; 2.3]	2.4 [20; 3.9]	<0.001[c]
CSF NfL	0.4 [0.3; 0.4]	0.5 [0.3; 0.8]	<0.001[a]	0.3 [0.2; 0.5]	0.7 [0.6; 0.8]	1.1 [0.7; 1.6]	<0.001[c]
Plasma NfL	0.8 [0.6; 1.1]	1.2 [0.7; 2.0]	0.006[a]	0.9 [0.6; 1.3]	1.3 [1.2; 1.9]	2.5 [2.0; 3.9]	<0.001[c]
NPS evaluation (DS with mild and moderate ID)							
CAMCOG-DS	–	73.5 [61.0; 83.8]	<0.001[a]	80.0 [69.0; 86.0]	72.5 [63.0; 76.8]	57.0 [46.0; 68.5]	<0.001[c]
mCRT	–	34.0 [27.0; 36.0]	<0.001[a]	36.0 [34.0; 36.0]	26.0 [20.8; 35.2]	18.5 [13.5; 24.8]	<0.001[c]
MMSE	30.0 [29.0;30.0]	–		–	–	–	–
	OC (*N* = 30)	**All AD (*N* = 63)**	***P* value**	**pAD (*N* = 43)**	**dAD (*N* = 20)**	***P* value**	
Demographics							
Age (years)	66.0 ± 5.0	70.1 ± 6.8	0.001[e]	70.3 ± 6.7	69.7 ± 7.0	0.747[e]	
Sex (female)	46.7%	63.5%	0.189[b]	65.1%	60.0%	0.911[b]	
APOE ε4 +	20.7%	54.5%	0.006[b]	62.2%	38.9%	0.181[b]	
APOE ε2 +	10.3%	3.6%	0.335[b]	5.4%	0.0%	1.000[b]	
Hypertension	38.5%	44.8%	0.838[b]	41.2%	50.0%	0.927[b]	
Dyslipidemia	38.5%	60.0%	0.180[b]	61.1%	58.3%	1.000[b]	
D. mellitus 2	7.7%	14.3%	0.670[b]	18.8%	8.3%	0.613[b]	
CMI prevalence							
Overall	10.0%	17.5%	0.543[d]	20.9%	10.0%	0.543[d]	
CSF and plasma biomarkers							
CSF Aβ40	13.0 [10.9; 15.7]	12.3 [10.9; 14.4]	0.606[a]	12.3 [11.4; 14.5]	12.6 [10.7; 14.3]	0.827[a]	
CSF Aβ42	1.3 [1.1; 1.6]	0.5 [0.4; 0.6]	<0.001[a]	0.5 [0.5; 0.6]	0.4 [0.4; 0.6]	0.029[a]	
CSF Aβ42/40	0.1 [0.1; 0.1]	<0.1 [< 0.1; < 0.1]	<0.001[a]	<0.1 [< 0.1; < 0.1]	<0.1 [< 0.1; < 0.1]	0.025[a]	
CSF p-tau	4.2 [3.3; 4.8]	10.6 [7.8; 16.2]	<0.001[a]	10.1 [7.5; 13.8]	16.3 [9.3; 22.6]	0.028[a]	
Plasma p-tau	1.0 [0.8; 1.5]	1.9 [1.5; 2.6]	<0.001[a]	1.9 [1.5; 2.4]	1.8 [1.5; 2.8]	0.724[a]	
CSF NfL	0.5 [0.4; 0.6]	0.9 [0.7; 1.1]	<0.001[a]	0.8 [0.6; 1.0]	1.0 [0.8; 1.2]	0.067[a]	
Plasma NfL	1.1 [0.8; 1.3]	1.5 [1.2; 1.8]	0.010[a]	1.4 [1.0; 1.7]	1.8 [1.4; 2.6]	0.133[a]	

(Continues)

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TABLE 1 (Continued)

	OC (*N* = 30)	All AD (*N* = 63)	*P* value	pAD (*N* = 43)	dAD (*N* = 20)	*P* value
NPS evaluation						
MMSE	29.0 [29.0; 30.0]	26.0 [24.0; 27.0]	<0.001[a]	27.0 [25.0; 28.0]	23.0 [19.5; 25.0]	<0.001[a]

Note: Data presented as: %, median [interquartile range] or mean ± standard deviation. Not all subjects in each group have data on *APOE* haplotype, hypertension, dyslipidemia, diabetes mellitus 2, CSF and plasma biomarkers, and cognition. The percentage in the table indicates the prevalence of each variable among those subjects with available data (Table S2 in supporting information).
CSF Aβ40 and CSF Aβ42 expressed in $.10^3$pg/mL; CSF and plasma p-tau expressed in 0.10^1pg/mL; CSF NfL expressed in 0.10^3pg/mL and plasma NfL expressed in 0.10^1pg/mL.
Abbreviations: Aβ, amyloid beta; aDS, asymptomatic Down syndrome; *APOE*, apolipoprotein E; AT(N), amyloid/tau/neurodegeneration; CAMCOG-DS, Cambridge Cognitive Examination for Older Adults with Down Syndrome (total score); CMI, cortical microinfarcts; CSF, cerebrospinal fluid; D. mellitus 2, diabetes mellitus type 2; DS, Down syndrome; dDS, Down syndrome-related Alzheimer's disease dementia; IQR, interquartile range; MMSE, Mini-Mental State Examination; mCRT, modified Cued Recall Test (total immediate recall score); NfL, neurofilament light; NPS, neuropsychological; OC, old controls; pDS, prodromal Down syndrome-related Alzheimer's disease; p-tau, phosphorylated tau 181, SD, standard deviation; YC, young controls.
[a]Kruskall-Wallis test.
[b]Chi-squared test.
[c]Analysis of variance.
[d]Fisher exact test.
[e]*t* test.

processed and stored as previously described.[33] CSF concentrations of Aβ40, Aβ42, and phosphorylated tau 181 (p-tau181) were measured with Lumipulse G600II automated platform (Lumipulse, Fujirebio-Europe).[21] CSF neurofilament light (NfL) concentration was quantified with an enzyme-linked immunosorbent assay (ELISA; NF-Light Assay; UmanDiagnostics), following the manufacturer's recommendations. CSF samples were analyzed at Hospital Sant Pau (Barcelona, Spain). Plasma concentrations of p-tau181 and NfL were measured with single molecule array (Simoa) technology (Quanterix) at the University of Gothenburg (Gothenburg, Sweden) and Hospital Sant Pau, respectively, following established protocols.[22,34,35] Apolipoprotein E (*APOE*) haplotype was determined by polymerase chain reaction amplification of DNA from blood samples.[36]

2.7 | Statistical analysis

Statistical analyses were conducted using R software (version 3.6.3, www.R-project.org).

To compare the study groups (DS, sporadic AD, and controls) regarding sex; *APOE* ε4 and *APOE* ε2 carriership; and the prevalence of arterial hypertension, dyslipidemia, and diabetes mellitus type 2, chi-squared test was used.

To assess CMI prevalence along the AD clinical continuum, Fisher exact test was used. DS participants were divided into aDS, pDS, and dDS, and sporadic symptomatic AD participants were divided into pAD and dAD.

To investigate the relationship of CMI prevalence and number with age in each study group (DS, sporadic symptomatic AD patients, and cognitively unimpaired controls), logistic regression and Poisson regression models were used, respectively.

Finally, to investigate the association between CMI and demographic data, neuroimaging findings, vascular risk factors, CAA diagnosis, fluid biomarkers, and neuropsychological data in DS, participants were divided based on CMI presence. DS participants with and without CMI were compared for each variable using Fisher exact, chi-squared, *t* test, analysis of variance, Mann–Whitney, and Kruskal–Wallis tests when appropriate. Cohen *d* coefficient, rank-biserial coefficient, and odds ratio (OR) were used as effect size measures when appropriate. Data analysis was performed in April 2023, with significance set at $P < 0.05$.

3 | RESULTS

3.1 | Participants and demographics

Table 1 summarizes the demographic data, CMI prevalence, fluid amyloid/tau/neurodegeneration (AT[N]) biomarkers, and cognitive performance in each study group. A total of 364 participants were included: 195 adults with DS (126 aDS, 29 pDS, and 40 dDS), 63 with sporadic AD (43 pAD and 20 dAD), and 106 controls (76 young and 30 old controls). Participants with DS were younger than young controls (44.4 [35.0; 50.9] vs. 52.6 [46.9; 56.2], years, $P < 0.001$) and had a lower proportion of females (42.1% vs. 69.7%; $P = 0.001$) and *APOE* ε4 carriers (19.2% vs. 34.7%, $P = 0.013$). Participants with sporadic AD had a higher proportion of *APOE* ε4 carriers than old controls (54.5% vs. 20.7%, $P = 0.006$; Table 1).

In DS, the prevalence of arterial hypertension and dyslipidemia was lower than in young controls (2.1% vs. 13.2% [$P = 0.002$] and 19.2% vs. 34% [$P = 0.035$], respectively), while the prevalence of diabetes mellitus type 2 in both groups was not different ($P = 0.345$; Table 1).

3.2 | CMI prevalence and number

The prevalence of CMI was 11.8% in DS overall compared to 2.6% in young euploid controls (OR: 4.73; $P = 0.031$; Table 1). In DS, CMI

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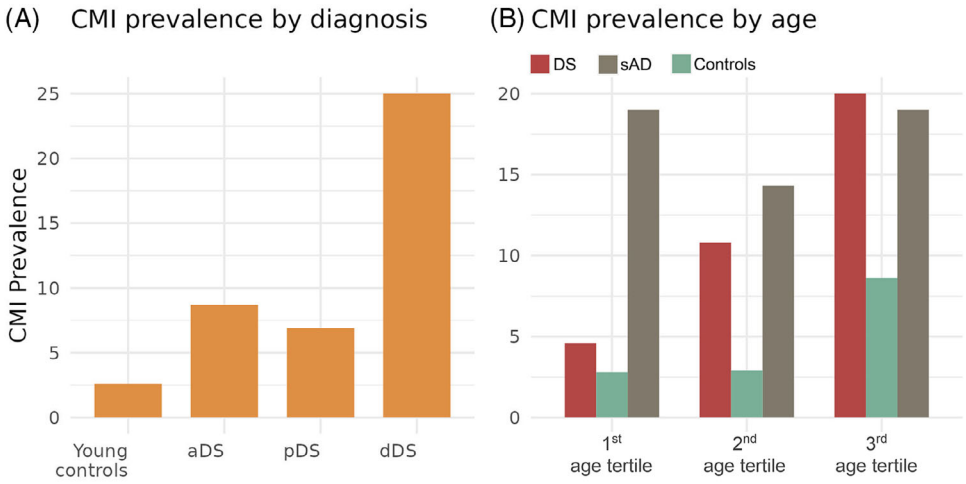

FIGURE 2 CMI prevalence along the AD clinical continuum in DS and with age in all study groups. AD, Alzheimer's disease; aDS, asymptomatic Down syndrome; CMI, cortical microinfarcts; dDS, Down syndrome-related Alzheimer's disease dementia; DS, Down syndrome; pDS, prodromal Down syndrome-related Alzheimer's disease; sAD, symptomatic Alzheimer's disease

prevalence increased along the AD continuum from 8.7% in aDS and 6.9% in pDS to 25% in dDS (aDS vs. dDS, OR: 3.48; $P = 0.012$; Table 1, Figure 2A). In euploid individuals, the prevalence of CMI was 10.0% in old controls and 17.5% in symptomatic sporadic AD (20.9% in pAD and 10% in dAD; OR: 1.74, $P = 0.543$; Table 1). The average number of CMI per participant with CMI was nominally higher in DS than in controls (3.1 vs. 1.0, d = 0.570, $P = 0.132$) and sporadic AD (3.1 vs. 2.0, d = 0.340, $P = 0.866$).

3.3 | CMI prevalence and number with age

We found that CMI prevalence and number increase with age in DS ($P = 0.027$ and $P < 0.001$, respectively), but not in AD ($P = 0.940$ and $P = 0.977$, respectively) or euploid controls ($P = 0.341$ and $P = 0.348$, respectively). Figure 2B shows the progression of CMI prevalence with age. For visualization purposes only, participants of each study group were divided into age tertiles.

3.4 | CMI topography

We identified 74 CMI in 23 adults with DS, mainly in posterior regions and predominantly in the parietal lobes. In euploid participants, we found 22 CMI in 11 sporadic AD patients and 5 CMI in 5 controls, predominantly distributed along parasagittal lines in frontoparietal regions (Figure 3).

3.5 | CMI relationship with sex, *APOE* haplotype, and vascular risk factors in DS

In DS, lacunes and cortico-subcortical infarcts were more prevalent among participants with CMI than in those without CMI ($P = 0.026$ and $P = 0.004$, respectively). A trend toward a higher prevalence of WMH (Fazekas ≥ 2) was also observed in participants with CMI ($P = 0.054$). We found no associations of CMI presence with lobar/infratentorial microbleeds, superficial siderosis, sex, *APOE* haplotype, arterial hypertension, diabetes mellitus type 2, or dyslipidemia (Table 2).

3.6 | CMI relationship with fluid AT(N) biomarkers, vascular neuroimaging findings, and cognitive performance in DS

Fluid amyloid and tau biomarkers were not associated with CMI presence in the overall DS sample or each of the three clinical subgroups. Plasma NfL concentration was higher in the overall sample of DS participants with CMI than those without ($P = 0.044$), but such difference was not observed within each stage of the AD clinical continuum (Table 2).

We found no differences in neuropsychological scores between participants with and without CMI (mild and moderate ID analyzed separately; Table 2).

The relationship of CMI number with demographic data, neuroimaging findings, fluid biomarkers, and neuropsychological data in DS and sporadic AD is summarized in Table S4 in supporting information. Additionally, we analyzed the relationship between the volume of CMI and vascular neuroimaging findings, fluid AT(N) biomarkers, and cognitive scores in DS. These results are summarized in Table S5 in supporting information.

The relationship of CMI presence to demographic data, neuroimaging findings, fluid biomarkers, and neuropsychological data in sporadic AD and euploid controls is summarized in Table S6 in supporting information.

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TABLE 2 Cortical microinfarct's relationship with demographic data, neuroimaging findings, fluid biomarkers, and neuropsychological data in DS.

	Down syndrome			
	CMI absent (*N* = 172)	CMI present (*N* = 23)	Effect size	*P* value
Demographics				
Age, years	43.9 [32.3;50.2]	49.9 [41.6;54.9]	RB: −0.17	0.016[a]
Sex (female)	43.6%	34.8%	OR: 0.45	0.075[b]
APOE ε4 +	19.3%	19.0%	OR: 0.99	1.000[b]
APOE ε2 +	11.2%	4.8%	OR: 0.40	0.703[b]
hypertension	2.3%	0.0%	OR: 0	1.000[b]
Dyslipidemia	18.7%	22.7%	OR: 1.28	0.773[b]
D. Mellitus 2	2.9%	4.5%	OR: 1.58	0.521[b]
Neuroimaging findings				
Lobar microbleeds	26.0%	36.4%	OR: 1.62	0.316[b]
Superficial siderosis	5.4%	13.6%	OR: 3.68	0.055[b]
Probable CAA	19.5%	31.8%	OR: 1.92	0.262[b]
WMH (Fazekas≥2)	2.9%	13.0%	OR: 4.94	0.054[b]
Lacunes	6.4%	21.7%	OR: 4.02	0.026[b]
Cortico-subcortical Infarcts	1.7%	17.4%	OR: 11.57	0.004[b]
CSF and plasma biomarkers				
CSF Aβ40	11.8 ± 4.2	9.9 ± 3.1	D: 0.45	0.078[c]
CSF Aβ42	0.7 [0.5;0.9]	0.6 [0.4;0.9]	RB: 0.88	0.343[a]
CSF Aβ42/40	0.1 [< 0.1;0.1]	0.1 [0.1;0.1]	RB: 0.82	0.961[a]
CSF pTau	4.2 [2.1;10.7]	5.2 [3.4;10.7]	RB: 0.67	0.515[a]
Plasma pTau	1.4 [0.9;2.3]	2.4 [1.1;3.7]	RB: 0.73	0.247[a]
CSF NfL	0.5 [0.2;0.7]	0.9 [0.5;1.3]	RB: 0.66	0.056[a]
Plasma NfL	1.2 [0.7;1.2]	1.9 [1.0;3.4]	RB: 0.67	0.045[a]
NPS evaluation				
DS-mild ID (*N* = 54)				
CAMCOG-DS	83.8 ± 7.6	86.3 ± 13.8	D: −0.27	0.650[c]
mCRT	36.0 [32.5;36.0]	36.0 [36.0;36.0]	RB: 0.27	0.786[a]
DS-moderate ID (*N* = 87)				
CAMCOG-DS	63.5 [54.2;72.8]	69.0 [57.0;72.0]	RB: 0.39	0.511[a]
mCRT	33.0 [24.0;35.0]	28.5 [23.0;34.0]	RB: 0.62	0.696[a]

Note: Data presented as: %, median [interquartile range] or mean ± standard deviation. CSF Aβ40 and CSF Aβ42 expressed in 0.10^3pg/mL; CSF and plasma p-tau expressed in 0.10^1pg/mL; CSF NfL expressed in 0.10^3pg/mL and plasma NfL expressed in 0.10^1pg/mL. Not all subjects in each group have data on *APOE* haplotype, hypertension, dyslipidemia, D. mellitus 2, CSF and plasma biomarkers, and cognition. The percentage in the table indicates the prevalence of each variable among those subjects with available data (Table S2 in supporting information).

Abbreviations: aDS, asymptomatic Down syndrome; Aβ, amyloid beta; *APOE*, apolipoprotein E; CAMCOG-DS, Cambridge Cognitive Examination for Older Adults with down Syndrome (total score); CSF, cerebrospinal fluid; CMI, cortical microinfarcts; D, Cohen d coefficient; DS, Down syndrome-related Alzheimer's disease dementia; D. mellitus 2, diabetes mellitus type 2; ID, intellectual disability; IQR, interquartile range; MMSE, Mini-Mental State Examination; mCRT, modified Cued Recall Test (total immediate recall score); NfL, neurofilament light; OR, odds ratio; pDS, prodromal Down syndrome-related Alzheimer's disease; p-tau, phosphorylated tau 181; RB, rank-biserial coefficient; SD, standard deviation.

[a]Mann–Whitney test.

[b]Fisher exact test.

[c]*t* test.

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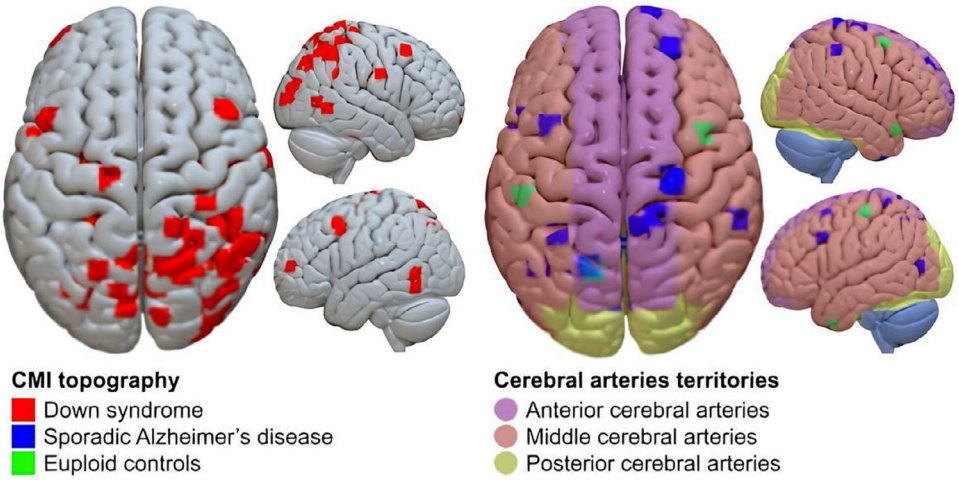

FIGURE 3 Topographic distribution of cortical microinfarcts. CMI, cortical microinfarcts

4 | DISCUSSION

This is the first study to assess CMI in adults with DS and their association with age, sex, *APOE* haplotype, vascular risk factors, AD clinical continuum, fluid AT(N) biomarkers, other vascular neuroimaging findings, and cognition. We showed that the CMI prevalence in DS increases with age and along the AD clinical continuum. In this population, CMI are predominantly located in the parietal lobes and are associated with other ischemic neuroimaging findings, namely lacunes, large cortico-subcortical infarcts, and WMH. However, they seem to be unrelated to vascular risk factors or hemorrhagic CAA manifestations, that is, lobar micro or macrobleeds and superficial siderosis in our sample.

We provide the first assessment of CMI prevalence in DS. We found a higher CMI prevalence in adults with DS compared to controls. In DS, CMI prevalence increased along the AD clinical continuum. The CMI prevalence in DS with prodromal AD and AD dementia was similar to that in sporadic symptomatic AD despite the lower vascular risk factors in DS, suggesting a higher contribution of CAA, which has been shown to be more prevalent in genetically determined AD than in sporadic AD.[14] In euploid controls > 60 years, CMI prevalence was similar to that of other studies in the general population.[7,9,12,37–39] However, studies in cohorts with a high burden of cerebrovascular disease and vascular risk factors[7,9,12,37–40] found a higher CMI prevalence in sporadic AD than we observed in our study, possibly due to the lower prevalence of cerebrovascular disease and vascular risk factors among our cognitively unimpaired controls.

The distribution of CMI in DS and euploid participants seemed to differ. In DS, CMI were mostly concentrated in the parietal lobes, while in euploid participants they were predominantly distributed along the parasagittal lines in the frontoparietal regions, resembling watershed areas. These differences might reflect distinct underlying mechanisms of CMI genesis in DS and euploid participants. In DS, the ubiquitous brain amyloidosis that leads to a higher CAA prevalence than in the general population is the most likely cause of CMI.[14] Yet, we observed no associations between CMI and classic CAA hemorrhagic lesions such as microbleeds or superficial siderosis. Instead, we found CMI associated with other ischemic neuroimaging findings, namely lacunes, cortico-subcortical infarcts, and WMH. Recently, Gokcal et al.[41] have also found an association of CMI with WMH and lacunes in CAA. However, the relationship of CMI with CAA hemorrhagic manifestations remains controversial. While studies have shown associations of CMI with cerebral microbleeds[10] and superficial siderosis,[42] van den Brink et al.[12] reported a lack of relationship between CMI and hemorrhagic findings in CAA. A recent neuropathological study has shown that microbleeds and CMI likely result from two different pathological mechanisms in CAA.[11] This study has also shown that, while the number of microbleeds detected on ex vivo 3T-MRI closely matches the number of microbleeds detected in histopathology, the number of CMI is largely underestimated in neuroimaging studies compared to neuropathology analysis.[11] Therefore, the lack of association between these lesions in our study could be explained by a combination of differences in their underlying pathology and in the sensitivity of in vivo MRI in detecting microinfarcts and microbleeds.

Previous studies have shown CMI to be associated with brain hypoperfusion, mostly caused by carotid stenosis, which is rare in DS, given the low prevalence of atherosclerosis in this population.[8,43] Nevertheless, people with DS often present with arterial hypotension,[44] which could lead to brain hypoperfusion and be accounted as a potential cause of CMI in this population.[45] However, studies have shown that, in the context of brain hypoperfusion, CMI are distributed in arterial watershed zones,[8,45,46] while in our group of adults with DS, CMI are concentrated in the parietal lobes. Also, the role of neuroinflammation in CMI genesis is not yet well established. A recent neuropathology study found activated macrophages and astrocytes in chronic CMI, but not in acute and subacute lesions, suggesting that neuroinflammation might be more of a secondary response to CMI rather than a primary causative factor.[47]

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In DS, we found no CMI association with fluid amyloid or tau biomarkers. Although previous studies reported reduced CSF Aβ42 levels in subjects with acute CMI,[48] data on the relationship between chronic CMI and fluid AT(N) biomarkers are lacking. In sporadic CAA, reduced CSF Aβ42 and Aβ40 concentrations have been reported.[49] However, no association between CAA (defined by the fulfillment of the modified Boston criteria) and CSF Aβ40 concentrations have been observed (neither in sporadic nor in genetically determined forms of AD).[14] Therefore, in AD-related CAA, core AD fluid biomarkers are not good predictors of in vivo CAA diagnosis, and we are still lacking good biomarkers for CAA beyond the manifestations found in MRI.

The main strength of our work is the large, well-characterized, and population-based cohort of adults with DS with clinical and multimodal AD biomarkers, allowing us to analyze the relationship of CMI with the AD clinical continuum, AT(N) biomarkers, vascular risk factors, and other neuroimaging findings. Despite basing our analysis on well-established criteria for visual CMI detection on 3T-MRI, the low sensitivity of in vivo neuroimaging for detecting CMI compared to neuropathology limits our study. CMI detected by in vivo MRI reflect only a fraction of the total CMI burden.[11] The low rate of CMI detection through in vivo 3T-MRI limits the statistical analysis to a binary approach according to the presence or absence of CMI, missing the nuances of CMI load on the correlations with neuroimaging and fluid biomarkers and neuropsychological evaluation. Also, the lack of DWI, T2w, and FLAIR sequences for all subjects precluded the analysis of acute CMI, limiting our study to chronic CMI. Future studies with larger sample sizes and more sensitive methods for detecting CMI in vivo would improve our understanding of the relationship of these lesions to other biomarkers. Also, despite the intensive training of the study's CMI rater at the UMC Utrecht, the lack of a second rater for the sample included in the study is a limitation of our work. Additionally, the imbalance in sample size between participants with prodromal sporadic AD and AD dementia, along with the limited age range in this group, constrains our analysis of the age-related prevalence of CMI in this subset of the study population. Last, the presence of motion artifacts in a population with intellectual disability and cognitive decline is inevitable and decreases the sensitivity of visual analysis for detecting CMI. Therefore, despite subjects' inclusion based on the MRI quality, some degree of motion artifact had to be tolerated to ensure sufficient sample size.

In conclusion, our study in adults with DS showed that a subgroup of individuals with dementia have cortical microinfarcts predominantly located in the parietal lobes related to other ischemic but, seemingly, not to hemorrhagic neuroimaging findings of CAA and might select a subgroup of individuals a non-hemorrhagic CAA imaging phenotype.

AUTHOR CONTRIBUTIONS

Mateus Rozalem Aranha and Juan Fortea conceived and designed the study. Victor Montal, Jordi Pegueroles, Alexandre Bejanin, Maria Carmona-Iragui, Laura Videla, Lucia Maure Blesa, Bessy Benejam, Sílvia Valldeneu, Isabel Barroeta, Susana Fernández, Laia Ribas, Daniel Alcolea, Sofía González-Ortiz, Núria Bargalló, Rafael Blesa, and Alberto Lleó acquired and interpreted the data. Mateus Rozalem Aranha performed the statistical analysis. Mateus Rozalem Aranha and Juan Fortea drafted the manuscript, which all authors critically reviewed for important intellectual content.

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CONFLICT OF INTEREST STATEMENT

DA reports receiving personal fees for advisory board services and/or speaker honoraria from Fujirebio-Europe, Roche, Nutricia, Krka Farmacéutica, Grifols, and Esteve outside the submitted work. AL has served as a consultant or on advisory boards for Fujirebio-Europe, Roche, Biogen, Grifols, Novartis, Eisai, Lilly, and Nutricia, outside the submitted work. JF reports serving on the advisory boards, adjudication committees, or receiving speaker honoraria from Roche, NovoNordisk, Esteve, Biogen, Laboratorios Carnot, Adamed, LMI, Novartis, Lundbeck, Roche, AC Immune, Alzheon, Zambon, Lilly, Spanish Neurological Society, T21 Research Society, Lumind foundation, Jérôme-Lejeune Foundation, Alzheimer's Association, National

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Institutes of Health USA, and Instituto de Salud Carlos III. DA, AL, and JF report holding a patent for markers of synaptopathy in neurodegenerative disease (licensed to ADx, EPI8382175.0). MRA has provided paid consultancy for Veranex. MRA is a partner and director of production at Masima-Soluções em Imagens Médicas LTDA. No other competing interests were reported. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

The authors may share de-identified data that underlie the results reported in this article. Data will be available upon receipt of a request detailing the study hypothesis and statistical analysis plan. All requests should be sent to the corresponding authors. The steering committee of this study will discuss all requests and decide, based on the novelty and scientific rigor of the proposal, whether data sharing is appropriate. All applicants will be asked to sign a data access agreement.

CONSENT STATEMENT

All participants and/or their legally authorized representatives gave written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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