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Cortical thinning 3 years after ischaemic stroke is associated with cognitive impairment and *APOE* ε4

Mohamed Salah Khlif [a,b], Natalia Egorova-Brumley [b,c], Laura J. Bird [d], Emilio Werden [b], Amy Brodtmann [a,b,e,f,*]

[a] Cognitive Health Initiative, Central Clinical School (CCS), Monash University, Melbourne, VIC 3004, Australia
[b] The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, VIC 3052, Australia
[c] Melbourne School of Psychological Sciences, University of Melbourne, Parkville, VIC 3010, Australia
[d] Turner Institute for Brain and Mental Health, Monash University, Clayton, VIC 3800, Australia
[e] Eastern Cognitive Disorders Clinic, Box Hill Hospital, Monash University, Box Hill, VIC 3128, Australia
[f] Department of Neurology, Royal Melbourne Hospital, Parkville, VIC 3052, Australia

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ABSTRACT

Cortical thinning has been described in many neurodegenerative diseases and used for both diagnosis and disease monitoring. The imaging signatures of post-stroke vascular cognitive impairment have not been well described. We investigated the trajectory of cortical thickness over 3 years following ischaemic stroke compared to healthy stroke-free age- and sex-matched controls. We also compared cortical thickness between cognitively normal and impaired stroke survivors, and between *APOE* ε4 carriers and non-carriers.

T1-weighted MRI and cognitive data for 90 stroke survivors and 36 controls from the Cognition And Neocortical Volume After Stroke (CANVAS) study were used. Cortical thickness was estimated using FreeSurfer volumetric reconstruction according to the Desikan-Killiany parcellation atlas. Segmentation inaccuracies were manually corrected and infarcted ipsilesional vertices in cortical thickness maps were identified and excluded using stroke lesion masks traced a-priori. Mixed-effects regression was used to compare cortical thickness cross-sectionally between groups and longitudinally between timepoints.

Healthy control and stroke groups did not differ on demographics and most clinical characteristics, though controls were less likely to have atrial fibrillation. Age was negatively associated with global mean cortical thickness independent of sex or group, with women in both groups having significantly thicker cortex. Three months post-stroke, cortical thinning was limited and focal. From 3 months to 3 years, the rate of cortical thinning in stroke was faster compared to that in healthy controls. However, this difference in cortical thinning rate could not survive family-wise correction for multiple comparisons. Yet, cortical thinning at 3 years was found more spread especially in ipsilesional hemispheres in regions implicated in motor, sensory, and memory processing and recovery. The cognitively impaired stroke survivors showed greater cortical thinning, compared to controls, than those who were cognitively normal at 3 years. Also, carriers of the *APOE* ε4 allele in stroke exhibited greater cortical thinning independent of cognitive status.

The temporal changes of cortical thickness in both healthy and stroke cohorts followed previously reported patterns of cortical thickness asymmetry loss across the human adult life. However, this loss of thickness asymmetry was amplified in stroke. The post-stroke trajectories of cortical thickness reported in this study may contribute to our understanding of imaging signatures of vascular cognitive impairment.

1. Introduction

Significant alterations in cortical thickness have been identified in many neurodegenerative disorders especially Alzheimer's disease. (Gupta, 2019; Racine, 2018) Cortical thickness is used, as a biomarker correlating with cognitive performance, (Cheng, 2018; Tuladhar, 2015) to identify mild cognitive impairment (MCI) subtypes, (Machulda, 2020) to follow the clinical progression of diseases such as Parkinson's

* Corresponding author at: Central Clinical School (CCS), Monash University, 99 Commercial Road, Melbourne, VIC 3004, Australia.
E-mail address: amy.brodtmann@monash.edu (A. Brodtmann).

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disease (Zarei, 2013) or the transition from MCI to Alzheimer's disease, (Cheng, 2018) and to assess the effectiveness of interventional and rehabilitation procedures targeting improvements in sensory, motor, and cognitive functions. (Pundik, 2018; Jiang, 2016).

A third of stroke survivors develop dementia within the first year and the incidence of post-stroke dementia is ~ 50 times higher than in general public. (Pendlebury and Rothwell, 2019) Multiple cognitive functions may become impaired, though slower information processing and executive dysfunction tend to be predominant features of vascular cognitive impairment. (Al-Qazzaz, 2014; Cumming et al., 2013) Imaging markers including hippocampal atrophy (Khlif, 2021) and brain parenchymal volume loss (Bu, 2021) have been associated with cognitive/functional outcomes following ischaemic stroke. We reported lower total brain volume 3 years post-stroke in survivors who were cognitively impaired (CI) at 3 months. (Brodtmann, 2021) We also reported greater degeneration of structural brain networks in subacute stroke, associated with attention, executive function, language, memory, and visuospatial function impairment. (Veldsman, 2020; Veldsman, 2020) Moreover, we found carriers of the *APOE* ε4 allele to have worse verbal memory performance and reduced entorhinal volume 1-year post-stroke. (Werden, 2019).

Assessment, especially longitudinal, of cortical thickness post-stroke is limited and rarely a stroke-free control group is included. In patients with left middle-cerebral-artery stroke, significantly thinner ipsilesional temporal lobe was associated with greater language impairment 3 to 24 months post-stroke. (Daria, 2019) In acute (≤3-days) brainstem ischaemic stroke, significant bilateral thickness decreases were found compared to healthy controls. (Chen, 2021) Remote focal cortical thinning and microstructural damage in white matter tracts connecting affected distant cortices to acute infarcts have also been reported. (Duering, 2015) In a study of patients imaged hyper-acutely (<3-hours) and again 3 months post-stroke, we demonstrated no change in global average thickness, but found increases in cortical thickness in contralesional paracentral, superior-frontal, and insular regions, (Brodtmann, 2012) corroborating the consistent involvement of contralesional motor areas reflecting cortical remodelling. (Calautti and Baron, 2003) We also reported no significant changes 1-year post-stroke in both contralesional and ipsilesional average cortical thickness. (Brodtmann, 2020).

Cortical thinning after stroke remains largely undescribed. In this study, we sought to investigate cross-sectional and longitudinal differences in cortical thickness over 3 years between healthy individuals and ischaemic stroke survivors. The inclusion of the control group facilitated the differentiation between normal-aging effects and potential pathological neurodegeneration. We also compared cortical thickness within stroke between survivors who were CI and those who were cognitively normal (CN), and we investigated the influence of *APOE* ε4 allele carriage on cortical thinning following ischaemic stroke.

2. Materials and methods

2.1. Participants

Participants were sampled from the Cognition And Neocortical Volume After Stroke (CANVAS) study. (Brodtmann, 2014) First-ever and recurrent stroke survivors were recruited excluding those with haemorrhagic stroke, transient-ischaemic-stroke (TIA), and significant medical comorbidities precluding survival in the study. Age- and sex-matched healthy controls with no history of stroke or TIA were also recruited. No participants had a history of pre-existing dementia, intercurrent delirium, neurological disorders, major psychiatric illness, or substance abuse. Ethical approval was granted by involved hospitals' Human Research Ethics Committees and all participants provided written informed consent in accordance with the Declaration of Helsinki.

2.2. MRI acquisition

MRI data available for 89 stroke participants (including six with recurrent stroke) and 36 controls were included in analyses assessing and comparing cortical thickness at 3-months and 3-years timepoints. An additional stroke participant who missed the 3-months assessment was included in the 3-years analyses. Whole brain images were acquired on a Siemens 3T Trio scanner: 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE) (160 sagittal slices, 1-mm isotropic, repetition time/TR = 1900 ms, echo time/TE = 2.6 ms, inversion time/TI = 900 ms, flip angle = 9°) and 3D high-resolution T2-weighted fluid-attenuated inversion recovery (FLAIR) (160 1-mm sagittal slices, TR = 6000 ms, TE = 380 ms, TI = 2100 ms, 120° flip angle).

2.3. MRI segmentation

Cortical reconstruction of T1-weighted scans was performed using longitudinal processing (Reuter, 2012) in FreeSurfer (version 6.0) which has been shown to be reliable in identifying regional cortical thickness correlates of cognitive task performance, (Dickerson, 2008) and procedures for cortical thickness measurement in FreeSurfer have been validated against histological analysis (Rosas, 2002) and manual measurements. (Salat, 2004).

FreeSurfer segmentation included motion correction, removal of non-brain tissue, automated Talairach transformation, segmentation of the subcortical white matter and deep grey matter structures, intensity normalization, tessellation of the grey matter-white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the grey/white and grey/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class.

Once the cortical models were completed, several deformable procedures were performed for further data processing and analysis including surface inflation, registration to a spherical atlas based on individual cortical folding patterns to match cortical geometry across participants, parcellation of the cerebral cortex into units with respect to gyral and sulcal structure, and creation of a variety of surface-based data including maps of curvature and sulcal depth. This method uses both intensity and continuity information from the entire three-dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the grey/white boundary to the grey/CSF boundary at each vertex on the tessellated surface. The cortical maps were created using spatial intensity gradients across tissue classes and are therefore not reliant on absolute signal intensity. The produced maps are not restricted to the voxel resolution of the original data (i.e., 1-mm) but can detect sub-millimeter differences between analysed groups. In this study, FreeSurfer parcellation of cortical regions was based on the Desikan-Killiany atlas (see Supplementary Fig. 1).

2.4. Quality control

T1-weighted images segmented by FreeSurfer were checked for hard and soft failures. Three stroke participants were excluded due to hard failures (not included in final reported sample size). Soft failures, due to generally high in-scanner motion, were checked for improper skull-stripping, Talairach transform issues, significant surface defects, and inaccurate pial surfaces. Given the nature of this investigation, blinded manual editing of the base pial surfaces from all scans was performed to remove any skull, dura mater, and/or blood vessels. This step was followed by rerunning base then longitudinal data. Manual checking of longitudinal data showed that the base pial edits and corrections were fully and accurately reflected in the longitudinal pial surfaces (see exemplars in Supplementary Fig. 2).

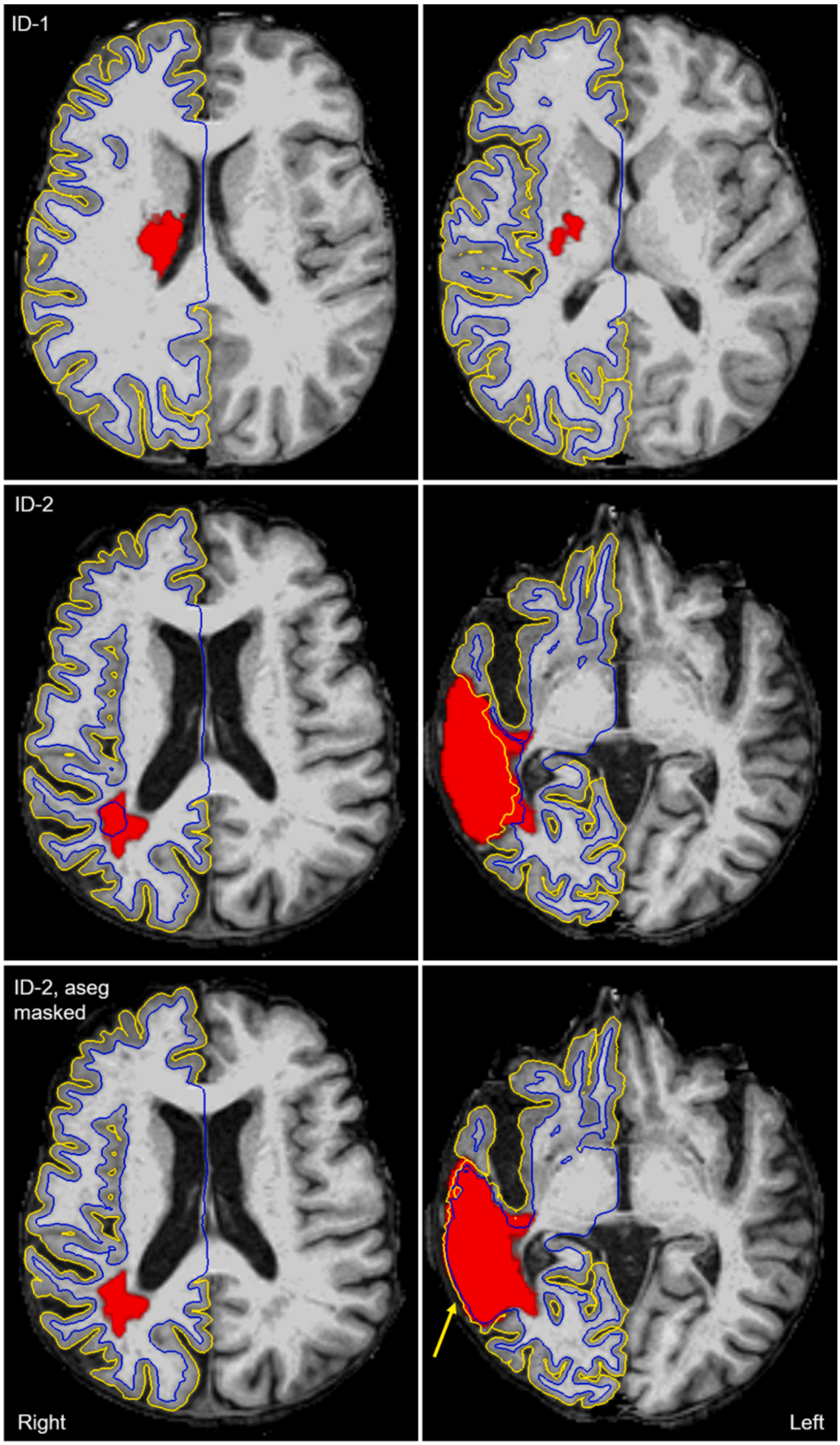

Fig. 1. Effects of stroke lesion masking on FreeSurfer determination of pial surfaces. Small thickness values (yellow arrow) are still produced after 'aseg' modification based on recommendations from prior study, (Ozzoude, 2020) thus requiring exclusion of infarcted vertices post-FreeSurfer processing (ID-1: pial surfaces identified by FreeSurfer for MRI of a participant with subcortical lesion (red); ID-2: pial surfaces for a second participant with both cortical and subcortical lesions with no modifications to 'aseg'; ID-2 aseg masked: pial surfaces after 'aseg' modifications).

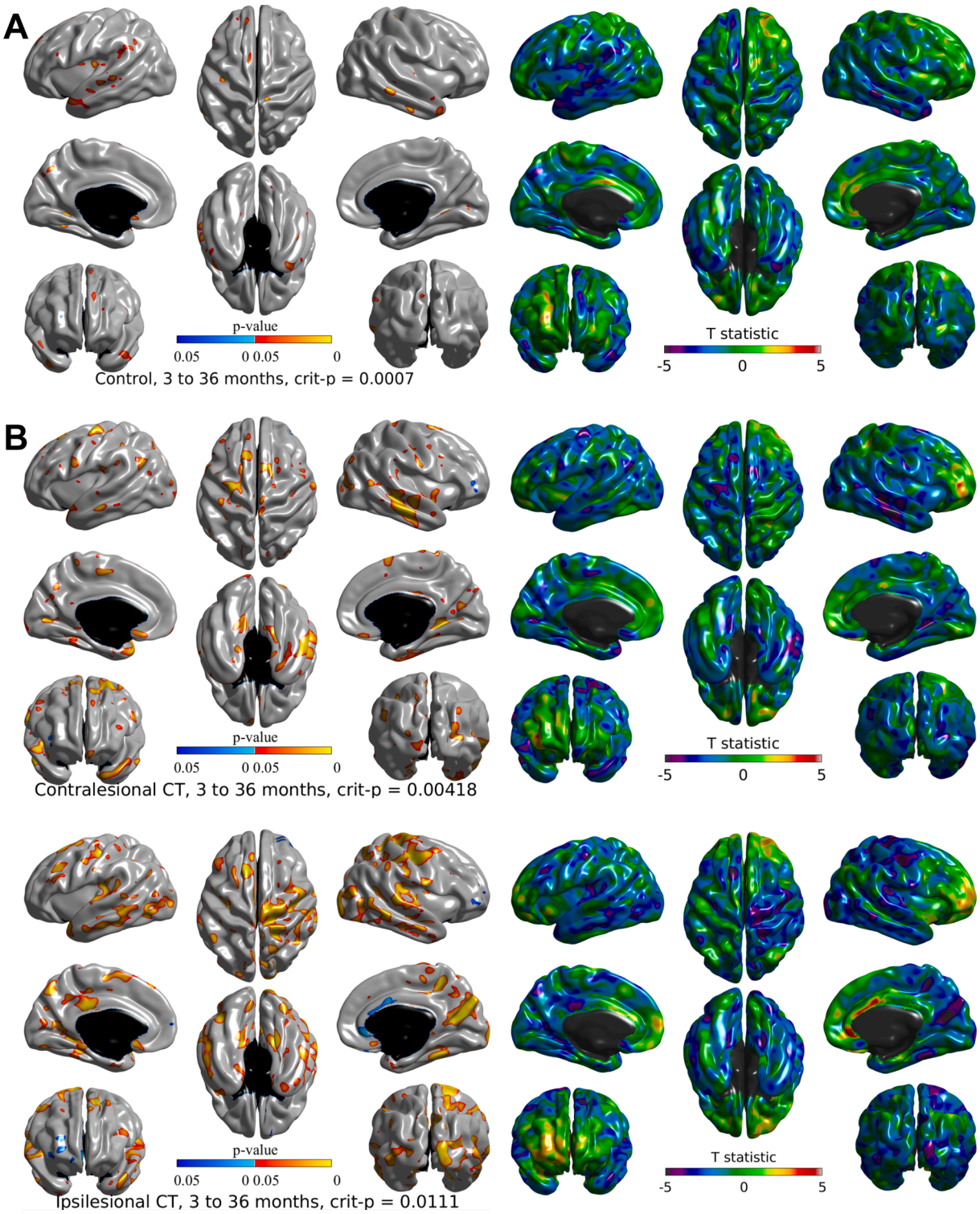

Fig. 2. Cortical thinning over time – Cortical thinning from 3 months to 3 years for healthy controls (**A**) on left and right hemispheres and for stroke survivors (**B**) on contralesional and ipsilesional hemispheres (left is left). The *T*-statistic maps (right column) show all cortical thickness changes while the p-maps (range rescaled to [0–0.05]) show only significant changes where $p \leq$ crit-p (crit-p = critical p-value determined by adaptable two-stage FDR correction, CT = cortical thickness). P and T-statistic maps in all figures were plotted using 'SurfStatView' from surfstat (https://www.math.mcgill.ca/keith/surfstat/).

2.5. Stroke lesion tracing and co-registration to subjects average template

Cortical thickness estimation in stroke is particularly challenged by the presence of distorting brain lesions. This is more so for cortical lesions and subcortical lesions stretching to cover portions of cortical grey matter causing distortions to the anatomy of the cortex. Corrective procedures have been proposed (Ozzoude, 2020) to enhance FreeSurfer estimation of cortical thickness in stroke. The corrective procedures involved three modifications to FreeSurfer reconstruction stages: 1) replacing FreeSurfer skull stripped mask (brainmask.mgz) by an improved skull stripped mask during '-autorecon1′ run; 2) integration of lesion masks (assigned a 77 label in aseg.presurf.mgz) during

'-autorecon2' run; and 3) completing the final '-autorecon2-noaseg -autorecon3' run using the modified brainmask.mgz and aseg.presurf.mgz as input. For stage 1, we chose to manually edit the cortical ribbon for all participants. Fig. 1 shows exemplars of output after FreeSurfer 2nd and 3rd reconstruction stages with and without lesion mask integration. It became clear that the integration of lesion masks does not solve the problem with cortical anatomical distortion as very small thicknesses at the cortical lesion sites are still produced as part of FreeSurfer final thickness maps.

We edited the thickness maps post-FreeSurfer and excluded all infarcted vertices using stroke lesion masks traced *a-priori* from FLAIR images, skull-stripped using BET (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/), then registered to 'fsaverage' group template. Stroke lesions were traced by our imaging analyst (MSK) then cross-checked by a stroke neurologist (AB). The volumetric lesion masks traced using FLAIR images were projected onto the 'fsaverage' template using the registration details obtained in the previous step (see FreeSurfer code below for obtaining < lh/rh >.lesion.mgh maps). Finally, the non-zero entries in the binary co-registered lesion masks were used to assign 'NaN' (missing) values to respective vertices in the thickness maps (<lh/rh >.thickness.mgh) which were already in the 'fsaverage' template space. There were 18 stroke participants at both timepoints with subcortical infarcts extending to the cortical grey matter layer (see Supplementary Fig. 3).

2.6. Spatial smoothing of cortical thickness maps

Spatial smoothing is a common procedure in vertex-wise cortical thickness analysis. Such procedure can increase the signal-to-noise ratio, suppress the influence of structural variability within/across subjects, and increase normality of data strengthening parametric inference. Concordant to several studies, (Ozzoude, 2020; Winkler, 2018) we spatially smoothed cortical thickness using a 10-mm FWHM (full-width-half-maximum) kernel.

2.7. Sociodemographic and clinical information

We collected information about age, years-of-education, stroke and dementia family history, obesity (BMI $\geq$ 30 kg/m^2), smoking ($\geq$1cigarette/day), alcohol consumption (high > 14 standard drinks/week); history of depression, hypertension, type-2 diabetes mellitus (T2DM), and hypercholesterolaemia and atrial fibrillation (AF) based on physician diagnosis or medication use. We compiled data about stroke severity (National Institute of Health Stroke Scale – NIHSS) and Oxfordshire stroke classes. We used the modified Rankin Scale (mRS) to estimate neurological disability and Charlson Comorbidity Index (CCI) to estimate general medical comorbidity. Venous blood was drawn for *APOE* allele determination: ε4 carriers or non-carriers.

2.8. Neuropsychological testing

Cognitive assessment included a comprehensive battery of neuropsychological tests described in CANVAS protocol. (Brodtmann, 2014) Tests' z-scores were computed using age-appropriate normative values, and pre-morbid-IQ was estimated using National-Adult-Reading-Test (NART). We also screened for anxiety (GAD-7 score) and depression (PHQ-9 score). A cognitive evaluation panel (Brodtmann, 2021) was tasked with assigning a cognitive status (CI, CN, or dementia) to each participant based on cognitive z-scores, mood scores, and information from clinical interviews.

Participants were classified as CN if there was no evidence of cognitive impairment in any of the assessed cognitive domains, particularly attention, memory, language, executive function, and visuospatial function. The CI class comprised participants with z-scores < -1.5 in at least one cognitive domain, without functional decline. A "dementia" classification was allocated for participants with z-score < -1.5 in at least two domains, in addition to functional decline. (Brodtmann, 2021) Twenty-three stroke patients were classified as cognitively impaired at 3 months. At 3 years, this number was reduced to 19. Given the small number of demented stroke survivors (n = 4 at 3 years), these were grouped with the CI participants.

2.9. Statistical analysis

Analyses were completed in MATLAB (R2019b, MathWorks).

2.9.1. Demographic, clinical, and neuropsychological data

Pairwise comparisons between groups were conducted using 1) Two-sample *t*-test (age, NART-IQ, total intracranial volume (TIV) which was measured using FreeSurfer), 2) Fisher exact test (sex, *APOE* ε4, depression, vascular risk factors, cognitive status, NIHSS (mild, 0–7) and mRS (mild, 0–1) severity, Oxfordshire stroke classes, stroke side, stroke recurrence), and 3) Wilcoxon rank sum test (years-of-education, CCI, lesion volume, NIHSS and mRS scores, white matter hyperintensities (WMH) volume adjusted by TIV).

2.9.2. Analysis of cortical thickness

Comparisons of smoothed vertex-wise cortical thickness cross-sectionally between control and stroke cohorts and longitudinally between timepoints were performed using linear mixed-effects random-intercept regression including group (e.g., control vs stroke), timepoint (3-months, 3-years), and group-timepoint interaction with age and sex as covariates (MATLAB model: CT ~ Group*Time + Age + Sex + 1|PID, where CT = cortical thickness and PID = participant identification). Separate comparisons were made between left and right thickness in the control group and counterpart contralesional and ipsilesional thickness in stroke (i.e., left side thickness in controls was compared to ipsilesional thickness in left-sided stroke and to contralesional thickness in right-sided stroke, while right side thickness in controls was compared to ipsilesional thickness in right-sided stroke and to contralesional thickness in left-sided stroke). The same regression model was used for region-wise (vertex-wise thicknesses averaged over cortical regions) comparisons at 3 years. Modelling residuals were checked for normality, auto-correlation, and heteroscedasticity. Outliers were excluded as needed to meet model assumptions; at most three participants were excluded simultaneously.

The non-inclusion of years-of-education and stroke lesion volume (for within-stroke analyses) as covariates in the modelling of cortical thickness was determined by comparing models (with and without these effects) using the MATLAB/Simulated Likelihood Ratio Test (500 replications, 95 % confidence level). Furthermore, WMH volume was linked to age and to cognition in both healthy and neurodegenerative cohorts. In this study, we performed our analyses without correction for WMH given that we also found the WMH volumes to be highly correlated to age beyond any sex, group (control, stroke), cognition (impaired, normal), or timepoint (3-months, 3-years) influence. Checks for collinearity in the regression design matrix revealed relatively high variance inflation factors (VIF) (1.7 for age and 1.8 for WMH) in addition to the joint condition of: a strong condition index of 24 and two high (>0.5) variance decomposition proportions (0.89 for age and 0.93 for WMH), thus constituting potential estimation problems (Belsley et al., 1980; Friendly and Kwan, 2009) Without WMH, the maximum VIF in the design matrix was 1.1.

Within stroke, CN participants were compared to CI participants at 3 years. Similarly, carriers of the *APOE* ε4 allele (comprised of one (5.9 %) ε2/ε4, fifteen (88.2 %) ε3/ε4, and one ε4/ε4 genotypes) among the stroke survivors were compared to non-carriers after further adjustment for cognitive status. Both CI and *APOE* ε4 carriers in stroke were respectively compared to CN and non-*APOE* ε4 carriers among controls. Family-wise corrections for multiple vertex-wise (~300,000 vertices) and region-wise (68 parcellation regions) comparisons were performed using adaptive linear two-stage control for false discovery rate (FDR).

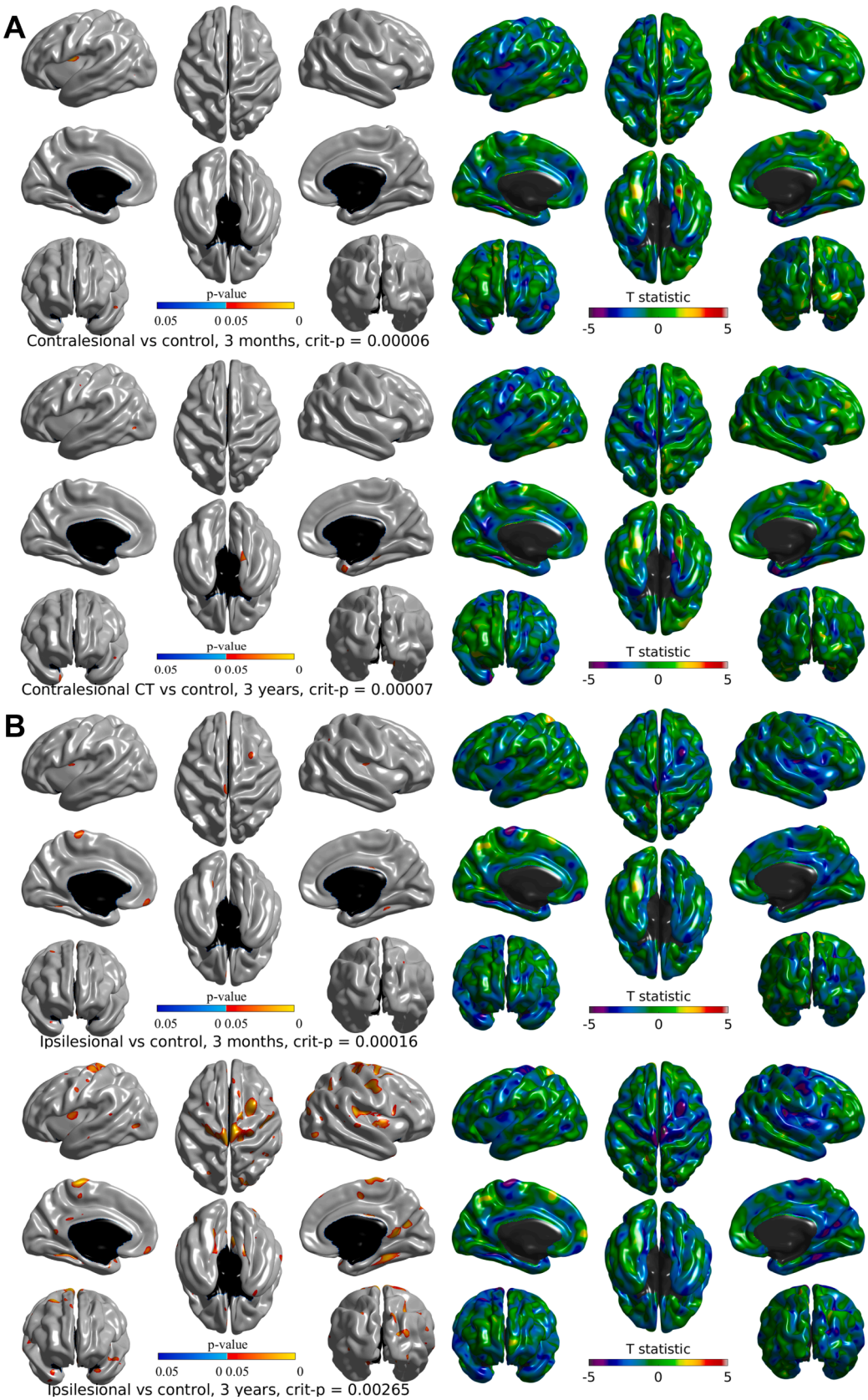

Fig. 3. Cross-sectional comparison of cortical thickness – Contralesional (**A**) and ipsilesional (**B**) cortical thickness differences at 3 months and 3 years between healthy controls and stroke participants. *T*-statistic maps show all cross-sectional cortical thickness differences while p-value maps (range rescaled to [0–0.05]) show only significant differences ($p \leq$ crit-p) following adaptive 2-stage FDR correction.

(Benjamini et al., 2006).

3. Results

We included 89 stroke participants (64 men, age 66.7 ± 12.2 years) and 36 healthy controls (21 men, age 68.9 ± 6.9 years) at 3 months and 90 stroke participants (65 men, age 69.2 ± 12.5 years) at 3 years.

3.1. Demographic and clinical data between stroke and control cohorts

Demographics and vascular risk factors at 3 months post-stroke (post-baseline for controls) are presented in Table 1. There were no significant differences in age and sex, but the stroke group had significantly less years-of-education ($p = 0.0013$) and scored lower on NART-IQ ($p = 0.001$). The two groups did not significantly differ with respect to medical comorbidities, *APOE* ε4 carriage, depression, and vascular risk factors except for AF ($p = 0.023$). Comparisons between healthy controls and stroke survivors based on stroke side are presented in Supplementary Table 1 and comparisons at 3 years were similar to those at 3 months.

3.2. Demographic, clinical and lesion characteristics in stroke at 3 years

CN (n = 71) and CI (n = 19) stroke survivors did not significantly differ in sex, years-of-education, *APOE* ε4 carriage, depression, vascular risk factors, NART-IQ, NIHSS and mRS scores and severity, stroke recurrence, stroke laterality, or stroke Oxfordshire classification (Table 2). However, the CI survivors were significantly older ($p = 0.033$) and had more comorbidities ($p = 0.0018$) and larger stroke lesions ($p = 0.045$). Table 2 also shows that there were no differences between *APOE* ε4 carriers (n = 17) and non-carriers (n = 70) in any of the demographic, clinical, cognitive, or stroke characteristics.

Table 1
Stroke vs control: Comparison of demographics and vascular risk factors between healthy controls and stroke patients at 3 months.

Group	Control	Stroke	P
Number, N	36	89	
Sociodemographic			
Age, years, mean ± SD	68.9 ± 6.9	66.7 ± 12.2	0.21*
Sex, men, no. (%)	21 (58.3)	64 (71.6)	0.15†
Education, years, median (Q1, Q3)	17 (11, 18)	12 (10, 15)	0.0013‡
Clinical			
CCI, median (Q1, Q3)	3 (2, 3)	3 (2, 4)	0.31‡
APOE ε 4, %	8.3	18.0	0.27†
Depression, %	11.1	109.1	>0.99†
Hypertension, %	44.4	55.1	0.33†
Hypercholesterolemia, %	38.9	39.3	>0.99†
Type 2 diabetes mellitus, %	11.1	21.3	0.21†
Atrial fibrillation, %	2.8	18.06	0.023†
Smoking, %	19.420	24.7	0.64†
Alcohol consumption, high, %	16.7	9.0	0.22†
Obesity, %	13.9	25.8	0.16†
Imaging			
TIV (cm^3), mean ± SD	1528 ± 127	1522 ± 165	0.83*
WMH (cm^3) adjusted by TIV, median (Q1, Q3)	2.4 (1, 4.2)	3.7 (1.8, 9.7)	0.017‡
Cognitive			
NART-FSIQ, mean ± SD	118 ± 10	111 ± 11	0.001*

Q1, Q3 = 25th, 75th percentiles, CCI = Charlson comorbidity index, NART-FSIQ = National Adult Reading Tests-Full Scale Intelligence Quotient, SD = standard deviation, TIV = total intracranial volume, WMH = white matter hyperintensities, *Two-Sample t-Test, †Fisher Exact test, ‡Wilcoxon Rank Sum test.

3.3. Effects of age and sex on cortical thickness

Age was negatively associated with global mean cortical thickness ($p < 0.001$) independent of sex or cohort. Female participants in both cohorts had significantly thicker cortex ($p = 0.002$) independent of age. There were no interactions between age and group, age and sex, or sex and cohort in their association with cortical thickness.

3.4. Cortical thinning between 3 months and 3 years

There were no significant interactions between cohorts and timepoints that could survive family-wise multiple comparisons correction. Although cortical thinning in contralesional and ipsilesional hemispheres were numerically larger between timepoints, they were not statistically different from cortical thickness reductions seen in controls, presumably normal aging effect. P-value and *T*-statistic maps for cortical thickness changes between timepoints are shown in Fig. 2.

For healthy controls (Fig. 2A), more significant cortical thinning between timepoints was seen in the left hemisphere, with relatively larger clusters on superior-temporal, middle-temporal, supra-marginal, superior-frontal and precuneus cortices. There were also significant clusters of cortical thinning on the right middle and inferior-temporal lobes. In stroke (Fig. 2B), cortical thinning was anatomically more spread, covering both hemispheres and more cortices including precentral and postcentral, cuneus and precuneus, lateral-occipital cortex, and posterior-cingulate-cortex (PCC). Interestingly, cortical thickness in the right ipsilesional hemisphere increased significantly in the anterior-cingulate-cortex (ACC) as well in the prefrontal cortex.

3.5. Cortical thickness between stroke and control groups at 3 months and 3 years

3.5.1. Contralesional thicknesses

At 3 months, there were couple relatively small clusters where contralesional cortical thickness was smaller compared to that in controls. These clusters were in left insula and superior-temporal area. At 3 years, there were still very limited areas with significant thinning in stroke compared to healthy controls. These areas included left precentral, superior-temporal, and lateral occipital and right parahippocampal and entorhinal cortices (Fig. 3A).

3.5.2. Ipsilesional thicknesses

Significant cortical thinning in the ipsilesional hemispheres was more spread compared to contralesional hemispheres. At 3 months, we found significant ipsilesional cortical thinning involving bilateral insula and fusiform; left paracentral, and medial-orbitofrontal; and right caudal-middle-frontal cortices. At 3 years, there were considerably more and larger clusters showing significant ipsilesional cortical thinning in areas including bilateral insula, precentral, paracentral, caudal-middle-frontal, fusiform, precuneus, superior-temporal, isthmus-cingulate, lateral-occipital, and temporal-pole cortices; left PCC and medial-orbitofrontal; and right superior-frontal cortices (Fig. 3B).

3.5.3. Mean regional cortical thickness

Fig. 4 shows the differences at 3 years between region-wise-based contralesional and ipsilesional cortical thickness in stroke and that in healthy controls. Findings were similar to those described above based on vertex-wise analysis (see also Supplementary Table 2). Between 3 and 36 months, regional cortical thickness in controls was reduced by 0.54 % on average (range: −1.25 % to + 0.14 %). Over the same period, cortical thickness reduction was 0.83 % (range: −1.77 % to + 0.14 %) in

Table 2
Comparison of demographic, clinical, and stroke characteristics for stroke survivors at 3 years: 1) Cognition: impaired vs normal, 2) *APOE* ε4: carriers vs non-carriers.

1) Cognition 2) *APOE* ε4	Normal	Impaired	p	Non-carriers	Carriers	P
Count, n	71	19		70	17	
Sociodemographic						
Age, years, mean ± SD	67.8 ± 12.6	74.3 ± 11.0	0.033*	69.4 ± 12.2	69.1 ± 11.3	0.92*
Sex, men, no. (%)	50(70.4)	15(78.9)	0.57†	50(71.4)	12(70.6)	>0.99†
Education, years,median (Q1, Q3)	13(10,15)	12(8.25,13)	0.11‡	12.5(10,15)	13(9.5,16)	0.94‡
Imaging						
WMH (cm^3),median (Q1, Q3)	4.7(2.4,10.8)	14.3(8,29.8)	0.0011‡	8.1(2.9,15.3)	4.7(1.4,11.3)	0.14‡
Clinical						
CCI, median (Q1, Q3)	3(2,4)	5(4,5.75)	0.0018‡	3(2,4)	4(2,5)	0.42‡
APOE ε4, %	15.9	33.3	0.11†			
Depression, %	11.3	5.3	0.68†	12.9	0	0.20†
Hypertension, %	50.7	68.4	0.20†	52.6	64.7	0.43†
Hypercholesterolemia, %	38.0	42.1	0.79†	40	35.3	0.79†
T2DM, %	19.7	26.3	0.54†	18.6	29.4	0.33†
Atrial fibrillation, %	16.9	21.1	0.74†	20	11.8	0.73†
Smoking, %	22.5	33.3	0.37†	27.5	11.8	0.22†
Alcohol, high, %	8.5	10.5	0.67†	7.1	5.9	>0.99†
Obesity, %	28.2	42.1	0.27†	30	35.3	0.77†
Cognitive						
NART-FSIQ, mean ± SD	112.4 ± 10.4	106.1 ± 12.8	0.083*	111.1 ± 11.3	114.1 ± 9.6	0.31*
Impairment, %				17.1	35.3	0.11†
Stroke Characteristics						
Lesion volume (cm^3)Median (Q1, Q3)	1.4(0.3,5.9)	2.9(1.8,19)	0.045‡	1.9(0.4,12.7)	1.9(0.1,10.9)	0.52‡
NIHSS scoreMedian (Q1, Q3)	2(1,4)	3(2,4)	0.20‡	2(1,4)	3(1,6)	0.71‡
NIHSS severityMild (0–7), %	94.4	84.2	0.16†	95.7	82.4	0.086†
mRS scoreMedian (Q1, Q3)	1(0,1)	1(0,2)	0.29‡	1(0,1)	1(0,1.25)	0.94‡
mRS severityMild (0–1), %	83.1	68.4	0.20†	81.4	76.5	0.73†
Recurrent stroke, %	7.0	5.3	>0.99†	7.1	5.9	>0.99†
Stroke side, right, %	59.2	68.4	0.60†	62.9	52.9	0.58†
Oxfordshire class, n (%)	11	0	0.081†	10	1	0.80†
LACI	(15.5)24	(0)7		(14.3)23	(5.9)6	
POCI	(33.8)36	(36.8)11		(32.9)36	(35.3)10	
PACI	(50.7)0	(57.9)1		(51.4)1	(58.8)0	
TACI	(0)	(5.3)		(1.4)	(0)	

Q1, Q3 = 25th, 75th percentiles; LACI = lacunar infarct, POCI = posterior cerebral infarct, PACI = partial anterior cerebral infarct, TACI = total anterior cerebral infarct, CCI = Charlson comorbidity index, NART-FSIQ = National Adult Reading Tests-Full Scale Intelligence Quotient, SD = standard deviation, SD = standard deviation, T2DM = type 2 diabetes mellitus, *Two-Sample t-Test, †Fisher Exact test, ‡Wilcoxon Rank Sum test.

contralesional stroke cortical regions and 0.86 % (range: −2.67 % to + 0.63 %) in ipsilesional regions.

3.6. Cortical thickness between CI and CN stroke survivors at 3 years

There was no significant vertex-wise difference in cortical thinning between CI and CN stroke participants. However, when compared to CN controls, the CI stroke participants (Fig. 5A) showed more cortical thinning than CN stroke participants (Fig. 5B) in areas such as pre-central, posterior-parietal, PCC, precuneus, insula, and anterior-temporal cortices including the entorhinal cortex; with more bilateral cortical thinning seen in right-sided stroke. Based on region-wise analysis, the right ipsilesional entorhinal cortex in CI stroke participants was found to be thinner ($p = 0.0013$) than its counterpart in CN stroke participants (Fig. 5C).

3.7. APOE ε4 carriers compared to non-carriers at 3 years

There was a significant vertex-wise thinning in the right ipsilesional precentral gyrus in *APOE* ε4 carriers compared to non-carriers in stroke after adjusting for age, sex, and cognitive status (Fig. 6A). Compared to non-carriers (n = 33) in healthy controls (Fig. 6B), *APOE* ε4 carriers in stroke exhibited more patterns of cortical thinning along the right ipsilesional superior-fronto-parietal and insula regions, paracentral, isthmus-cingulate, and entorhinal regions. Stroke ε4-carriers also had thinner contralesional cortices especially in precentral, postcentral, and paracentral areas, although this was found exclusively in the left contralesional hemisphere. That is, significant bilateral thinning for the *APOE* ε4 carriers was seen in right-sided stroke participants. For the left-sided stroke *APOE* ε4 carriers, there was limited cortical thinning in the ipsilesional hemispheres (e.g., medial-orbitofrontal cortex) as well as localised increase in cortical thickness in the ipsilesional postcentral cortex. In stroke *APOE* ε4 non-carriers, very limited thinning was observed in ipsilesional cortices such as precentral, paracentral, and fusiform (Fig. 6C).

4. Discussion

We assessed cortical thickness in stroke survivors cross-sectionally and longitudinally in comparison to age- and sex-matched healthy individuals. We found global mean cortical thickness in both cohorts to be negatively associated with age irrespective of sex. We also found women to have a thicker cortex independent of age. In a large (n = 17075) study of healthy individuals, Frangou et al. (Frangou, 2021) reported that for both sexes, cortical thickness increased between 3 and 10 years of age, decreased steeply during second and third decades of life, then gradually

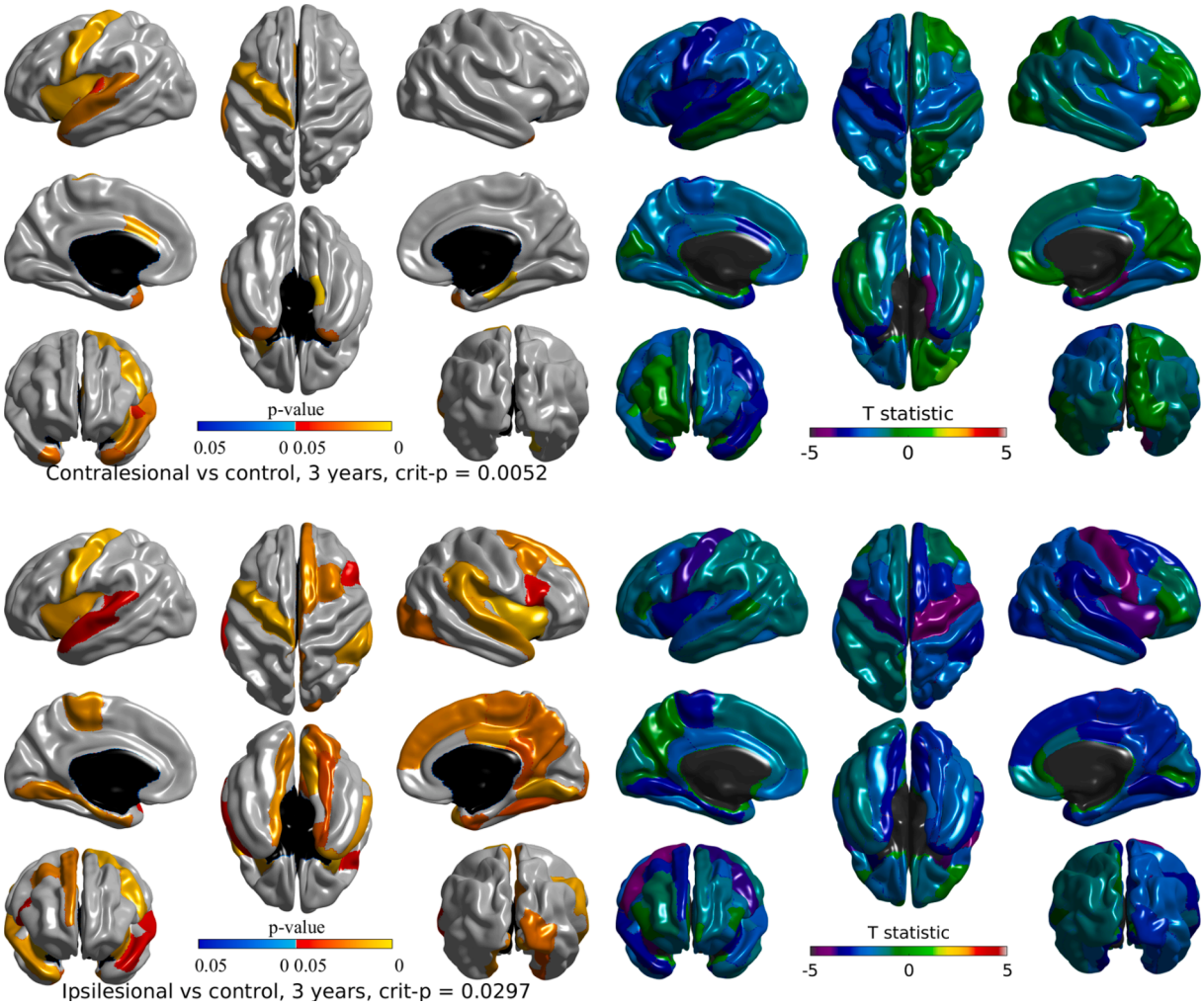

Fig. 4. Comparison of mean regional cortical thickness between control and stroke groups - Cortical areas showing significant thinning 3 years post-stroke based on mean thickness estimation after adaptive 2-stage FDR correction across 68 parcellation regions.

decreased thereafter. During mid-life (30–59 years), however, cortical thinning in men is faster compared to women. This explains our finding of a thinner cortex in men.

4.1. *Cortical thickness changes over 3 years*

The longitudinal changes in cortical thickness in both cohorts can be viewed in association with descriptions of cortical thickness asymmetry loss across the human adult-life. Large studies of normal aging (Kong, 2018; Plessen, 2014; Roe, 2021) reported structural patterns of cortical thickness asymmetry along the fronto-occipital axis. Regions with leftward-asymmetry (left > right) include frontal, postcentral, and superior-parietal cortex, ACC, PCC, and anterior-temporal lobe. Rightward-asymmetry regions include insula, lateral/medial parts of parietal cortex, occipital cortex, and temporal cortex including entorhinal. Cortical thickness asymmetry loss is gradual from early adulthood but is remarkably accelerated from 60 years. Asymmetry loss also follows the fronto-occipital axis yielding faster thinning of the previously thicker cortices. (Roe, 2021) Notably, the alterations in cortical thickness asymmetry are amplified in Alzheimer's disease. (Roe, 2021).

Both stroke and stroke-free participants in our study were mostly older than 60 years and were experiencing more cortical thinning especially in the left frontal and anterior-temporal cortices resulting in asymmetry loss in these leftward-asymmetry regions. While the right frontal cortex in healthy controls saw minimal thickness changes, there were localized thickness increases in the right prefrontal cortex in stroke, both contralesionally and ipsilesionally, resulting in greater thickness asymmetry loss in this leftward-asymmetry region. Other leftward-asymmetry areas seeing loss in thickness asymmetry were ACC and PCC. Although cortical thickness in ACC and PCC tends to increase bilaterally in late-life, we observed significant thickness increase ipsilesionally in the right ACC in stroke yielding asymmetry loss in this leftward-asymmetry region. In stroke, more so ipsilesionally, we also observed more thinning in right rightward-asymmetry regions such as lateral/medial parietal, occipital, and middle-temporal cortices.

Cortical thickness in ACC was shown to be positively associated with age in healthy individuals older than 60 years, (Frangou, 2021) in contrast to areas such as medial-parietal and superior-temporal cortices which continue to be negatively associated with age. That is, thickness in ACC exhibits an attenuated U-shaped association with normal aging. Consistent with this, the thickness-age relationship in stroke regions where we recorded increases in cortical thickness (i.e., prefrontal and ACC) was generally positive and significant particularly in right ipsilesional ACC (see Supplementary Fig. 4). Thickness increase in ACC was also observed in healthy controls and contralesionally in stroke but did not survive family-wise correction. In a separate *meta*-analysis (n = 529) of major depressive disorder, (Li, 2020) analogous cortical thickness increases were found in ACC, PCC, and ventromedial-prefrontal cortex.

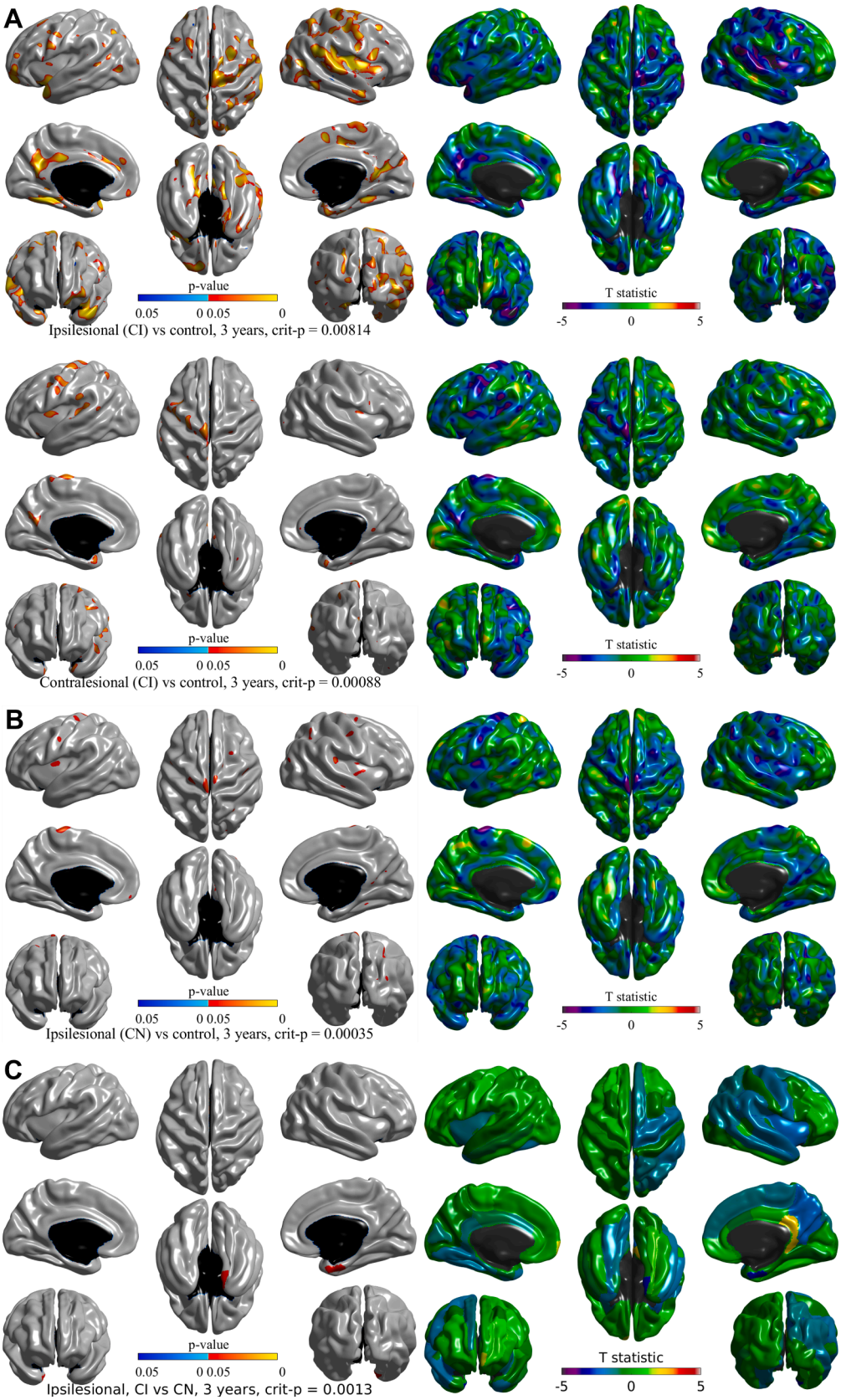

Fig. 5. Thickness comparison at 3 years based on cognitive status – **A)** Ipsilesional and contralesional cortical thinning in cognitively impaired (CI) stroke patients compared to cognitively normal (CN) healthy controls. **B)** Cortical thinning in CN stroke patients compared to CN controls. C) Region-wise comparison of ipsilesional cortical thinning between CI and CN stroke survivors (crit-p = critical p-value determined by adaptable two-stage FDR correction; the p-value maps were rescaled to a [0–0.05] range).

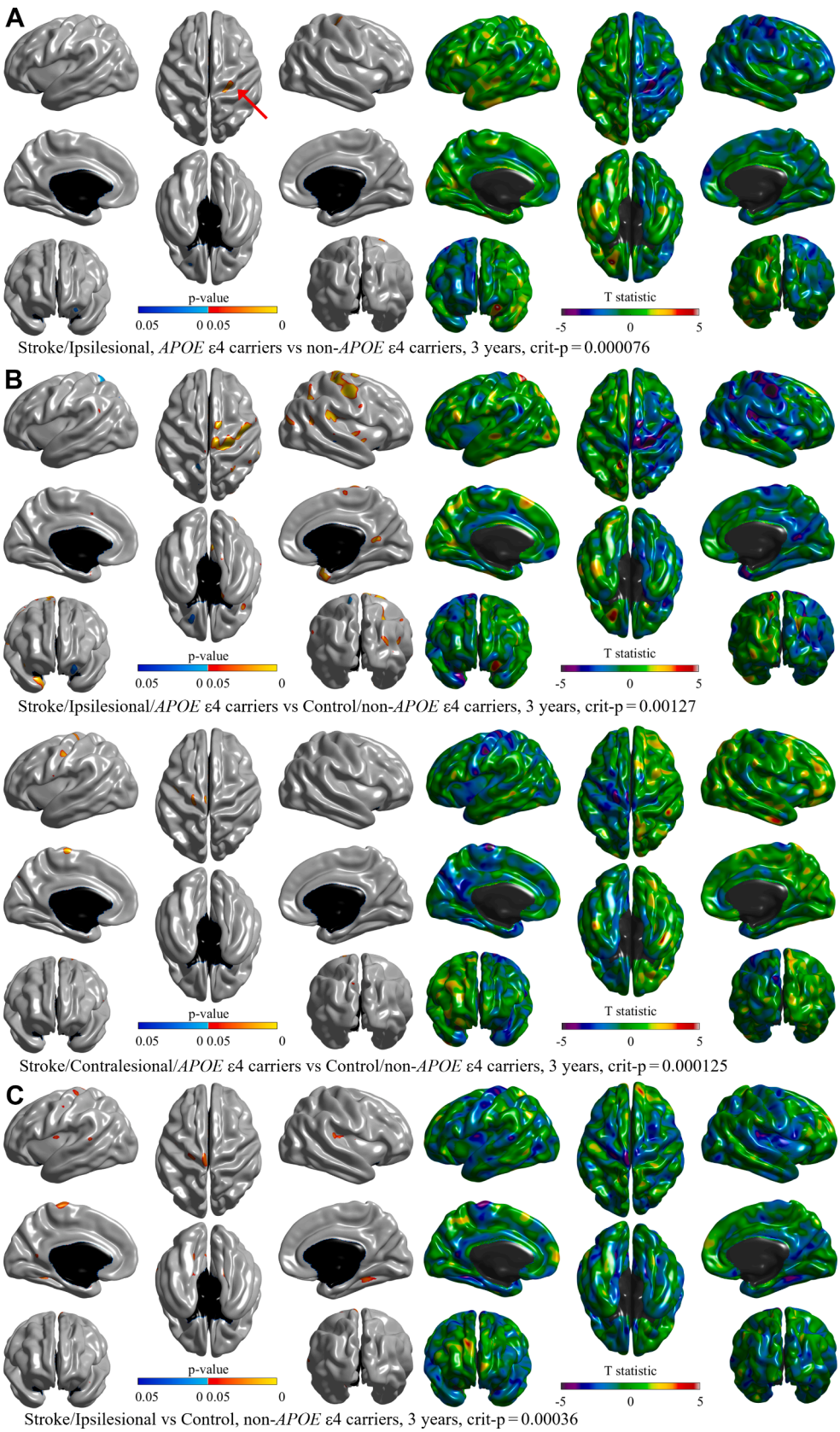

Fig. 6. Thickness comparison based on *APOE* ε4 carriage – **A)** Within stroke: Cortical thinning in the right precentral gyrus and sulcus between precentral and post-central gyri (arrow) in the *APOE* ε4 carriers. **B)** The *APOE* ε4 carriers in stroke were compared to non-carriers in the control group. **C)** The non-*APOE* ε4 carriers in stroke were compared to non-carriers in the control group (crit-p = critical p-value determined by adaptable two-stage FDR correction; the p-value maps were rescaled to [0 0.05] range).

4.2. Cortical thickness: Control vs stroke at 3 years

Three months post-stroke, cortical thinning in both ipsilesional and contralesional hemispheres was limited. Over 3 years, the areas of significant thinning expanded and this expansion was more pronounced in the ipsilesional hemisphere. The topology of thickness differentiation between control and stroke individuals mirrored the loss in thickness asymmetry discussed above. Areas of significant thinning at 3 years included regions implicated in motor, sensory, and cognitive networks such as memory processing and new learning, including precentral, insula, PCC, superior-temporal, medial-temporal (entorhinal and fusiform), and precuneus cortices. The region-wise analysis revealed more ipsilesional areas with significant thickness reduction in stroke including middle-frontal, paracentral, supra-marginal, lingual, and medial-orbitofrontal cortices. The differences in control thinning between healthy controls and stroke survivors remained unchanged after they were reassessed following the exclusion of six participants with recurrent stroke.

4.3. Cortical thickness in CI stroke survivors at 3 years

Vertex-wise analysis showed no difference in cortical thickness between CI and CN stroke participants even though the CI participants were significantly older with more comorbidities and larger stroke lesions. However, by comparing CI and CN stroke survivors to CN healthy controls, it was shown that cortical thinning in stroke was mostly contributed by the CI individuals. Still, the CN stroke survivors showed some significant thinning compared to healthy controls and this may explain why we did not see a significant difference between CI and CN stroke survivors, especially after family-wise correction for multiple comparisons. Also, cortical thinning in the contralesional cortex in CI stroke participants was even greater, especially in precentral gyrus, than in ipsilesional cortex in CN stroke participants. Interestingly, Albert et al. (Rojas Albert, 2022) reported that contralesional cortical thickness including the precentral gyrus positively related to post-stroke outcome. We also note that cortical thinning was greater in the right-sided stroke participants in both hemispheres. This may be explained by the frequency of right-sided strokes (68 %) among the CI survivors. Indeed, simulations where we randomly duplicated thickness data from left-sided strokes (for equal sample size between left and right-sided stroke) resulted in nearly doubling the statistical threshold for FDR correction.

Region-wise analysis revealed a significantly thinner entorhinal cortex in the right ipsilesional medial-temporal lobe in CI stroke survivors. The entorhinal cortex links the hippocampus to the temporal neocortex and is essential for cognitive processing and memory formation. Decline in entorhinal thickness precedes hippocampal atrophy. (Desikan, 2010) Across the adult lifespan, there are minimal age-related changes to entorhinal thickness until the sixth to eighth decade of life. (Frangou, 2021; Hasan, 2016) Several large studies (Ewers, 2012; Li, 2021; Zhou, 2016) found the entorhinal cortex to be one of the first regions affected by Alzheimer's disease, even before changes to the hippocampus. (Li, 2021) Left-right asymmetries have also been reported in Alzheimer's disease with the right entorhinal exhibiting greater atrophy than the left entorhinal, (Zhou, 2016) analogous to our finding. Thickness reduction in Alzheimer's disease has also been reported in bilateral PCC, precuneus, prefrontal, and parietotemporal association area. (Cho, 2013; Richards, 2009) Accordingly, we see a significant overlap with regions of significant cortical thinning in our CI stroke survivors. Moreover, we demonstrated greater cortical loss in primary motor (precentral) and somatosensory (postcentral) regions.

4.4. Cortical thickness in stroke APOE ε4 carriers at 3 years

We found limited cortical thinning in the right ipsilesional hemisphere in *APOE* ε4 carriers compared to non-carriers in stroke survivors but found relatively more thinning affecting both hemispheres in ε4-carriers in right-sided stroke participants compared to healthy controls. For non-ε4 carriers, more cortical thinning was observed in the left-sided stroke individuals. This disparity could not be attributed to stroke lesion laterality nor to cognitive status. Also, we did not find any association with demographic, clinical, vascular, or stroke variables to explain the disparity in cortical thinning given the interaction of *APOE* ε4 carriage with stroke side (see Supplementary Table 3).

4.5. Strengths and limitations

Strengths include our closely phenotyped ischaemic stroke cohort, the inclusion of age- and sex-matched control participants, acquisition of all MRI on the same scanner, and cognitive assessments completed all at equivalent timepoints. We used a well-established cortical estimation method, strengthened with manual correction, and used robustly designed mixed-effects regression for analysis with appropriate choice of covariates and random variables. With relatively small sample sizes, we could observe longitudinal cortical thinning conforming to reports from large studies involving thousands of participants.

Potential limitations arise from firstly the inclusion of stroke survivors with cortical lesions. However, the estimation of vertex-wise cortical thickness following procedures proposed in this study is preferred over standard cortical grey matter volume estimation, given that only infarcted vertices, not whole regions, were excluded. This is particularly critical for studies with small sample sizes. While we agree with prior stroke-specific modifications (Ozzoude, 2020) to FreeSurfer, we emphasise on mandatory post-FreeSurfer processing and exclusion of infarcted vertices for accurate ipsilesional thickness estimation; thus, cortical thinning post-stroke does not have to be restricted to contralesional hemisphere. Secondly, we acknowledge the relatively small sample sizes when assessing cortical thinning in CI or *APOE* ε4 carriers in stroke. However, our finding of entorhinal cortex thinning in CI stroke survivors, for instance, is well aligned with prior reports indicating thinning in medial-temporal lobe which is associated with cognitive performance. (Burggren, 2011) Nevertheless, future studies might include larger cohorts sampled from the ENIGMA–Stroke Recovery Working Group dataset. Finally, we had a relatively mild stroke cohort. The reported deficits in cortical thickness 3 years post-ischaemic stroke may have been found more amplified had the cohort included more participants with higher stroke severity.

5. Conclusions

Cortical thickness has been promoted as an imaging biomarker of brain function and cognitive performance. For stroke in particular, cortical thickness is preferred over cortical grey matter volume, especially when sample size is small and/or the frequency of cortical infarcts is high. Our findings conformed to reports from prior large studies. Age and sex were found to be independently associated with cortical thickness and longitudinal cortical thinning in our cohorts followed previously reported patterns of age-driven cortical thickness asymmetry loss along the fronto-occipital axis. This loss was more pronounced in stroke survivors especially in the ipsilesional hemispheres. The contributions to cortical thinning in stroke came mostly from CI participants, and carriage of the *APOE* ε4 allele negatively impacted on cortical thickness independent of cognitive status. Our findings confirm pathological brain aging post-stroke and may contribute to a greater understanding of imaging signatures of vascular cognitive impairment.

CRediT authorship contribution statement

Mohamed Salah Khlif: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Natalia Egorova-Brumley:** Conceptualization, Writing – review & editing. **Laura J. Bird:**

Investigation, Data curation, Writing – review & editing. **Emilio Werden:** Investigation, Data curation, Writing – review & editing, Project administration. **Amy Brodtmann:** Conceptualization, Investigation, Resources, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103200.

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