Dickie, D. A., Gardner, K., Wagener, A., Wyss, A., Arba, F., Wardlaw, J. M. and Dawson, J. (2019) Cortical thickness, white matter hyperintensities, and cognition after stroke. *International Journal of Stroke*, (doi:10.1177/1747493019851291).

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Cortical thickness, white matter hyperintensities, and cognition after stroke

David Alexander Dickie[1*], Kirstyn Gardner[1&], Annika Wagener[1,3&], Annick Wyss[1,2], Francesco Arba[4], Joanna M. Wardlaw[5], Jesse Dawson[1], on behalf of the VISTA-Prevention Collaborators[+]

[1]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Queen Elizabeth University Hospital, 1345 Govan Road, Glasgow, G51 4TF, United Kingdom

[2]Department of Health Sciences and Technology, Swiss Federal Institute of Technology (ETH), Zurich, Switzerland

[3]Interdisciplinary Center for Neurosciences, Heidelberg University, Heidelberg, Germany

[4]Stroke Unit, Careggi University Hospital, Florence, Italy

[5]Centre for Clinical Brain Sciences, Chancellor's Building, 49 Little France Crescent, EH16 4SB, United Kingdom

*Corresponding author: david.dickie@glasgow.ac.uk
[&]These authors contributed equally

[+]VISTA-Prevention Steering Committee: H. C. Diener (Chair), S. Davis, J. P. Greving, G. Hankey, K. R. Lees, B. Ovbiagele, C. J. Weir.

Word count: 4083
Abstract word count: 253

Key words: Brain MRI, white matter hyperintensities, cortical thickness, cognition, ischaemic stroke

Abstract

Background: A thinner cerebral cortex is associated with higher white matter hyperintensity (WMH) burden and cognitive impairment in community-dwelling and dementia cohorts. It is important to assess these associations in people with ischaemic stroke because their cerebrovascular disease profiles are different to these cohorts.

Aims: We aimed to determine whether cortical thickness was related to WMH burden and cognition after ischaemic stroke.

Methods: We measured cortical thickness using Advanced Normalisation Tools' "KellyKapowski" function in 244 patients with ischaemic stroke or transient ischaemic attack from the Virtual International Stroke Trials Archive (VISTA). We measured WMH burden via quantitative volumes and Fazekas score. We extracted data on vascular risk factors at baseline and Mini Mental State Examination (MMSE) scores at one-year. We assessed associations between imaging and clinical data using correlations and multiple linear regression.

Results: Pairwise correlation showed that higher WMH Fazekas score was associated with a thinner cortex (rho=-0.284, $P<0.0001$). WMH were generally distributed adjacent to and above the lateral ventricles. Voxel-wise analyses showed statistically significant negative associations between cortical thickness and WMH across fronto-temporal and inferior parietal cortical regions. Mean cortical thickness was positively related to MMSE in pair-wise correlation (r=0.18, $P=0.004$) but there was no independent association after adjustment for age and WMH (beta=0.06, $P=0.352$).

Conclusions: Cortical thickness was not an independent predictor of cognition after ischaemic stroke. Further work is required to understand how WMH are associated with a thinner cortex in temporal regions but less so in more superior regions where WMH are generally found in people with stroke.

Introduction

Brain atrophy and white matter hyperintensities (WMH) are common in people with ischaemic stroke and both are independently associated with worse outcome (1–3). Methods for measuring brain atrophy from magnetic resonance imaging (MRI) include assessment of grey and white matter volumes, cerebrospinal fluid volume, and more recently, cortical thickness (4,5). Cortical thickness is the distance between grey and white matter surfaces and measurement allows for voxel- or vertex-wise analyses across the cortex; potentially increasing sensitivity to detect associations with cognitive impairment (4,6–8).

A thinner cortex is associated with higher WMH burden and lower cognition in community-dwelling ageing, cognitively impaired, and small vessel disease (SVD) cohorts (7–11). These studies found associations between higher WMH burden and a thinner cortex in fronto-temporal and inferior parietal regions. WMH are generally found adjacent to and above the lateral ventricles in ischaemic stroke and ageing cohorts, regions that underlie superior-parietal/frontal and occipital lobes rather than temporal cortices (12,13). A longitudinal study of community-dwelling participants did not find a relationship between WMH progression and cortical thinning (14). We found no prior study to assess the relationship between WMH and cortical thickness, nor the association between cortical thickness and cognition, in people with ischaemic stroke.

There is current considerable interest in identifying overall “cerebrovascular health” from MRI and whether this can predict cognitive impairment and dementia (3,15,16). These studies have shown that combined measures of atrophy and small vessel disease are more predictive of cognitive impairment than individual measures. It would be useful to quantify the predictive power of cortical thickness and whether it may add to burgeoning brain health measures in stroke.

Aims

We aimed to determine: 1) regions of the cortex negatively associated with WMH burden; 2) whether cortical thickness was predictive of cognition, as assessed by Mini-Mental State Examination (MMSE); and 3) whether WMH burden attenuated the association between cortical thickness and cognition in ischaemic stroke.

Methods

Participants and data extraction

Brain MRI and clinical data were obtained from the Virtual International Stroke Trials Archive (VISTA) Prevention sub-archive (http://virtualtrialsarchives.org/vista). VISTA holds fully anonymised data from completed clinical trials, and had ethical approval for its procedures. Our project, to assess brain MRI markers in stroke, was approved by the VISTA steering committee. We extracted baseline brain MRI and vascular risk factors, and one-year follow-up Mini-Mental State Examination (MMSE) scores from VISTA where available. Vascular risk factors included reported diagnosis of hypertension, hypercholesterolemia, diabetes, smoking, atrial fibrillation and measured systolic and diastolic blood pressure.

Brain MRI acquisition and processing

Brain MRI was acquired at baseline and parameters are fully described in supplementary material. Intracranial volume (ICV), white matter hyperintensity (WMH) and normal-appearing tissue volume processing was described previously (17); all processing outputs were checked and edited according to STRIVE guidelines (18). Fazekas scores of WMH burden were assessed by a trained rater (FA) with FLAIR, or T2 if FLAIR was not available. FLAIR was not available for N=28 participants and this was required to measure WMH volumes. Therefore, we used Fazekas score as a measure of WMH burden in our main analyses. Stroke infarcts were manually masked by a trained image analyst consistent with STRIVE. Cortical thickness was measured across the cortex using the "KellyKapowski" function within Advanced Normalisation Tools (4,19). The distance to diffeomorphically register the white matter surface to grey matter surface is defined as cortical thickness in this tool. We calculated voxel-wise cortical thickness maps and mean cortical thickness for each participant. Mean cortical thickness is the mean of all voxel-wise measurements of cortical thickness within each subject.

Statistical analyses

All statistical analyses were performed using MatrixLaboratory (MATLAB) R2017b (© 1994-2018 The MathWorks, Inc.). We assessed pair-wise correlations between mean cortical

thickness, WMH, vascular risk factors, and MMSE using Pearson and Spearman correlations. We used multiple linear regression with standardised beta to assess whether statistically significant pair-wise associations with mean cortical thickness and MMSE remained significant in adjusted co-variate models including age and WMH. Statistical normality of variables and regression residuals was assessed by visual interpretation of histogram plots. Heteroscedasticity and non-linearity were assessed via residual versus predicted value plots. Multicollinearity was assessed via the variance inflation factor.

Voxel-wise cortical thickness analyses

Voxel-wise multiple linear regression models were performed - to assess which regions of the cortex were associated with WMH burden and MMSE - using cortical thickness maps. At each voxel across the cortex we tested the association between cortical thickness, WMH burden, and MMSE. We ran these models with and without adjustment for co-variates. We corrected for multiple comparisons in voxel-wise analyses using false discovery rate with critical value 0.05 (20).

Results

Participant characteristics

Of N=454 participants in the VISTA Prevention sub-archive who had brain MRI, N=158 did not have a useable T1 MRI and an additional N=52 had missing clinical, demographic and/or cognitive data. This left N=244 participants that were included in our analyses. Participants were not excluded for any other reason than missing data. Full characteristics of the N=244 included participants are provided in table 1. Briefly, mean age was 66 years, 66% were male, median Fazekas score was 2, mean WMH volume was approximately 13ml, mean cortical thickness was 3.27mm, and mean MMSE was 26. WMH volumes were generally distributed adjacent to and above the lateral ventricles (figure 1). WMH volume and Fazekas score were highly correlated (rho=0.884, $P<0.0001$). WMH burden was quantified via Fazekas score in all remaining analyses.

Pairwise associations with mean cortical thickness

Pairwise associations with mean cortical thickness are in table 2. A thinner cortex was associated with older age, female sex, higher WMH burden, lower ICV, higher blood pressure, and lower MMSE.

Prediction of MMSE by cortical thickness after adjustment

Mean cortical thickness was no longer significantly predictive of MMSE after adjustment for age and WMH Fazekas score (table 3). Voxel-wise models showed that a thinner cortex in fronto-temporal and inferior parietal regions was associated with lower MMSE but this was greatly attenuated after adjustment for age, sex, ICV, and vascular risk factors. Following inclusion of Fazekas score in the adjusted model there was no significant relationship between cortical thickness across the cortex and MMSE (figure 2). There was evidence for non-normality of residuals, non-linearity, and heteroscedasticity in these models. Variance inflation factor was low, between 1.05 and 1.26.

Adjusted associations between cortical thickness and WMH burden

Higher WMH burden was associated with a thinner cortex in fronto-temporal and inferior parietal regions, the extent of these associations was attenuated but remained intact after adjustment for age, sex, ICV, and vascular risk factors (figure 3). There was limited evidence for non-normality of residuals, non-linearity, and heteroscedasticity between WMH burden and cortical thickness; variance inflation factor was low (between 1.04 and 1.98).

Although data are not shown here, we repeated all main analyses in the subset of participants with useable FLAIR MRI, substituting WMH volume for Fazekas score, and results were broadly similar.

Discussion

We have shown that higher WMH burden is associated with a thinner cortex in fronto-temporal and inferior parietal regions in ischaemic stroke. These associations remained after adjustment for age, sex, head size and vascular risk factors. This pattern of association across fronto-temporal and inferior parietal regions is similar to those found in community-dwelling ageing, cognitively impaired, and SVD cohorts (10,14,21). We found that a thinner cortex in these regions and lower mean (overall) cortical thickness was associated with lower one-year follow-up MMSE score in pairwise analyses. However, these associations were attenuated to non-statistical significance after adjustment for age, sex, head size, vascular risk factors, and WMH. This is unlike ageing and cognitive impairment studies that found cortical thickness to be predictive of cognition, even after adjustment for co-variates (8,11,16).

The negative associations we found between WMH burden and cortical thickness were in very similar regions to those in ageing and dementia studies (10,14,21). Temporal cortical regions do not directly overlie the general distribution of WMH in ageing and ischaemic stroke cohorts; which commonly extends adjacent to and above the lateral ventricles (12,13). Additionally, previous work has shown that progression of WMH and cortical thinning were not related in a longitudinal study of community-dwelling participants (14). It should be noted however that the associations we found here are cross-sectional and further work is required to understand the mechanism(s) of WMH progression and cortical thinning. Whether or not there is a causal relationship between increasing WMH burden and cortical thinning in stroke can only be answered in a longitudinal study. Stroke patients have a higher burden of WMH than community-dwelling participants (22) and this may allow for any longitudinal relationship to be identified.

There was no statistically significant association between mean cortical thickness and MMSE when we included WMH burden (Fazekas score) into our models. The higher burden of WMH in stroke patients (22) may explain why the association between WMH and cognition was demonstrable but that between cortical thickness and cognition was not. Whole brain cerebrospinal fluid volume, which includes ventricular expansion not captured by cortical thickness, may be a more useful marker of brain atrophy in stroke (3).

Our study has limitations. Although we had a relatively large sample of participants, larger samples may be required to reveal adjusted associations between cortical thickness and cognition in stroke. Our results are cross-sectional and future work in longitudinal studies is

required to determine if there is a causal relationship between WMH progression and cortical thinning in stroke. As we used data from clinical trials with MRI our results may not be generalised to people not well or motivated enough to take part in trials or tolerate MRI. Additionally, there was large variation in time from stroke to inclusion in each contributing study and we did not have data on whether or not participants had stroke prior to inclusion, i.e., whether their stroke event for inclusion in a contributing study was recurrent. We did not assess associations between stroke infarct volume and cortical thickness as this has been done previously (23). Neither MMSE, WMH volume, nor Fazekas score were distributed statistically normal and this could have led to a violation of the assumptions of our parametric-based regression analyses. However, there was limited evidence for non-normality of residuals, heteroscedasticity and non-linearity in the WMH models and, as shown in table 2, parametric- and nonparametric-based analyses generally showed very similar results. This is except for the parametric (that showed statistical significance) and non-parametric (that did not show statistical significance) correlations between MMSE and cortical thickness. There was evidence for heteroscedasticity, non-linearity, and non-normality of residuals in the MMSE and cortical thickness models and this likely explains these differing results. However, accepting the nonparametric result would only underline our conclusion that cortical thickness has limited utility for predicting cognition in stroke. Future work may assess potential non-linear relationships between MMSE and cortical thickness. We had a limited battery of vascular risk factors but included those which have been shown to contribute to most of the population attributable risk of stroke (24). Brain MRI were acquired at several different centres with differing image acquisition parameters, including non-isometric T1 scans. This may have limited our ability to accurately measure cortical thickness. However, this at least shows that stroke imaging studies should consistently acquire high resolution isometric T1 images for cortical thickness to be useful. MMSE is a crude measure of global cognitive function but it has been shown that MMSE is a reasonable and quick tool to detect cognitive impairment in stroke survivors (25). Future work is needed to assess associations between cortical thickness and specific cognitive domains, e.g., as assessed by Montreal Cognitive Assessment (MoCA), which may be stronger than the associations between cortical thickness and global cognitive function reported here. Finally, we did not have assessments of cognition prior to stroke, e.g., years of education, therefore could not adjust for premorbid cognitive ability which has been shown to be a strong predictor of post-stroke cognition (26).

Notwithstanding these limitations, our study provides data on the relationships between cortical thickness, WMH, and cognition in ischaemic stroke. Unlike in ageing and dementia cohorts, a thinner cortex may not be an independent predictor of cognitive impairment in ischaemic stroke. Further work is required to understand how WMH are associated with a thinner cortex in temporal regions but less so in more superior regions where WMH are generally found in people with stroke.

Acknowledgements

We are very grateful to the VISTA collaboration, particularly Myzoon Ali, for providing access to the data used.

Funding

We would like to sincerely thank the Stroke Association UK for funding David Alexander Dickie through a postdoctoral fellowship (TSAPDF2017/01) and Medical Research Scotland for funding Kirstyn Gardner through a vacation scholarship (Vac-1245-2018).

Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest.

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Table 1. Participant characteristics

Age	65.5±12.3 (median=67, range=22.6-89.5) years
Sex	Male=161 (66%)
	Female=83 (34%)
Fazekas score	Median=2, IQR=3
White matter hyperintensities volume	12.5±12.6ml (median=8ml, IQR=15ml)
Mean cortical thickness	3.27±0.20mm
Intracranial volume	1331.7±137.0ml
Current smoking	N=55 (22.5%)
Past smoking	N=72 (29.5%)
Hypertension	N=184 (75.4%)
Hypercholesterolaemia	N=128 (52.5%)
Atrial fibrillation	N=9 (3.7%)
Death during study	N=22 (9.0%)
Systolic blood pressure	140±29mm/Hg
Diastolic blood pressure	81±16mm/Hg
Diabetes	N=70 (28.7%)
Mini Mental State Examination	25.5±5.2 (median=28, IQR=6)
Transient ischaemic attack	N=47 (19.3%)
Time from stoke to baseline assessment	67.1±61.4 (range=0-328) days

Note: IQR=interquartile range.

Table 2. Pair-wise correlations with cortical thickness

Parameter	Pearson	Spearman
Age	r=-0.243, *P*<0.0001*	rho=-0.194, *P*=0.0023*
Male sex	r=0.154, *P*=0.0161*	rho=0.150, *P*=0.0189*
White matter hyperintensities Fazekas score	r=-0.299, *P*<0.0001*	rho=-0.284, *P*<0.0001*
Intracranial volume	r=0.398, *P*<0.0001*	rho=0.345, *P*<0.0001*
Current smoking	r=-0.014, *P*=0.8324	rho=-0.010, *P*=0.8822
Past smoking	r=-0.002, *P*=0.9705	rho=0.000, *P*=0.9984
Hypertension	r=-0.124, *P*=0.0528	rho=-0.105, *P*=0.1032
Hypercholesterolaemia	r=-0.010, *P*=0.8793	rho=0.017, *P*=0.7929
Atrial fibrillation	r=0.011, *P*=0.8685	rho=0.030, *P*=0.6433
Death during study	r=0.016, *P*=0.8041	rho=-0.013, *P*=0.8423
Systolic blood pressure	r=-0.188, *P*=0.0032*	rho=-0.132, *P*=0.0391*
Diastolic blood pressure	r=-0.130, *P*=0.0430*	rho=-0.045, *P*=0.4854
Diabetes	r=-0.022, *P*=0.7311	rho=0.000, *P*=0.9904
Mini Mental State Examination	r=0.167, *P*=0.0088*	rho=0.094, *P*=0.1437

Note: *$P<0.05$.

Table 3. Multiple linear regression adjusted associations between mean cortical thickness and MMSE

Model	Mean cortical thickness beta	Age beta	WMH beta
MMSE ~ MCT	0.167±0.063 (*P*=0.0088)*	N/A	N/A
MMSE ~ MCT + Age	0.064±0.059 (*P*=0.2854)	-0.428±0.059 (*P*<0.0001)*	N/A
MMSE ~ MCT + WMH	0.051±0.062 (*P*=0.4060)	N/A	-0.388±0.062 (*P*<0.0001)*
MMSE ~ MCT + Age + WMH	0.016±0.059 (*P*=0.7874)	-0.323±0.064 (*P*<0.0001)*	-0.244±0.065 (*P*=0.0002)*

Note: MMSE was the dependent variable and cortical thickness, age and WMH were independent variables; Standard error for beta are shown after ±; MCT=mean cortical thickness; WMH=white matter hyperintensities measured by Fazekas scale; MMSE= Mini Mental State Examination; *$P<0.05$.

Figure 1. White matter hyperintensity (WMH) volume distribution map. WMH were most commonly found adjacent to and above the lateral ventricles (red≥50%) and were less frequently found in anterior frontal, inferior parietal and temporal regions (blue to purple≤10%).

Figure 2. Associations between baseline cortical thickness and one-year follow-up Mini-Mental State Examination (MMSE) score across the cortex. Regions in red/yellow show where there were statistically significant associations between higher MMSE score and a thicker cortex. Yellow regions have the lowest false discovery rate (FDR) corrected *P*-values ($P \geq 0.001$) towards red regions with the highest FDR corrected, statistically significant *P*-values ($P < 0.05$). Grey regions show no statistically significant association. The top panel shows unadjusted pairwise associations between MMSE and cortical thickness, the middle panel shows associations adjusted for intracranial volume (ICV), age, sex, and vascular risk factors, and the bottom panel shows adjustment with ICV, age, sex, vascular risk factors, and white matter hyperintensity (WMH) Fazekas score (no voxel-wise associations survived adjustment).

Figure 3. Associations between white matter hyperintensity (WMH) Fazekas score and cortical thickness across the cortex. Regions in red/yellow show where there were statistically significant associations between higher WMH score and a thinner cortex. Yellow regions have the lowest false discovery rate (FDR) corrected *P*-values ($P \geq 0.001$) towards red regions with the highest FDR corrected, statistically significant *P*-values ($P < 0.05$). Grey regions show no statistically significant association. The top panel shows unadjusted pairwise associations between WMH and cortical thickness and the bottom panel shows associations adjusted for intracranial volume (ICV), age, sex, and vascular risk factors.