Cerebral microbleeds: A study on white matter tract integrity and cognition

Ai Wern Chung1, Bhavini Patel1, Andrew J. L. Lawrence1, Philip Rich2, Andrew MacKinnon2, Robin G. Morris2, Hugh S. Markus1, and Thomas R. Barrick1
1Stroke and Dementia Unit, St George’s University of London, London, London, United Kingdom, 2Neuropsychology, St George’s Hospital, London, United Kingdom, 3Department of Psychology, Institute of Psychiatry, London, United Kingdom

Introduction
Cerebral microbleeds (CMB) are hemosiderin deposits, associated with hemorrhagic events and are a feature in small vessel disease (SVD) patients. They appear on gradient-recalled echo (GRE) magnetic resonance imaging (MRI) as signal voids due to their paramagnetic properties. The effect of CMB on cognitive function is unclear. They have been linked to cognitive impairment for example, executive dysfunction in stroke1 and CADASIL2 patients; however no such relationships have been found in Alzheimer’s disease3 or in a separate CADASIL study after controlling for MRI markers4. We aim to further our understanding of the effect of CMB on cognition in SVD patients by investigating the structural integrity of associated white matter via diffusion tensor imaging (DTI) and tractography. For comparison, we extended analyses to include lacunar infarcts (LC) as they are known to cause disruption to white matter.

Methods
Patients: 121 recruited SVD patients were administered a battery of standard neuropsychological tests including cognitive measures of executive function, working memory, processing speed, long term memory and verbal IQ. MRI protocol: Data were acquired on a 1.5T GE Signa LX scanner: Axial EPI GRE (TR/TE/FOV=300ms/30ms/240mm2), 28 slices (5mm thick), coronal T1-weighted SPGR (TR/TE/FOV=11.5ms/5ms/240mm2), 176 slices, 1.1mm isotropic voxels, flip angle=18°) and axial single-shot EPI diffusion-weighted (TR/TE/FOV=15000ms/93.4ms/240mm2, 55 slices, 2.5mm isotropic voxels, b=0 s mm−2 volumes and b=1000 s mm−2 in 25 non-collinear gradient directions in positive and negative directions to remove cross-terms.

DTI Preprocessing: FA and MD maps were computed for all patients. GRE and T1 images were coregistered to the average b = 0 s mm−2 image. ROI Analysis: CMB were identified as foci areas of low signal <10mm in diameter on GRE images. LC were defined as CSF-filled cavities between 3-20mm diameter on T1 images. 48 patients were CMB positive and 73 CMB negative. A 6-neighbourhood connectivity dilation technique was applied to the centre voxel (referred to as the seed) of each CMB and LC to delineate the pathology region of interest (ROI). This semi-automated process computed a threshold boundary condition for which dilation would iteratively continue until it terminated at the edge of the pathology. After computation of the pathology ROI two further threshold-free dilations were performed to identify two ‘normal’ tissue regions (N1 and N2) adjacent to and surrounding the pathology ROI. Examples of this procedure are illustrated in Figure 1. CMB and LC ROI were analysed if they were within white matter, giving 61 CMB and 157 LC for statistical analysis. Averaged median FA and MD were computed for all ROI, N1 and N2. Tractography Analysis: Whole brain subvoxel streamline tractography7 was performed (FA > 0.2, step, length 1mm) on ten patients (five CMB and five LC). For each patient a single CMB (or LC) located within a recognised white matter pathway was chosen, and tracts passing through the pathology ROI (ROI=N1+N2) were retained. Control tracts passing through manually drawn regions of the same size and location as the pathology region in the contra-lateral hemisphere were also extracted. Mean FA, MD and tract volume (TV, in mm3) were computed from ipsi- and contra-lateral tracts within a 3cm radius sphere centred on the ROI.

Results
Cognition: No significant differences in cognitive measures were found between patients with and without CMB (p>0.6). No significant relationship was found between the number of CMB and cognition (p=0.5), however, a significant negative correlation was found between number of LC with cognition (p=0.03). ROI Analysis: No significant change was found in FA between CMB ROI and surrounding regions N1 (p=0.2) and N2 (p=0.9) or for MD (N1: p=0.9; N2: p=0.3). Conversely, FA significantly decreased in LC ROI compared to regions N1 and N2 with MD showing significant increase (all p<0.0001). Tractography Analysis: No significant change in FA, MD or TV difference were found between ipsi- and contra-lateral tracts in CMB pathologies (FA: p=0.8; MD: p=0.9; TV: p>0.6). In contrast, tracts containing LC exhibited significantly lower FA (p=0.035) and TV (p=0.046) measures and greater MD (p=0.027) compared to their contra-lateral tracts.

Discussion
To the authors’ knowledge, there have been no previous studies investigating the diffusive properties of CMB and their effect on adjacent white matter. DTI is sensitive to white matter damage in various pathological states and abnormalities have been detected early in disease progression i.e. in amyotrophic lateral sclerosis where tractography showed changes in white matter structure prior to the appearance of clinical symptoms8. DTI revealed no white matter damage associated with CMB but did detect significant changes to white matter in the vicinity of LC. We found no evidence to suggest CMB in SVD patients are detrimental to white matter integrity local or distal to the pathology. In support of this, our neuropsychology results showed no causal link between CMB and cognitive function.

References

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![Figure 1: 2D examples of the dilation process for (A) CMB and LC (C) showing on coregistered GRE and T1 images, respectively. Seed voxels representing the centre of pathologies are shown in yellow. The dilation process is illustrated in (B) and (D). Purple voxels represent the pathology ROI, with green and red representing the adjacent regions N1 and N2, respectively.](image1)

![Figure 2: Example white matter tracts through a CMB (top row) and LC (bottom row). Anatomical location of pathologies are in (A) and (F). Pathology ROI (in orange) and corresponding undamaged contra-lateral ROI (green) are in (E) and (J). Tractography results are shown (B-D, G-I) with hemispheres labelled. White circles represent 3cm radius spheres centred on pathology and contra-lateral ROI.](image2)