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

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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 stroke[1] and CADASIL[2] patients; however no such relationships have been found in Alzheimer's disease[3] or in a separate CADASIL study after controlling for MRI markers[4]. 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/240mm^2, 28 slices 5mm thick), coronal T1-weighted SPGR (TR/TE/FOV=11.5ms/5ms/240mm^2, 176 slices, 1.1mm isotropic voxels, flip angle=18°) and axial single-shot EPI diffusion-weighted (TR/TE/FOV=15600ms/93.4ms/240mm^2, 55 slices, 2.5mm isotropic voxels, 8 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 focal 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 137 LC for statistical analysis. Averaged median FA and MD were computed for all ROI, N1 and N2.

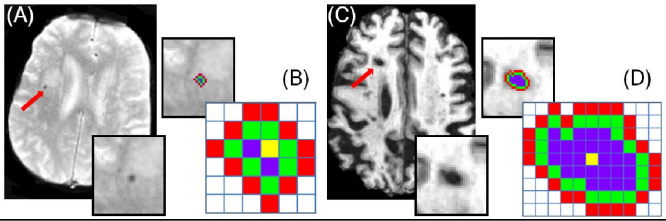

Figure 1: 2D examples of the dilation process for (A) CMB and LC (C) shown on coregistered GRE and T1 images, respectively. Seed voxels representing the centre of pathologies are shown in yellow. The dilation process is illustracted in (B) and (D). Purple voxels represent the pathology ROI, with green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

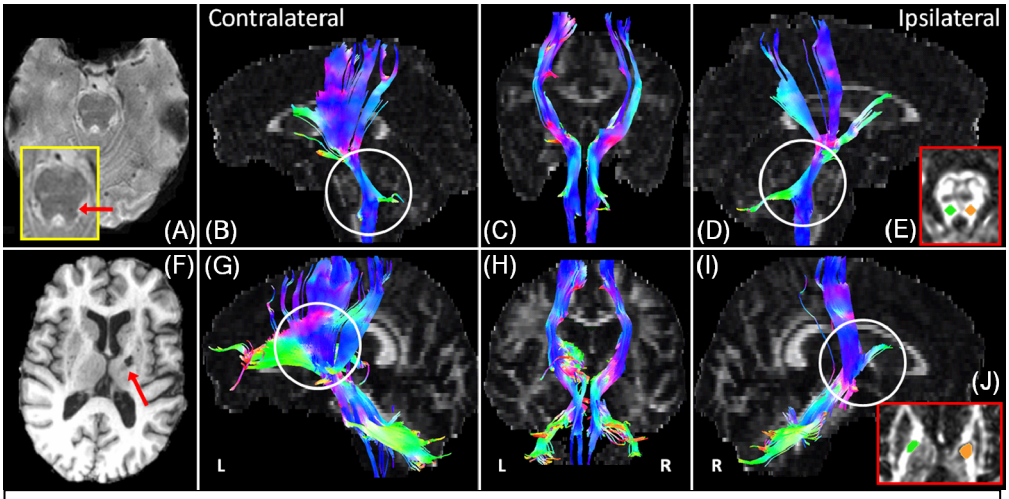

Figure 2: Example white matter tracts through a CMB (top row) and LC (bottom row). Anatomical location of pathologies are in (A) and (F). Pathology ROI (in orange) and corresponding undamaged contra-lateral ROI (green) are in (E) and (J). Tractography results are shown (B-D, G-I) with hemispheres labelled.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

Tractography Analysis: Whole brain subvoxel streamline tractography[5] 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 region (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 mm^3) were computed from ipsi- and contra-lateral tracts within a 3cm radius sphere centred on the ROI.

Statistical Analysis: Relationships between cognitive measures and the absence/presence of CMB were investigated using unpaired t-tests. Spearman's rank correlation was used to determine the relationship between number of CMB with cognition, and Pearson's correlation for the relationship between the log of LC count with cognition. To determine whether the pathology region had an effect on surrounding white matter tissue paired t-tests were performed between the ROI and N1 regions, and ROI and N2 for both CMB and LC. Similarly, unpaired t-tests were used to compare ipsi- and contra-lateral tract-specific diffusion measures and TV for each CMB and LC group.

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 FA, MD or TV differences 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. Tractography results for a CMB and LC subject are in Figure 2.

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 symptoms[6]. 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 [1] Werring et al., Brain 2004; 127:2265-2275 [2] Liem et al., Neurology 2009; 72:143-148 [3] Pettersen et al., Arch Neurol 2008; 65:790-795 [4] Viswanathan et al., Neurology 2007; 69:172-179 [5] Barrick et al., NeuroImage 2004; 22:481-491 [6] Ciccarelli et al., Brain 2006; 129: 1859-1871

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