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Strategic lacunes and their relationship to cognitive impairment in cerebral small vessel disease

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ABSTRACT

Objectives: Lacunes are an important disease feature of cerebral small vessel disease (SVD) but their relationship to cognitive impairment is not fully understood. To investigate this we determined (1) the relationship between lacune count and total lacune volume with cognition, (2) the spatial distribution of lacunes and the cognitive impact of lacune location, and (3) the whole brain anatomical covariance associated with these strategically located regions of lacune damage.

Methods: One hundred and twenty one patients with symptomatic lacunar stroke and radiological leukoaraiosis were recruited and multimodal MRI and neuropsychological data acquired. Lacunes were mapped semi-automatically and their volume calculated. Lacune location was automatically determined by projection onto atlases, including an atlas which segments the thalamus based on its connectivity to the cortex. Lacune locations were correlated with neuropsychological results. Voxel based morphometry was used to create anatomical covariance maps for these 'strategic' regions.

Results: Lacune number and lacune volume were positively associated with worse executive function (number $p < 0.001$; volume $p < 0.001$) and processing speed (number $p < 0.001$; volume $p < 0.001$). Thalamic lacunes, particularly those in regions with connectivity to the prefrontal cortex, were associated with impaired processing speed (Bonferroni corrected $p = 0.016$). Regions of associated anatomical covariance included the medial prefrontal, orbitofrontal, anterior insular cortex and the striatum.

Conclusion: Lacunes are important predictors of cognitive impairment in SVD. We highlight the importance of spatial distribution, particularly of anteromedial thalamic lacunes which are associated with impaired information processing speed and may mediate cognitive impairment via disruption of connectivity to the prefrontal cortex.

1. Introduction

Cerebral small vessel disease (SVD) is the major cause of vascular cognitive impairment in the elderly (Pantoni, 2010) producing a characteristic cognitive profile which includes reduced information processing speed and executive dysfunction, but relatively preserved episodic memory (Charlton et al., 2006). SVD is thought to impair cognition by disrupting the efficiency of white matter pathways that connect the networks that underlie cognitive processes (O'Sullivan et al., 2004). Magnetic resonance imaging (MRI) is essential to diagnosis and a useful tool to investigate the mechanisms of cognitive impairment in SVD. A number of MRI markers of cognitive impairment in SVD have been proposed, of which T2 white matter hyperintensities (WMH) and lacunes (3–15 mm CSF filled cavities of presumed vascular origin) are best described (Wardlaw et al., 2013). Here we focus on lacunes and the mechanisms by which they lead to cognitive impairment in SVD.

Lacune number has been associated with cognitive impairment in some studies in SVD (Gold et al., 2005; Visvanathan et al., 2007; Lee et al., 2011), but not in others (Nitkunan et al., 2008). However lacunes vary in size and the relationship might be stronger with total lacune volume. This has been suggested in CADASIL

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(Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy), a young-onset genetic form of SVD (Viswanathan et al., 2007), but not yet examined in sporadic SVD. We investigate the relationship between both lacune count and total lacune volume with cognition in sporadic SVD and assess whether any associations are independent of other pathological markers of SVD determined from MRI.

The impact of lacunes on cognition is likely to depend not only on their total load but also on their location. Thalamic lacunes in particular have been associated with cognitive impairment in SVD (Benisty et al., 2009) and CADASIL (Duering et al., 2011). The thalamus is a complex structure with multiple subcomponents possessing unique architecture and connectional properties. Previous studies using probabilistic tractography in human brains have showed that the thalamus can be segmented into distinct subregions based on cortical connectivity patterns that correspond to thalamic nuclei described in histological studies (Behrens et al., 2003). In view of this we investigate the spatial distribution of lacunes to define the specific cognitive impact of strategically located lacunes, particularly those in the thalamus using a thalamic atlas based on its connectivity to the cerebral cortex (Johansen-Berg et al., 2005). Guided by the results of our lacune spatial analysis, we identify a region of interest (ROI) within the thalamus. We then use voxel based morphometry (VBM) to investigate whether there are any significant associations between this ROI and other brain regions. This technique, termed anatomical (or structural) covariance, has previously been used to show that regions that are structurally or functionally related 'covary' in grey matter (GM) density (Alexander-Bloch et al., 2013; Soriano-Mas et al., 2013). Determining 'strategic' lacune locations within the thalamus may improve our understanding of the disconnected cortical–subcortical pathways underlying cognitive impairment in SVD.

2. Methods

2.1. Patients

Patients with SVD were recruited as part of the prospective St George's Cognition and Neuroimaging in Stroke (SCANS) study (Lawrence et al., 2013). For this analysis data from the SCANS baseline assessment was used. Patients were recruited between March 2007 and October 2010 from the inpatient and outpatient stroke services of three hospitals covering a geographically contiguous area of South London (St George's, King's College and St Thomas' Hospitals). Inclusion criteria comprised a clinical lacunar stroke syndrome (Bamford et al., 1987) with an anatomically corresponding lacunar infarct on MRI in addition to confluent white matter hyperintensities (WMH) on MRI (Fazekas grade 2 or higher, Fazekas et al., 1993). Exclusion criteria were as follows: any cause of stroke mechanism other than SVD (e.g., cardioembolic source or extra- or intra-cerebral artery stenosis of >50%), other major central nervous system disorders, major psychiatric disorders, any other cause of white matter disease, contraindications to MRI, or non-fluent in English. The study was approved by the local ethics committee and all patients gave written informed consent. MRI acquisitions and cognitive assessments were performed at least 3 months after the last stroke to exclude acute effects on cognition. Imaging was performed at a median of 7 months after their symptomatic stroke (minimum: 3 months, maximum: 36 years). 59% of patients were scanned within 12 months of their index stroke. All patients were also screened for cardiovascular risk factors including hypertension (defined as systolic blood pressure > 140 mm Hg or diastolic > 90 mm Hg or treatment with antihypertensive drugs), hypercholesterolaemia (defined as a serum total cholesterol > 5.2 mmol/l or treatment with a statin), diabetes mellitus and smoking.

2.2. Magnetic resonance imaging acquisition

Images were acquired on a 1.5 T Signa HDxt scanner (General Electric, Milwaukee, WI, USA) with maximum gradient amplitude of 33 mTm^{-1} and a proprietary head coil. All image sequences were acquired across the whole brain and total imaging time was approximately 45 min. Patients were placed in the head coil in a neutral position with an alignment marker at the nasal bridge to standardise head position. Minimal movement was ensured by use of foam pads and a Velcro strap across the forehead.

The imaging protocol included the following: (1) Fluid Attenuated Inversion Recovery (FLAIR) sequence — TR/TE/TI = 9000/130/2200 ms, field-of-view (FOV) = 240 × 240 mm^2, matrix = 256 × 192, 28 axial slices of 5 mm thickness and (2) spoiled gradient echo recalled T1-weighted (SPGR) 3D coronal sequence — TR/TE = 11.5/5 ms, FOV = 240 × 240 mm^2, matrix = 256 × 192, flip angle = 18°, 176 coronal slices of 1.1 mm thickness reconstructed to an in plane resolution of 1.1 mm.

2.3. Structural image pre-processing

Structural image preprocessing was performed to compute accurate deformation field maps to align T1-weighted volume images to a group-average template generated from the data cohort used in this study. The preprocessing also involves computation of Tissue Probability Maps (TPMs) for grey matter (GM), white matter (WM), cerebrospinal fluid (CSF) and white matter hyperintensities (WMH) to increase tissue segmentation accuracy across the cohort. T1-weighted images were segmented using New Segment in SPM12 into isotropic (1 mm^3 voxel resolution) GM, WM and CSF tissue classes. These were used to estimate deformations to a group-average template generated from the data cohort using the Shoot toolbox in SPM12 (Ashburner and Friston, 2011). The T1-weighted and FLAIR images were skull-stripped using the segmentations at a threshold of 0.1 and warped to the group-average template. These were used to create population specific TPMs using a modified multivariate mixture of Gaussians (mMoG) (Lambert et al., 2013). This was performed to increase segmentation accuracy across the cohort, and provide TPMs for WMH from the FLAIR and T1 weighted images, allowing automatic segmentation at an individual level. It is necessary to note that GM FLAIR hyperintensities were not segmented using this technique. Instead, these would have been included in the GM tissue class, and were not analysed. Three population specific TPMs for GM, WM and CSF were created using the warped T1-weighted images, and a WMH lesion TPM was created from T1-weighted and FLAIR images. The default SPM TPMs were replaced by the population specific TPMs and New Segment was re-run on the native space images to generate improved segmentation maps for GM, WM and CSF, and a WMH segmentation map for each individual. These WMH segmentation maps were binarised at a threshold set for each individual by checking results manually to ensure accurate correspondence with lesions on the FLAIR image. Results were manually refined where necessary to optimise accuracy.

An additional step was performed to repair the segmentations for regions of tissue damage. This was motivated by the observation that regions affected by pathology are frequently misclassified during routine segmentation. For example, regions of gliosis are misclassified as CSF and regions of WMH as GM leading to erroneous deformation estimations and subsequent inaccuracies in estimating warps to the group-average space. For this reason, WMH regions were automatically reclassified as WM and any erroneously classified tissue was removed from the GM and CSF segmentation maps. Regions with lacunes were also corrected using the most likely tissue type for each voxel derived from the population TPMs. All images were visually inspected for quality.

All corrected tissue segmentations (including GM, WM and CSF)