NeuroImage: Clinical 9 (2015) 194–205

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Characterising the grey matter correlates of leukoaraiosis in cerebral small vessel disease

Christian Lambert[a,*], Janakan Sam Narean[a], Philip Benjamin[a], Eva Zeestraten[a], Thomas R. Barrick[a], Hugh S. Markus[a,b]

[a] Neurosciences Research Centre, Cardiovascular and Cell Sciences Research Institute, St George's University of London, United Kingdom
[b] Stroke Research Group, Division of Clinical Neurosciences, University of Cambridge, United Kingdom

ARTICLE INFO

Article history:
Received 17 January 2015
Received in revised form 30 June 2015
Accepted 3 July 2015
Available online 13 August 2015

ABSTRACT

Cerebral small vessel disease (SVD) is a heterogeneous group of pathological disorders that affect the small vessels of the brain and are an important cause of cognitive impairment. The ischaemic consequences of this disease can be detected using MRI, and include white matter hyperintensities (WMH), lacunar infarcts and microhaemorrhages. The relationship between SVD disease severity, as defined by WMH volume, in sporadic age-related SVD and cortical thickness has not been well defined. However, regional cortical thickness change would be expected due to associated phenomena such as underlying ischaemic white matter damage, and the observation that widespread cortical thinning is observed in the related genetic condition CADASIL (Righart et al., 2013).

Using MRI data, we have developed a semi-automated processing pipeline for the anatomical analysis of individuals with cerebral small vessel disease and applied it cross-sectionally to 121 subjects diagnosed with this condition. Using a novel combined automated white matter lesion segmentation algorithm and lesion repair step, highly accurate warping to a group average template was achieved. The volume of white matter affected by WMH was calculated, and used as a covariate of interest in a voxel-based morphometry and voxel-based cortical thickness analysis. Additionally, Gaussian Process Regression (GPR) was used to assess if the severity of SVD, measured by WMH volume, could be predicted from the morphometry and cortical thickness measures.

We found significant (Family Wise Error corrected $p < 0.05$) volumetric decline with increasing lesion load predominately in the parietal lobes, anterior insula and caudate nuclei bilaterally. Widespread significant cortical thinning was found bilaterally in the dorsolateral prefrontal, parietal and posterio-superior temporal cortices. These represent distinctive patterns of cortical thinning and volumetric reduction compared to ageing effects in the same cohort, which exhibited greater changes in the occipital and sensorimotor cortices. Using GPR, the absolute WMH volume could be significantly estimated from the grey matter density and cortical thickness maps (Pearson's coefficients 0.80 and 0.75 respectively).

We demonstrate that SVD severity is associated with regional cortical thinning. Furthermore a quantitative measure of SVD severity (WMH volume) can be predicted from grey matter measures, supporting an association between white and grey matter damage. The pattern of cortical thinning and volumetric decline is distinctive for SVD severity compared to ageing. These results, taken together, suggest that there is a phenotypic pattern of atrophy associated with SVD severity.

1. Introduction

Cerebral small vessel disease (SVD) refers to a heterogeneous group of pathological disorders that, by definition, affect the small vessels of the brain (Pantoni, 2010). They are characterised by typical radiological changes on MRI including white matter hyperintensities (WMH), lacunar infarcts (LI) and cerebral microbleeds (Gouw et al., 2011). It is a highly prevalent disease that increases with age (De Leeuw et al., 2001). SVD is part of a clinical spectrum that ranges from asymptomatic disease through to extensive WMH and LI in symptomatic patients with stroke and vascular dementia (Patel and Markus, 2011; Pantoni, 2010). There is increasing evidence of more subtle morbidities in those with apparently asymptomatic disease. These include cognitive impairment (Lawrence et al., 2013; Pantoni et al., 2007; Prins et al., 2005), gait disturbance (de Laat et al., 2012; de Laat et al., 2010) and depression (Poggesi et al., 2011).

* Corresponding author. Tel.: +44 (0)20 8266 6468; fax: +44 (0)20 8725 2950
E-mail address: clambert112358@gmail.com (C. Lambert).

http://dx.doi.org/10.1016/j.nicl.2015.07.002

Cognitive impairment in SVD has been shown to associate with a number of different MRI features of SVD including lacunar infarcts, WMH, and less consistently microbleeds (Patel & Markus, 2011); recent evidence suggest that these pathologies are mediated via disruption of complex cortical–subcortical networks (Lawrence et al., 2013). An additional consistent feature associated with cognition impairment in SVD is brain atrophy; whether this occurs due to primary cortical SVD pathology or secondary to white matter changes. Additionally, the mechanism leading to cognitive impairment remains poorly understood. In this study we used a variety of image analysis techniques to further characterise the pattern of cortical atrophy in SVD and define the relationship between grey matter changes and WMH.

1.1. Cortical atrophy in cerebral small vessel disease

Whole brain atrophy is a widely reported feature of SVD (Nitkunan et al., 2011; Jokinen et al., 2012), and has been proposed as a simple surrogate of disease progression (Patel and Markus, 2011). However, this measure provides no spatial information regarding the pattern of cortical loss that gives rise to volumetric changes. Furthermore, whole brain atrophy is a feature of a diverse range of potentially overlapping neurological disorders (Fox and Schott, 2004; Sluimer et al., 2010; Schott et al., 2010) as well as in normal ageing (Fjell et al., 2009) and whole brain atrophy measurements fail to distinguish between these different pathologies (Smith et al., 2002). However, characterising the spatial distribution of atrophy may define phenotypic specific patterns (Fox and Schott, 2004), providing a more sensitive and specific means of disease differentiation. Voxel based morphometry (VBM) is a widely used technique that characterises voxel-wise changes in volume within a statistically robust framework (Ashburner and Friston, 2000) and provides insight into spatial patterns that contribute to changes in whole brain volumes (Rohrer et al., 2010). Previous work in SVD using VBM (Raji et al., 2012; Wen et al., 2006) found a correlation between WMH volume (WMHV) and grey matter volume in the dorsolateral prefrontal cortex and posterior portions of the superior and middle temporal gyri. Further evidence for the link between WMH and grey matter changes is found in CADASIL, an autosomal dominant early onset form of SVD, where selective anterior temporal grey matter atrophy has been associated with increasing WMHV (Rossi Espagnet et al., 2012). This work seeks to further these observations by characterising the pattern of GM changes associated with WMHV in sporadic SVD, and differentiate related age associated changes.

1.2. Cortical thickness in cerebral small vessel disease

Cortical thickness (CT) studies in SVD are more limited, but may be a promising area, as several pathologies present in SVD would be expected to impact on these measurements. These include disrupted white matter connections due to lacunar infarcts (Duering et al., 2012) or WMH, and the presence of cortical microinfarcts (Smith et al., 2012). Previous attempts to characterise the association between CT and WMHV (van Velsen et al., 2013; de Laat et al., 2012; Reid et al., 2010) in cerebral SVD have yielded few significant results at a global level. However, sub-group analysis by age has indicated a significant negative correlation between WMHV and cortical thickness particularly in the primary auditory cortex (BA 44–45), ventromedial prefrontal cortex (BA10), cingulate gyrus and Broca's area (Reid et al., 2010). The absence of CT changes using whole group analysis techniques may be due, in part, to the region of interest (ROI) based approaches adopted by these previous studies. In particular, these studies averaged CT measurements over automatically parcellated *a priori* regions for which the regional sizes and boundaries have high inter-individual variability when examined histologically (Amunts et al., 2000), resulting in a potential reduction in statistical and spatial sensitivity. Previous studies have also applied surface-based approaches that fit a deformable surface model to an individual brain allowing computation of cortical thickness (Fischl and Dale, 2000). These models rely on accurate surface extraction and have been reliably generated in healthy control subjects. However, difficulties arise in fitting deformed surfaces to deep sulci, buried cortex or abnormally structured brains (Hutton et al., 2008) potentially contributing to the lack of observed findings in SVD using this technique.

Voxel-based cortical thickness (VBCT) (Hutton et al., 2008) is a toolbox implemented in SPM. It uses a voxel-wise layer-growing technique on tissue segmentations in native space to produce a scalar measure of cortical thickness at each voxel location. This enables voxel-wise statistical analysis of cortical thickness using a standard SPM framework and has been previously used to study ageing effects on the cortex (Hutton et al., 2009). This VBCT analysis is a complementary technique to statistical analysis of modulated grey matter in standard VBM analysis, and has been shown to provide a more sensitive measure of healthy age-related grey matter changes (Hutton et al., 2009) due to the fact that cortical folding and surface area have less influence on CT measurements compared to VBM. Whilst it should be noted that voxel-wise methods do not completely circumvent the problems relating to inter-individual anatomical variance at the voxel level due to their reliance on normalisation procedures, the use of newer diffeomorphic-warping techniques (Ashburner and Friston, 2011) with higher anatomical precision (Klein et al., 2009) can allow for less smoothing of the data and therefore improve the sensitivity to detect localised changes in brain structure compared to ROI based approaches.

1.3. Machine learning in cerebral small vessel disease

Machine learning techniques are multivariate methods that allow spatial patterns in high dimensional, complex data to be determined. Analysis of these learned patterns is usually performed by classification or regression algorithms with these techniques attempting to generalise or provide predictions from unseen data. Classifiers partition the data into two or more groups and have been clinically used for many tasks such as predicting language outcome after stroke from fMRI data (Saur et al., 2010), diagnosing dementia syndromes (Klöppel et al., 2008) and predicting tumour grade (Zacharaki et al., 2009). Regression methods aim to predict a continuous variable, such as clinical score, from the features within the dataset and have been previously used to predict variables such as age (Franke et al., 2010) and MMSE (Stonnington et al., 2010) from MRI data. Predictive regression methods provide additional anatomical information by determining the spatial features that significantly contribute to the predictions. Here we use a probabilistic regression technique known as Gaussian Process Model Regression (GPR), a Bayesian supervised machine-learning technique for multivariate non-linear regression (Rasmussen, 2006). This technique has been successfully applied to predict recovery of speech function following stroke based on MRI lesion data (Hope et al., 2013). We use it as a complementary multivariate anatomical method to standard univariate VBM and VBCT analyses to better characterise the grey matter correlates of WMH and provide the foundations for future clinical prediction models in SVD.

1.4. Hypotheses

This work addresses four hypotheses based on the observations from previous work that, taken together, aim to clarify and define a phenotypic specific pattern of grey matter atrophy (Fox and Schott, 2004) associated with increasing cerebral SVD severity. Our hypotheses are that there is a relationship between SVD severity and volumetric whole brain changes that can be detected using VBM (Raji et al., 2012; Wen et al., 2006). There is a significant inverse association between SVD severity and regional cortical thickness, which can be demonstrated by employing voxel-wise techniques for measuring and analysing cortical thickness measures (Hutton et al., 2008). Furthermore, the