AN ARTERIAL SPIN LABELLING STUDY REVEALING ALTERED NEUROVASCULAR STATUS IN IDIOPATHIC PARKINSON'S DISEASE; COMPARISONS WITH CEREBROVASCULAR DISEASE

Sarah Al-Bachari[1], Hedley Emsley[2], Rishma Vidyasagar[1,3], and Laura Parkes[4]

[1]Imaging, University of Manchester, Manchester, United Kingdom, [2]Neurology, Royal Preston Hospital, Preston, Lancashire, United Kingdom, [3]Department of Anatomy and Neurosciences, University of Melbourne,Victoria, Victoria, 3010, Australia, [4]Imaging, Manchester University, Manchester, United Kingdom

Target Audience: Clinicians with an interest in stroke and idiopathic Parkinson's disease (IPD) and MRI researchers interested in the application of ASL in cerebrovascular disease/neurodegeneration.

Purpose: Idiopathic Parkinson's disease (IPD) is the second most common neurodegenerative disorder, yet effective disease modifying agents are lacking. Alterations in neurovascular status (NVS) have been identified in preclinical studies in IPD, yet clinical studies quantifying these changes are lacking (1). IPD exhibits significant heterogeneity in respect of both motor and non motor clinical features, resulting in the classification of 2 main phenotypes; the tremor dominant (TD) and postural instability and gait dominant (PIGD), based on predominant motor features. It is felt their distinct motor features may be reflective of varying underlying pathophysiologies (2), perhaps related to NVS.

ASL is emerging as a suitable, noninvasive, imaging technique for quantifying cerebral haemodynamics; most focus has been on cerebrovascular disease (CVD) manifesting as acute stroke and transient ischaemic attack (TIA), usually as a diagnostic tool (3). However little focus has been placed on using ASL to better understand the chronic haemodynamic changes that ensue after the acute insult of stroke or to understand the vascular burden in IPD. Recent modifications to the standard ASL sequences, the Look Locker ASL (LL-ASL), provides efficient collection of multiple time-point measurements allowing quantification of both cerebral blood flow (CBF) and arterial arrival time (AAT) (4). The central aim of this study is to determine whether ASL measurements of CBF and AAT are altered in IPD, whether they differ according to phenotype, and to determine whether these changes are similar to those of established CVD.

Methods: 12 subjects with CVD (manifesting as minor stroke or TIA within the previous 2 years [at least 3 months post onset, mean time, in years, since diagnosis 1.1±0.5; mean age 68.9± 7.8]), 19 TD IPD subjects (mean age 67.2± 0.6), 17 PIGD IPD subjects (mean age 70.7± 6.6) and 23 healthy control (C) subjects (mean age 65.1± 5.7) were scanned on a 3T Philips Achieva MRI system. The number of cerebrovascular risk factors for the control (mean 1.3± 1.0), TD (mean 1.9±1.6) and PIGD (mean 1.5±1.3) groups were matched, but the CVD group had significantly more (mean 3.6± 1.1). *Scan protocol*: A Look-Locker ASL sequence was used with STAR labelling and 4 readout times of 800, 1400, 2000, 2600 ms, TR: 3500 ms; 3.5 x3.5 x 6 mm voxels; 15 slices; FA: 40 deg; TE: 22 ms with bipolar field gradients to reduce large vessels signal (vascular crushers). *Analysis*: ASL data were analysed using in-house MATLAB routines using a single blood compartment model (5) adapted for LL readout (6), to produce quantitative maps of CBF and AAT. Voxel-wise analysis was also performed using SPM8 to compare CBF and AAT maps between the groups.

Results:

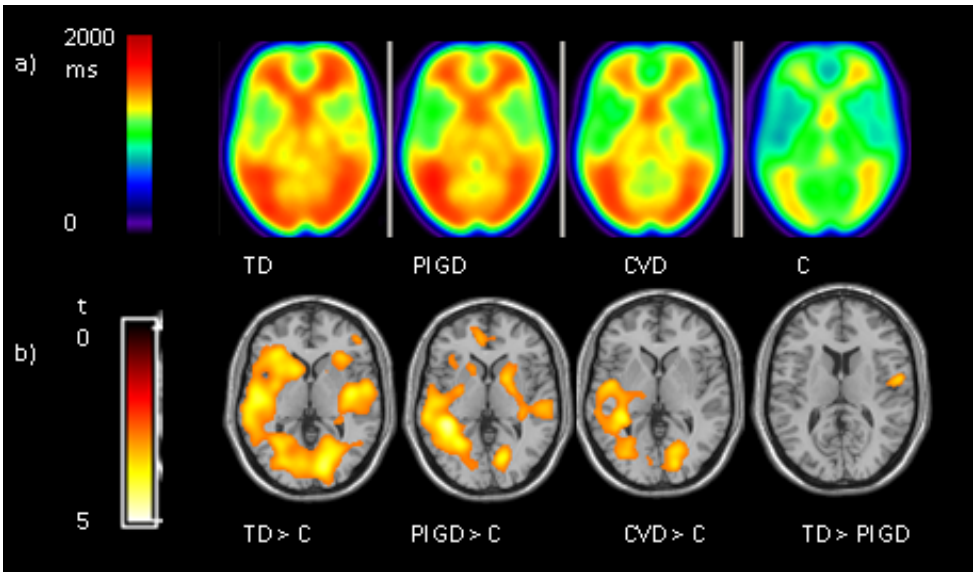

Fig. 1 Regions of prolonged arrival time in IPD and CVD groups compared to controls. a) Mean arrival time maps. b) t statistic maps obtained by comparison of AAT between various groups, thresholded to $p < 0.001$ uncorrected, minimum cluster size 100 voxels.

All participants were scanned, whilst on their regular mediations. The results revealed a significant widespread increase in baseline AAT in the 2 IPD phenotypes (TD and PIGD) and the CVD group when compared to controls. There was only one area of significantly prolonged AAT in the TD group compared to the PIGD group. Voxel-based analysis of CBF revealed significant focal regions of hypoperfusion in the TD, PIGD and the CVD group when compared to controls. This was predominantly in the posterior cortices, yet the AAT changes seem to be more diffuse and prominent.

Discussion and Conclusion: Despite significantly fewer CV risk factors, IPD subjects of both the TD and PIGD phenotypes had similar patterns of diffuse, prolonged AAT to those of known CVD, with the IPD group prolongation being more pronounced. The prolonged AAT seems to be more extensive and pronounced than the CBF changes, this could perhaps be indicative of chronic vascular alterations in order to maintain CBF. Prolonged AAT has been attributed to increased collateral circulation, chronic vasodilatation and/or increased tortuosity of vessels in other studies (7). Earlier ASL studies in IPD focus mostly on CBF changes, using single time points so AAT cannot be estimated (8). AAT has been measured with ASL in acute stroke/TIA but few studies focus on chronic changes. These earlier stroke studies have demonstrated correlations in ischaemic territories between prolonged AAT and Mean Transit Time (MTT), as measured with DSC-MRI. Wang et al. revealed prolonged AAT particularly in leptomeningeal regions (i.e. areas of collateral flow) but less so in regions of acute stroke or perforator regions (3, 9, 10), suggesting prolonged AAT reflects the recruitment of collateral circulations.

This study demonstrates the potential role of ASL in investigating neurovascular status in IPD, indicating that alterations in neurovascular status occurs in IPD, independent of CV risk factors, yet produces patterns of haemodynamic changes comparable to chronic CVD. This may be as a direct consequence of the neurodegenerative process. Interestingly despite the heterogeneity of clinical features within IPD, the TD and PIGD phenotypes revealed very similar patterns of prolonged AAT. In addition the chronic changes of AAT in CVD despite heterogeneity of loci of the lesions warrant further investigation. Understanding altered neurovascular status in neurodegenerative disease such as IPD and in CVD may help to direct future therapeutic targets.

• **References –**1) Grammas P et al. (2011). Expert Rev Mol Med.13; E19 2) Jankovic J et al. (1990). Neurology; 40 (10):1529-34 3) Wang DJ et al. (2013). Neuroimage Clin 3:1-7. 4) Gunther M et al. (2001) Magn Reson Med 46(5):974-984. 5) Parkes LM, Tofts PS (2002). Magn Reson Med; 48 (1):27-41.6) Al-Bachari et al. (2014). Neuroimage Clin 1;6:1-8. 7) Liu Y et al (2012), Magn Reson Med: 68:912–922 8) Fernandez-Seara et al. (2012).Neuroimage 59; 2743-2750 9) MacIntosh VJ et al. (2010). AJNR 1892-1895. 10) Zaharchuk G et al. (2012). Cerebrovasc Dis 34:221-228.