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Arterial spin labelling reveals prolonged arterial arrival time in idiopathic Parkinson's disease

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ABSTRACT

Idiopathic Parkinson's disease (IPD) is the second most common neurodegenerative disease, yet effective disease modifying treatments are still lacking. Neurodegeneration involves multiple interacting pathological pathways. The extent to which neurovascular mechanisms are involved is not well defined in IPD. We aimed to determine whether novel magnetic resonance imaging (MRI) techniques, including arterial spin labelling (ASL) quantification of cerebral perfusion, can reveal altered neurovascular status (NVS) in IPD.

Fourteen participants with IPD (mean ± SD age 65.1 ± 5.9 years) and 14 age and cardiovascular risk factor matched control participants (mean ± SD age 64.6 ± 4.2 years) underwent a 3T MRI scan protocol. ASL images were collected before, during and after a 6 minute hypercapnic challenge. FLAIR images were used to determine white matter lesion score. Quantitative images of cerebral blood flow (CBF) and arterial arrival time (AAT) were calculated from the ASL data both at rest and during hypercapnia. Cerebrovascular reactivity (CVR) images were calculated, depicting the change in CBF and AAT relative to the change in end-tidal CO_2.

A significant ($p = 0.005$) increase in whole brain averaged baseline AAT was observed in IPD participants (mean ± SD age 1532 ± 138 ms) compared to controls (mean ± SD age 1335 ± 165 ms). Voxel-wise analysis revealed this to be widespread across the brain. However, there were no statistically significant differences in white matter lesion score, CBF, or CVR between patients and controls. Regional CBF, but not AAT, in the IPD group was found to correlate positively with Montreal cognitive assessment (MoCA) scores. These findings provide further evidence of alterations in NVS in IPD.

1. Introduction

Idiopathic Parkinson's disease (IPD) is the second most common neurodegenerative disorder, affecting 1–2% of the population over the age of 65, with the incidence increasing steeply with age (Van Den Eeden et al., 2003). Progression is variable and difficult to predict, but IPD is often associated with significant disability. Treatment remains symptomatic, with an absence of effective disease modifying or neuroprotective agents.

Alterations in neurovascular status (NVS) – including measures of cerebral hemodynamic function as well as more conventional clinical and radiological measures of cerebrovascular disease (CVD) – might be expected in IPD for two principal reasons. Firstly, neurodegeneration is considered to comprise multiple interacting pathological pathways (Collins et al., 2012). Recently there has been considerable interest in the disturbance of neurovascular unit (NVU) function and the 'neurovascular model' of neurodegeneration (Grammas et al., 2011; Zlokovic, 2008). The NVU is a complex, metabolically active system of

Abbreviations: ASL, arterial spin labelling; AAT, arterial arrival time; AD, Alzheimer's disease; CBF, cerebral blood flow; CO_2, carbon dioxide; CV, cerebrovascular; CVD, cerebrovascular disease; CVR, cerebrovascular reactivity; CVR_{AAT}, cerebrovascular reactivity measures of arterial arrival time; CVR_{CBF}, cerebrovascular reactivity measures of cerebral blood flow; DS, digit span; DSST, digit symbol substitution test; DWMH, deep white matter hyperintensity; EPI, echo planar imaging; $ETCO_2$, end-tidal carbon dioxide; FAS, (verbal) fluency assessment scale; FLAIR, fluid attenuation inversion recovery; fMRI, functional magnetic resonance imaging; FWE, family-wise error; HAM-D, Hamilton depression rating scale; IPD, idiopathic Parkinson's disease; LARS, Lille apathy rating scale; L-dopa, levodopa; LEDD, levodopa equivalent daily dose; MCI, mild cognitive impairment; MoCA, Montreal cognitive assessment; MRI, magnetic resonance imaging; NPI, neuropsychiatric inventory; NVU, Neurovascular unit; O_{2-}, oxygen; PET, positron emission tomography; PIGD, Postural instability and gait disorder; PL, parietal lobe; PVH, periventricular hyperintensity; ROI, region of interest; SPECT, single positron emission computed tomography; SPM, statistical parametric mapping; STAR, signal targeting with alternating radiofrequency; TD, tremor dominant; TE, echo time; 3T, 3 Tesla; TI, inversion time; TL, temporal lobe; TMT-B, trail making test B; TR, repetition time; UKPDS BB, United Kingdom Parkinson's Disease Society Brain Bank; UPDRS, Unified Parkinson's disease Rating Scale; WAIS-R, Wechsler adult intelligence scale-revised; WML, white matter lesion.

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endothelial cells and glial cells in close proximity to a neuron. Whether altered NVU function is primary or secondary to neurodegeneration, or even attributable to the effect of pharmacotherapy, remains unclear. Secondly, as IPD is strongly associated with ageing, an increased burden of comorbid CVD might be expected, but the evidence is somewhat conflicted probably on account of varying study designs and endpoints (Morley and Duda, 2012). Currently, the extent to which NVS is altered in IPD is poorly defined.

There is also substantial heterogeneity within IPD with respect to clinical phenotype, including motor and non-motor features and it is possible that differences in NVS might be influential in these differing phenotypes (Lee et al., 2009). Tremor dominant (TD) and postural instability and gait disorder (PIGD) phenotypes are recognised, based on the predominant motor features (Jankovic et al., 1990). Non-motor features (in particular neuropsychiatric and cognitive dysfunction) have been reported in a significant proportion of IPD patients; with cognitive decline being associated with worse motor and non-motor features (Aarsland et al., 1999; Hu et al., 2014). Studies suggest distinct clinical courses and even variable involvement of the dopaminergic system and other pathways between phenotypes (Eggers et al., 2012; Mito et al., 2006).

Magnetic resonance imaging (MRI) can provide valuable measures of NVS, such as white matter lesion (WML) burden and cerebral blood flow (CBF). Arterial spin labelling (ASL) employs magnetically labelled endogenous arterial blood water to quantify cerebral perfusion. ASL can also measure arterial arrival time (AAT), the time taken for blood to travel from the labelling slab to the tissue of interest (Wang et al., 2003; Zappe et al., 2007). AAT is longest in distal branches, especially in border zone (or watershed) areas (Hendrikse et al., 2008; Petersen et al., 2006). Alterations in resting state AAT are considered likely to reflect chronic arteriolar vasodilation or collateral flow (Derdeyn et al., 2002; Farkas and Luiten, 2001). Cerebrovascular reactivity (CVR) can be measured by combining ASL with a hypercapnic challenge. CVR reflects the capacity of the blood vessels to dilate in response to a hypercapnic challenge and can be used as a measure of brain vascular reserve (Hajjar et al., 2010).

We hypothesise that NVS is altered in IPD. This was tested by comparing MRI measurements of NVS between a group of people with IPD and age and cardiovascular risk matched controls. In addition MRI images were correlated against cognitive and neuropsychiatric scores to determine any association between NVS measurements and such non-motor features of IPD.

2. Methods

2.1. Participants

Relevant approvals were obtained including ethics (North West — Preston Research Ethics Committee), research governance and local university approvals. Eligibility criteria for IPD participants were a clinical diagnosis of IPD fulfilling the UK Parkinson's Disease Society (UKPDS) Brain Bank (BB) criteria (http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/GetPdf.cgi?id=phd000042) without known clinical CVD (no history of transient ischaemic attack or stroke) or dementia (Emre et al., 2007) or radiological evidence of large vessel cortical/subcortical infarct >1.5 cm. Control participants (without IPD or above exclusion criteria) were matched for age and cardiovascular risk factors. All participants were required to provide written informed consent and had the capacity to do so. All underwent a scan protocol on a 3T Philips Achieva MRI system using an 8 channel head coil at Salford Royal Hospital. Involuntary movements in participants were minimised using padding within the head coil. All participants were scanned 'ON' their medications. IPD phenotype was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) (http://www.etas.ee/wp-content/uploads/2013/10/updrs.pdf) during the scan visit. Participants were further classified into three subtypes (TD, PIGD, and intermediate) by Jankovic's method (Jankovic et al., 1990). Disease severity was measured using the Hoehn and Yahr rating scale (Hoehn and Yahr, 1967). No alterations were made to the participants' medications for the study protocol. Routine clinical baseline data were also recorded and the levodopa equivalent doses (LEDD) calculated (Tomlinson et al., 2010). A battery of clinical scales was administered, including the Montreal Cognitive Assessment (MoCA) (http://www.MoCAtest.org), the O'Sullivan brief cognitive assessment for participants with cerebral small vessel disease (O'Sullivan et al., 2005), the Lille apathy rating scale (LARS) (Sockeel et al., 2006), the Hamilton depression scale (HAM-D) (Muller and Dragicevic, 2003) and the neuropsychiatric inventory (NPI) psychosis subscale (Fernandez et al., 2008). Demographics and clinical data were compared between IPD and control participants using the unpaired Student t-test with p-value set at <0.05.

2.2. MRI protocol

A T2-weighted FLAIR image was acquired with the following parameters: TR 11 s, TI 2.8 s, TE 120 ms, in-plane resolution of 0.45 mm, 30 axial slices of 4 mm thickness with 1 mm gap covering the whole brain. A Look-Locker ASL sequence was used (Gunther et al., 2001), with STAR labelling (Edelman et al., 1994) and 4 readout times of 800, 1400, 2000, and 2600 ms, TR: 3500 ms; TE 22 ms; flip angle 40°; $3.5 \times 3.5 \times 6$ mm voxels with a 1 mm gap between slices; 15 slices covering the cerebrum but not the cerebellum with bipolar 'vascular crusher' gradients added to dephase fast flowing spins and so remove large vessel signal. The labelling slab was 15 cm with a 10 mm gap between the labelling and imaging regions. 112 pairs of labelled and control images were collected, with scan duration approximately 13 min. To allow quantification of CBF an additional scan was acquired with TR = 10 s and 15 read-out times (from 800 to 9200 ms) in order to estimate the equilibrium magnetisation of the brain. An additional echo planar image (EPI) was collected with the same slice positioning and the same voxel dimensions but with TE = 35 ms to give typical fMRI contrast for registration and normalisation purposes. A 3D T1-weighted image with 1 mm isotropic resolution was also collected.

During the ASL acquisition a CO_2 (hypercapnic) challenge was carried out. After 5 min of breathing room air (from which the baseline perfusion images were extracted) there followed 6 min of hypercapnia, administered using a non-rebreathing circuit using the Fenn and Craig technique (Fenn and Craig, 1963) and a final 2 min of return to room air. This method involves a thin stream of gas (79% CO_2 balanced with 21% O_2) being delivered through larger tubing allowing it to mix with room air. This mixture then passes through a 3-way valve which directs it to a filter and a mouth piece (Vidyasagar et al., 2013). End-tidal CO_2 ($ETCO_2$) and O_2 were continuously monitored using Powerlab (LabChart7 V7.2.1, 2011) and the CO_2 flow-rate was altered to ensure all participants reached an increased end tidal level approximately 1% above their baseline $ETCO_2$. Prior to each scanning session the gas analysers were calibrated using a canister of gas with known concentrations of 5.03% CO_2 and 21.0% O_2, each participant also had a trial session of inhaled gas to allow them to become accustomed to the apparatus, this also provided an opportunity to assess an appropriate flow rate required to induce a 1% change in $ETCO_2$.

2.3. Data analysis

WML burden was assessed semi-quantitatively using visual rating scales (Fazekas et al., 1993; Wahlund et al., 2001). Between group comparisons were made using Student's unpaired t test analysis. ASL data were analysed using in-house MATLAB (Mathworks, MA, USA) routines using a single blood compartment model, adapted for Look-Locker readout (Parkes L.M., 2012). Further details of the ASL modeling are given in the appendix.

Baseline CBF and AAT maps were calculated using the first 5 min of ASL data, during breathing of air. CVR maps were calculated using