Multi-delay multi-parametric arterial spin labeling perfusion MRI and mild cognitive impairment in early-stage Parkinson's disease

Short title: ASL in PD with mild cognitive impairment

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Abstract

Mild cognitive impairment (MCI), a well-defined non-motor manifestation of Parkinson's disease (PD), greatly impairs functioning and quality of life. However, the contribution of cerebral perfusion, quantified by arterial spin labelling (ASL), to MCI in PD remains poorly understood. The selection of an optimal delay time is difficult for single-delay ASL, a problem which is avoided by multi-delay ASL. This study uses a multi-delay multi-parametric ASL to investigate cerebral perfusion including cerebral blood flow (CBF) and arterial transit time (ATT) in early-stage PD patients exhibiting MCI using a voxel-based brain analysis. MRI data were acquired on a 3.0 T system at rest in 39 early-stage PD patients either with MCI (PD-MCI, N=22) or with normal cognition (PD-N, N=17), and 36 age- and gender-matched healthy controls (HC). CBF and ATT were compared among the three groups with SPM using analysis of variance followed by post hoc analyses to define regional differences and examine their relationship to clinical data. PD-MCI showed prolonged ATT in right thalamus compared to both PD-N and HC, and in right supramarginal gyrus compared to HC. PD-N showed shorter ATT in left superior frontal cortex compared to HC. Prolonged ATT in right thalamus was negatively correlated with the category fluency test ($p = 0.027$, $r = -0.495$) in the PD-MCI group. This study shows that ATT may be a more sensitive marker than CBF for the MCI, and highlights the potential role of thalamus and inferior parietal region for MCI in early stage PD.

Keywords: Parkinson's disease; mild cognitive impairment; arterial spin labeling; multi-delay; arterial transit time; cerebral blood flow.

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INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease (Jankovic, 2008). Mild cognitive impairment (MCI) is a well-defined non-motor manifestation of PD, which greatly impairs functioning and quality of life and frequently progresses to dementia (Svenningsson et al., 2012). PD patients exhibiting MCI (PD-MCI) are candidates for disease-modifying intervention before irreversible changes occur, and this has prompted the search for objective imaging biomarkers to predict cognitive decline and monitor disease progression.

Arterial spin labeling (ASL) is a magnetic resonance imaging (MRI) method for quantifying cerebral blood flow (CBF) and arterial transit time (ATT) by using magnetically labeled arterial blood water as an endogenous tracer. Because it is entirely non-invasive, and needs no radioactive tracer or other contrast agent (Detre et al., 1992), ASL has been increasingly used to investigate perfusion in healthy controls (HC) and several neurological and psychiatric disorders (Hales et al., 2014; Lin et al., 2016; Lui et al., 2009), including PD (Al-Bachari et al., 2014; Al-Bachari et al., 2017; Fernandez-Seara et al., 2012; Lin et al., 2016; Melzer et al., 2011; Wei et al., 2016).

ASL studies in PD have generally employed a single post-labeling delay (PLD) time for estimating CBF (Fernandez-Seara et al., 2012; Lin et al., 2016; Melzer et al., 2011). The main limitation of single-delay ASL is that the delay time between labelling in the feeding arteries and arrival of labeled blood in tissue (i.e. the ATT) can have a large effect on the perfusion signals (Wang et al., 2014), and a long ATT, larger than the PLD, could result in underestimation of brain perfusion. The selection of a single optimal delay time is difficult

because ATT varies widely among patients with different vascular and perfusion characteristics (Johnston et al., 2015). Acquisition of serial ASL images at multiple PLDs offers potential advantages over single PLD ASL, allowing calculation of multiple hemodynamic parameters (ATT and CBF) and improving accuracy of CBF quantification (Wang et al., 2013). Furthermore, by combining single-shot 3D gradient and spin echo (GRASE), background suppression and pseudo-continuous ASL (pCASL), the temporal stability of ASL image series has been improved within a clinically reasonable total scan time (Gunther et al., 2005). ATT and CBF alterations have previously been reported in ASL studies of PD clinical phenotypes (Al-Bachari et al., 2017). However, little is known about how such changes might be associated with MCI.

Another limitation of previous studies in PD is that the patients have usually represented a broad disease spectrum of disease severity, collected in a single 'non-dementia' group (Syrimi et al., 2017). By contrast the separation of non-demented PD patients into PD-MCI and PD with normal cognition (PD-N) promises greater discrimination in identifying underlying brain changes prior to PD with dementia (PD-D) (Melzer et al., 2012), avoiding this potential confounding effect.

Thus, the aim of this study was to apply a multi-delay multi-parametric pCASL protocol with background-suppressed 3D GRASE readout to study cerebral perfusion using voxel-based whole brain analysis in early-stage PD-MCI patients, and investigate possible relationships with clinical variables.

MATERIALS AND METHODS

Participants

A total of 39 right-handed PD patients were recruited from the movement disorders outpatient clinic of West China Hospital of Sichuan University. All met UK Parkinson's Disease Society's criteria. Twenty-two PD-MCI patients and 17 PD-N patients were diagnosed in accordance with the new Movement Disorder Society (MDS) Task Force criteria, Level II (Litvan et al., 2012). At the initial visit all patients were either drug-naïve or in an 'off' state defined as at least 12 hours after the last dose of dopaminergic medication; they received a comprehensive assessment (Helmich et al., 2010), including neurological examination, neuropsychological testing, and MRI scan. Clinical assessments were performed by an experienced neurologist blinded to the MRI results. The Unified PD Rating Scale (UPDRS) part III was used to assess motor disability (Goetz et al., 2008), and Hoehn and Yahr stage (H&Y stage) to evaluate disease severity (Hoehn and Yahr, 2001). Exclusion criteria at recruitment included atypical Parkinsonian disorder, prior learning disability, and history of other neurologic conditions including moderate or severe head injury, stroke, vascular dementia, major psychiatric or medical illness.

Thirty-six HC with no history of neurologic and psychiatric disease were recruited from the local area by poster advertisements. HC underwent a multidimensional assessment, including neurological and global cognitive evaluation, and were included in the study only if all items were normal.

This study was approved by the Research Ethics Committee of the West China Hospital of Sichuan University. Written informed consent was obtained from all participants before

enrollment in the study.

Neuropsychological assessment

Cognitive performance was evaluated by trained neurologists using a standardized neuropsychological battery. Global cognition was evaluated using the Mini Mental State Examination (MMSE) (Folstein et al., 1975) and Montreal Cognitive Assessment (MoCA) (Dalrymple-Alford et al., 2010). As recommended by the MDS Task Force 2012, specific cognitive domains including attention and working memory, executive function, language, memory, and visuospatial function were assessed (Litvan et al., 2012). Attention and working memory was assessed using the Trail Making Test Part A (TMT-A) and the digit span backward task; executive function was evaluated with category fluency test and 10 points Clock Drawing Test (CLOX-1); language was evaluated with WAIS-IV Similarities and Boston Naming Test (BNT); memory was evaluated with Hopkins Verbal Learning Test (HVLT) and Brief Visuospatial Memory Test–Revised (BVMT-R); visuospatial function was evaluated with Benton's Judgment of Line Orientation (JLO) and Clock Copying (CLOX-2).

To assess concordance with MDS level 2 criteria for PD-MCI, performance on the suggested five cognitive domains (attention/working memory, executive function, language, memory, and visuospatial function) was analyzed, and impairment was defined as test performance 1.5 standard deviation (SD) below appropriate norms. Categorization as PD-MCI required impairment on at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains. PD patients who did not fulfill criteria for PD-MCI or PD-D were classified as PD-N.

MRI Acquisition

The MRI data were acquired on a 3T Siemens Tim Trio system with a 12-channel phased-array head coil. Participants were fitted with soft ear plugs, positioned comfortably in the coil and instructed to relax and keep still. Head motion was minimized using foam pads. ASL scans were performed using a 4-delay pCASL protocol with background-suppressed single-shot 3D GRASE readout. Imaging parameters were as follows: 4 PLD times 1400/1800/2200/2600 ms; labelling pulse duration 1500 ms; repetition time (TR) 3500/3500/3500/3500 ms; echo time (TE) 22 ms; echo-train length 15; voxel size 3.44×3.44×5.00 mm^3; 26 slices covering the whole brain; 12 pairs of tag/control images for each delay with a total scan time of 5.9 min. An M0 image was acquired using TR = 5000 ms and PLD = 4000 ms (scan time = 15 s).

Image Processing

Images were processed using a self-compiled MATLAB program called ASLFit (provided by Siemens Healthcare, MR Collaborations NE Asia) based on SPM8 (Welcome Trust Centre for Neuroimaging, UCK, UK) and MATLAB 2010a (Mathworks, Natick, MA). First, motion correction was performed for all control and label images of the same series using the M0 image as a reference. After motion correction, mean perfusion difference images ΔM(i) were generated for each PLD by subtracting the label and control images, followed by averaging. The weighted delay (WD) was calculated using the images ΔM(i) by equation (1):

$$WD = \left[\sum_{i=1}^{4} W(i)\Delta M(i)\right] \Big/ \left[\sum_{i=1}^{4} \Delta M(i)\right] \quad (1)$$

and converted to ATT based on the theoretical relationship between the WD and ATT (Dai et al., 2012; Wang et al., 2013). The CBF at each delay was calculated using the equation (2):

$$CBF(i) = \frac{\lambda \Delta M(i) R}{2\alpha M0\left[\exp\left(\left(\min\left(ATT - W(i), 0\right) - ATT\right)R\right) - \exp\left(-\left(\tau + W(i)\right)R\right)\right]} \quad (2)$$

where λ (= 0.9 g/ml) is the blood/tissue water partition coefficient, R (= 0.61 s^{-1}) is the longitudinal relaxation rate of blood at 3T, α (= 0.8) is the tagging efficiency, M0 is the equilibrium magnetization of brain tissue, w(i) is the PLD (= 1400/1800/2200/2600 ms), and τ (= 1500 ms) is the duration of the labelling pulse. The final CBF was taken as the mean of the estimated CBF at each PLD. All of the ASL images were spatially normalized to the Montreal Neurological Institute (MNI) template space with 79×95×68 dimension using SPM8, and smoothed using a 6 mm full width at half-maximum (FWHM) Gaussian kernel.

Voxel-based brain mapping analysis

Whole-brain voxel-wise analysis of ATT and CBF tested the main effect of diagnosis (PD-MCI, PD-N and HC) using ANOVA in SPM8 with the age, gender, years of education and LEDD as covariates. The global ATT and CBF were not different among groups ($p > 0.05$ in ANOVA), and were therefore not included as covariates in the analysis. Post hoc evaluations of significant ANOVA findings in these regions were then performed with secondary two-tailed independent sample t-tests. Values for the regions showing significant differences among three groups were extracted using the Mars Bar toolbox (http://marsbar.sourceforge.net).

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The comparison of ATT, CBF at 1400 ms, 1800 ms, 2200 ms and 2600 ms, and mean CBF between all PD patients and HC was performed using two-sample t tests. Statistical maps were overlaid onto a high-resolution brain template in the standard MNI space using MRIcron software (http://www.mccauslandcenter.sc.edu/crnl/mricron/index.html).

The voxel-wise ANOVA and t tests were performed with the threshold set at $p < 0.001$ corrected using AlphaSim (http://afni.nimh.nih.gov/afni/doc/manual/ AlphaSim) taking a contiguous cluster of at least 48 voxels as significant. To correct for multiple comparisons, a cluster analysis was conducted using a Monte Carlo simulation applied with the Resting-State fMRI Data Analysis Toolkit (REST) (Song et al., 2011) of the AlphaSim program, smoothed with a 6-mm Gaussian kernel with 1000 iterations. The vertex-wide threshold was set at $p < 0.001$ for simulation and clustering, and the results where cluster size ≥ 48 were considered significant if they survived a clusterwise probability of $p < 0.05$.

We conducted partial correlation analyses between the average regional values in these affected regions with cognitive scores with age, gender, years of education and Levodopa equivalent daily dose (LEDD) as covariates. In addition, voxel-wise regression analyses were performed to evaluate the relationship between ATT and CBF and five cognitive domain z scores in PD, with age, gender, years of education and UPDRS III as covariates. Raw scores for cognitive tests were transformed to z scores on the basis of normative data from HC at our center. Cognitive domain scores were calculated by averaging z scores for neuropsychological tests within each of the specific domains. Separate regression models were performed for each cognitive domain. All regression results were corrected for multiple comparisons using family wise error (FWE corrected, $p<0.001$).

Statistical analysis

Quantitative variables were compared across groups using the independent-sample t test and Kruskal–Wallis test or ANOVA (followed by Tukey post-hoc pairwise comparisons if significant). Qualitative variables were compared using a chi-squared test. The threshold for

these analyses was set at $p < 0.05$. Statistical analysis of the demographic and clinical data was performed in SPSS 16.0 software (http://www.spss.com).

RESULTS

Demographic and Clinical Comparisons

The demographic and clinical data are summarized in Table 1. Age, gender, years of education and MMSE did not differ significantly among the three groups. PD-MCI and PD-N were similar in age at onset, disease duration, H&Y stage, LEDD, and UPDRS III scores. PD-MCI had lower global cognition (MoCA: 19.1 vs 24.3, $p < 0.001$) scores compared with PD-N. PD-MCI demonstrated significantly poorer performance on executive function, memory and language abilities.

Three-group and between-group comparisons

There were no significant differences in CBF **among** the three groups.

The three groups had significant differences of ATT in right supramarginal gyrus (SMG), right thalamus, and left superior frontal gyrus (SFG) (Figure 1, Table 2). Post-hoc t tests showed the following: PD-MCI compared to HC showed prolonged ATT in right SMG and right thalamus; PD-N compared to HC showed shorter ATT in left SFG; PD-MCI compared to PD-N showed prolonged ATT in right thalamus ($p < 0.001$). Figure 2 illustrates the changes in the ATT values in these affected regions. Comparisons between all pairs of groups using unpaired t-tests are shown in Tables S1-S3.

All PD patients and HC comparison

All PD patients showed prolonged ATT in right SMG, right precuneus and bilateral middle

occipital gyrus (MOG) ($p < 0.001$) (Table 3, Figure 3). The CBF at 1800 ms in right caudate and the CBF at 2200 ms in right orbitofrontal cortex were decreased ($p < 0.001$) (Table 3, Figure 4).

Correlation analysis

In PD-MCI, prolonged ATT in right thalamus (MNI coordinates: x = 8, y = −26, z = 2) was negatively correlated with the category fluency test of executive function ($p = 0.027$, $r = -0.495$) (Figure 5). There were no significant correlations between other neuropsychological assessments and prolonged ATT in right thalamus and right SMG. In PD-N, there were no significant correlations between ATT and neuropsychological assessment. As all patients had a diagnosis of PD, with MCI determined by the cognitive assessment, the two patients groups were pooled in an exploratory analysis using nominal significance thresholds to examine associations of ASL findings with neuropsychological tests. Only the negative correlation between category fluency test and ATT in right thalamus was significant ($p = 0.039$, $r = -0.521$).

Results from voxel-wise multiple regression to evaluate the relationship between mean CBF and cognitive domain scores in PD are reported in Table 4 and Figure S1. The mean CBF in left middle frontal gyrus (MFG) were positively correlated with the executive ($r = 0.359$, $p = 0.034$) and visuospatial function z scores ($r = 0.339$, $p = 0.046$). No significant association was identified between mean CBF and any other cognitive domain score, nor were CBF at 1400ms, 1800ms, 2200ms, 2600ms or ATT significantly correlated with the cognitive domain scores.

DISCUSSION

In this study we investigated cerebral perfusion alterations in early stage PD-MCI patients using multi-delay multi-parametric pCASL. ATT was more sensitive than CBF in detecting altered cerebral perfusion in PD-MCI patients. The most prominent abnormality in PD-MCI was a significant prolongation of ATT in right thalamus and right SMG compared to PD-N and HC. This prolonged right thalamus ATT in PD-MCI was negatively correlated with executive function. In addition, PD-N showed shorter ATT in prefrontal cortex relative to HC. By contrast we found no differences in CBF among the three groups. Comparing all PD patients with HC, there was prolonged ATT in right SMG, right precuneus and bilateral MOG, as well as decreased CBF at 1800 ms PLD in right caudate and at 2200 ms PLD in right orbitofrontal cortex.

What do these findings mean in physiological terms? ATT represents the time taken for the magnetically labeled blood to flow from the labeling region to the vascular compartment of the imaging sections (Wang et al., 2003; Yoshiura et al., 2009b). Prolonged ATT in PD patients compared to controls has been previously reported (Al-Bachari et al., 2014; Al-Bachari et al., 2017). Pathological studies of PD have shown endothelial degeneration with preservation of basement membrane leading to increased string vessel formation (Yang et al., 2015), which may suggest a possible pathological relevance for this prolonged ATT. Prolonged ATT in some non-PD studies has been postulated to reflect age-driven structural cerebrovascular changes, e.g. increased vessel tortuosity, increased rarefaction and arteriolar wall damage (Liu et al., 2012), inflammation or chronic vasodilation of the resistance vessels in multiple sclerosis (Paling et al., 2014), or recruitment of collateral pathways in acute

ischemia (MacIntosh et al., 2010). In short, prolongation of ATT might be attributed to any factor which increases path length or decreases flow velocity.

The prolonged ATT of right thalamus was found in PD-MCI compared to PD-N and HC, and correlates with the executive cognitive domain. Grey matter atrophy and cortical thinning in the thalamus have been reported in PD-MCI (Chen et al., 2016; Danti et al., 2015). Previous ASL studies found decreased thalamic CBF in PD patients including PD-D with relatively advanced disease (Lin et al., 2016; Melzer et al., 2011). The current study shows that a thalamic hemodynamic abnormality also occurs in PD-MCI with early-stage disease. Besides sensory and motor functions (Herrero et al., 2002), the thalamus plays an important role in cognitive function, and lesions may lead to abnormalities of multiple cognitive domains, covering attention, executive function, language, memory, and visuospatial function (De Witte et al., 2008; Radanovic et al., 2003; Van der Werf et al., 2003). Here, the executive function reflected by the category fluency test was negatively correlated with ATT in the thalamus, in line with recent research showing that the thalamic local shape volume in PD-MCI is associated with semantic fluency tests (Chung et al., 2017). Poor performance in semantic fluency tests has been associated with a higher risk of developing dementia (Williams-Gray et al., 2009). A recent SPECT study found that cognitive functions in PD patients were positively correlated with CBF in the thalamus (Wakamori et al., 2014). The present ASL data strengthens the evidence for the hemodynamics of the thalamus as a potential biomarker for the development of cognitive impairment in PD.

Furthermore, we also identified a prolonged ATT in the right SMG of PD-MCI compared to HC. SMG has been shown to be involved in a wide range of cognitive tasks including

spatial perception, mental imagery, action observation, visual-motor control, or motor skills cognitive control (Nickel and Seitz, 2005). The SMG is also part of the inferior parietal lobe, the core brain region of the default mode network, which is highly relevant for cognitive processes (Raichle et al., 2001). Previous structural and functional studies found cortical thinning and reduced functional connectivity in the inferior parietal lobe in PD-MCI (Hou et al., 2016; Pereira et al., 2014). Our results align with the pattern of posterior hypoperfusion and hypometabolism characterized by prolonged ATT and decreased CBF in PD, PD-MCI and PD-D previously detected by ASL, SPECT and PET studies (Al-Bachari et al., 2014; Al-Bachari et al., 2017; Eckert et al., 2007; Lin et al., 2016; Melzer et al., 2011; Nobili et al., 2009; Pappata et al., 2011; Syrimi et al., 2017), which can be assumed to contribute to impaired cognition. ASL-derived functional connectivity analyses with seeds in thalamus have revealed increased connectivity in SMG in PD patients (Fernandez-Seara et al., 2015). Together with the present results, this all suggests that early involvement of subcortical (thalamus) and posterior cortical regions (SMG) could be early markers of cognitive deficit in PD patients. The utility of this pattern in predicting prodromal dementia needs to be evaluated in longitudinal studies.

By contrast, compared with HC, PD-N showed shorter ATT in the left SFG. There are reports of reduced gray matter density and cortical thickness in frontal lobe in PD-N compared to HC (Chen et al., 2016; Hanganu et al., 2013; Nishio et al., 2010), but other studies have found no evidence of anatomical, functional or metabolic brain abnormalities in PD-N (Amboni et al., 2015; Lyoo et al., 2010; Weintraub et al., 2011). This apparent discrepancy may be due to differences in definitions of MCI, disease severity, image analysis

techniques, sample sizes and neuropsychological tests, and merits further study. Although medication was withdrawn in treated PD at least 12 hours prior to MRI scanning, we cannot completely rule out the potentially confounding effects of chronic dopaminergic drugs, which may also have obscured alterations in the frontal cortex, as L-DOPA has been shown to modulate perfusion in this region (Lin et al., 2016). Additionally, involvement of the prefrontal cortex contributes to distinct motor manifestations, such as in PD patients with tremor (Picco et al., 2015). The decreased ATT we found in the PD-N group compared with HC may represent a compensatory response to the hypodopaminergic state. This would be consistent with studies showing enhanced prefrontal activity in cognitively intact PD at rest and during tasks (Picco et al., 2015; Zheng et al., 2014). On combining the two patients groups, we found the CBF in left MFG was positively correlated with z scores of executive and visuospatial function: the lower the z scores, indicating greater cognitive impairment, the lower CBF in the left MFG. In PD, executive function is positively correlated with ^{18}F-DOPA uptake and FA in the frontal regions (Picco et al., 2015; Zheng et al., 2014), and the visuospatial impairment is associated with frontal gray matter reductions (Pereira et al., 2009). In combination with our present observations, this suggests that frontal areas may also play an important role in the cognitive impairments of PD.

We found no differences in CBF between the three groups. A similar lack of statistically significant differences in CBF between 14 PD patients and 14 controls has been also reported (Al-Bachari et al., 2014). The small sample size may potentially account for differences not reaching statistical significance. Small regions of lower CBF were found in 51 PD patients by comparison with 34 controls (Al-Bachari et al., 2017). When comparing all PD patients with

HC we found decreased CBF in right caudate and right orbitofrontal cortex. This is in agreement with the parallel circuits linking the basal ganglia and cortex (Alexander et al., 1986). This parallel loop model of striatal organization is broadly supported by studies of striatal anatomical and functional connections, hypoperfusion and hypometabolism using ASL and PET (Fernandez-Seara et al., 2012; Lehericy et al., 2004; Pappata et al., 2011; Postuma and Dagher, 2006; Wang et al., 2017; Wei et al., 2016). In addition, we found prolonged ATT in right precuneus and bilateral MOG in PD patients, in keeping with studies showing a similar pattern of posterior cortical hypoperfusion in PD patients compared to HC (Al-Bachari et al., 2017; Barzgari et al., 2018; Fernandez-Seara et al., 2012; Melzer et al., 2011; Syrimi et al., 2017). Hypoperfusion in neurodegenerative states has been attributed to direct tissue loss or the result of loss of functional connectivity (Borghammer et al., 2010; Yoshiura et al., 2009a). Although the mechanism of occipital hypoperfusion in PD is unclear, it may be related to loss of dopaminergic neurons in the retina (Kamagata et al., 2011). ATT parameters have been shown to be more sensitive than CBF for characterizing stroke (MacIntosh et al., 2010) and neurovascular status in PD (Al-Bachari et al., 2014). The current study shows that ATT parameters may be more sensitive than CBF for characterizing PD with cognitive impairment. The lack of any significantly prolonged ATT in right thalamus when comparing PD with HC further suggests that alteration of ATT may be more likely to be related to MCI rather than to PD disease as such.

This study has a number of limitations. First, the relatively small sample size and unequal group size may have limited the detection of group differences. Our results need to be

confirmed in future studies with large sample size of PD patients with MCI. Second, although the medications were withdrawn in some patients during MRI scanning, we still cannot completely eliminate the potentially confounding effects of chronic dopaminergic drugs. Third, in this cross-sectional study we are unable to observe the time course of brain changes associated with cognitive function decline. Fourth, unexpectedly, the 4-delay pCASL CBF showed no significant between-group difference compared to CBF acquired at the PLD of 1800 ms and 2200 ms. Previous studies found that mean CBF showed slight improvement compared to the CBF at a single PLD in patients with stroke (Wang et al., 2013). A factor that might contribute to these discrepancies is that the estimated CBF reported in the current study is the mean of CBF at 4 PLDs; it did not take into account that different CBF at each PLD need to be fitted, which might weaken the differences observed at each PLD. Fifth, we used 4 PLD time-points for the ASL acquisition, which was necessary in order to cover the cerebrum with vascular crushing gradients enabled (Al-Bachari et al., 2014). More time points may have increased the precision of the ATT measurements.

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CONCLUSION

This study revealed alterations of regional cerebral perfusion in the brains of PD patients with MCI using multi-delay multi-parametric ASL perfusion MRI to estimate the parameters of ATT and CBF. We have identified a cerebral functional abnormality in thalamus and inferior parietal cortex in early-stage PD-MCI patients, which may be a potential biomarker for the cognitive impairment; in particular ATT may be a more sensitive marker of changes in cerebral perfusion in PD-MCI than CBF. ASL perfusion MRI is completely noninvasive compared to nuclear imaging techniques and can safely be used for repeated assessments.

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Figure legends

Figure 1. Arterial transit time (ATT) differences among PD-MCI, PD-N and HC. PD-MCI showed prolonged ATT in right thalamus compared to both PD-N and HC, and right supramarginal gyrus compared to HC. PD-N showed shorter ATT in left superior frontal cortex compared to HC. Statistical inferences were made with a voxel-level statistical threshold of $p < 0.05$ (corrected). Abbreviations: PD, Parkinson's disease; PD-MCI, PD with mild cognitive impairment; PD-N, PD with normal cognition; HC, healthy controls; L, left; R, right; SFG, superior frontal gyrus; SMG, supramarginal gyrus.

Figure 2. Arterial transit time (ATT) differences among PD-MCI, PD-N and HC compared by post-hoc contrasts within ANOVA. PD-MCI showed prolonged ATT in right thalamus compared to both PD-N and HC, and right supramarginal gyrus compared to HC. PD-N showed shorter ATT in left superior frontal cortex compared to HC. Abbreviations: PD, Parkinson's disease; PD-MCI, PD with mild cognitive impairment; PD-N, PD with normal cognition; HC, healthy controls; L, left; R, right; SFG, superior frontal gyrus; SMG, supramarginal gurus; THA, thalamus. * $P < 0.05$.

Figure 3. Arterial transit time (ATT) differences between all PD patients relative to HC using two-sample t tests. PD patients showed prolonged ATT in right SMG, right precuneus and bilateral MOG. Abbreviations: PD, Parkinson's disease; HC, healthy controls; L, left; R, right; SMG, supramarginal gyrus; MOG, middle occipital gyrus.

Figure 4. Cerebral blood flow (CBF) differences between all PD patients relative to HC using two-sample t tests. The CBF at 1800 ms in right caudate and the CBF at 2200 ms in right OFC were decreased. Abbreviations: PD, Parkinson's disease; HC, healthy controls; L, left; R, right; OFC, orbitofrontal cortex.

Figure 5. Correlation between arterial transit time (ATT) and cognitive functions in the PD-MCI group. Prolonged ATT in right thalamus (MNI coordinates: x=8, y=−26, z=2) was negatively correlated with category influence test. Abbreviations: PD, Parkinson's disease; PD-MCI, PD with mild cognitive impairment.