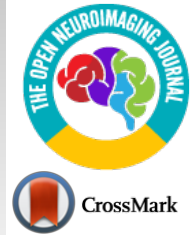




The Open Neuroimaging Journal

Content list available at: <https://openneuroimagingjournal.com>



RESEARCH ARTICLE

Regional Parieto-occipital Hypoperfusion on Arterial Spin Labeling Associates with Major Depressive Disorder

Shingo Kihira^{1*}, Clara Koo¹, Kambiz Nael² and Puneet Belani¹

¹Department of Diagnostic, Molecular and Interventional, Radiology Icahn School of Medicine at Mount Sinai, Mount Sinai Hospital, One Gustave Levy Place, New York, NY10029 USA

²Department of Radiological Sciences, David Geffen School of Medicine at University of California, Los Angeles 10833 Le Conte Ave, Los Angeles, CA90095, USA

Abstract:

Background:

Reduced cerebral blood flow in parieto-occipital regions has been reported in neurodegenerative disorders using ASL. We aimed to investigate neuropsychiatric and neurodegenerative comorbidities that may associate with parieto-occipital region hypoperfusion.

Methods:

This was a retrospective single-center study. Between March 2017 to May 2018, adult patients who underwent brain MRI with the inclusion of ASL perfusion and who had bilateral reductions of CBF in the parieto-occipital regions were included. ASL was performed using a pseudo-continuous arterial spin labeling (pCASL) technique on 1.5T MR system. Age and gender-matched patients with no perfusion defect were concurrently collected. Comorbidity data was collected from EMR, including major depressive disorder, Alzheimer's disease, Parkinson's disease, Schizophrenia, anxiety disorder, hypertension, diabetes mellitus type II, coronary artery disease, and chronic kidney disease. A Pearson's Chi-Square test was performed to assess for comorbidities associated with hypoperfusion of the parieto-occipital lobes.

Results:

Our patient cohort consisted of 93 patients with bilateral hypoperfusion in the parieto-occipital lobes and 93 age and gender-matched patients without corresponding perfusion defects based on ASL-CBF. Among the comorbidities assessed, there was a statistically significant association between hypoperfusion of the parieto-occipital lobes and major depressive disorder ($p=0.004$) and Parkinson's disease ($p=0.044$). There was no statistically significant association for Alzheimer's disease, generalized anxiety disorder, diabetes mellitus type II, hypertension, coronary artery disease, or chronic kidney disease.

Conclusion:

Major depressive disorder may be linked to regional parieto-occipital hypoperfusion on ASL.

Keywords: Arterial spin labeling, Cerebral blood flow, Major depressive disorder, Parkinson's disease, Perfusion, Parieto-occipital Hypoperfusion.

Article History

Received: March 17, 2020

Revised: August 08, 2020

Accepted: August 25, 2020

1. INTRODUCTION

Arterial Spin Labeling (ASL) is a noninvasive MR perfusion method for quantifying Cerebral Blood Flow (CBF) by utilizing arterial water as a freely diffusible endogenous tracer [1 - 3]. These studies are easily reproducible and performed without gadolinium contrast. Among the ASL methods, the most commonly utilized is continuous ASL

(CASL) and pulsed ASL (PASL). CASL induces continuous inversion of blood water spin as it passes a particular plane [4]. Conversely, PASL employs a single pulse to define a volume containing arterial blood for labeling. CASL has a greater signal-to-noise ratio, however, it is limited by imperfect practical implementation [5, 6]. Recently, pseudo-continuous ASL (pCASL), a hybrid ASL variant, is increasingly employed combining aspects of CASL and PASL by maintaining a high signal-to-noise ratio while being compatible with widely available body coils [5, 7, 8].

With increasing interest and applicability of ASL studies,

* Address correspondence to this author at the Department of Diagnostic, Molecular and Interventional Radiology Icahn School of Medicine at Mount Sinai, Mount Sinai Hospital One Gustave Levy Place, New York, NY10029 USA; Tel: (650) 766-3539; Fax: (212) 241-6500; E-mail: shingokihira@gmail.com

there is a clinical interest in studying patterns of CBF as it relates to neuropsychiatric diseases. ASL studies for cerebral-occlusive disease [9 - 11], major depressive disorder (MDD) [12 - 16], Alzheimer’s disease (AD) [5, 17 - 19], chronic migraine [20], and Parkinson’s disease (PD) [21, 22] have been previously reported. Much of the earlier work in functional neuroimaging entailed measured baseline cerebral blood flow (CBF) and glucose metabolism using positron emission tomography (PET) and single-photon emission computer tomography (SPECT) [23, 24]. Resting-state fMRI studies subsequently followed examining the functional connectivity pattern among regions of the brain, however, there was a limitation when assessing objective biomarkers and specific regions of abnormal flow [25].

Given the considerable success and utility of these prior modalities in neurodegenerative populations and relative ease of obtaining ASL in conjunction with conventional MR sequences, ASL has been under investigation for similar purposes. A growing number of ASL studies have emerged in recent years, assessing its utility in assessing neurodegenerative disorders that have been reported in prior ASL studies. For example, studies in patients with PD report hypoperfusion in the parieto-occipital region [22, 26 - 28]. ASL studies in patients with AD have reported hypoperfusion in the parieto-occipital [20, 22] and frontotemporal region [17, 19]. However, neuropsychiatric disorders associated with CBF abnormality have not been studied extensively in prior ASL studies. Current

literature show variable results in MDD [24, 29] with CBF abnormality in the prefrontal cortex [13, 14, 30, 31], anterior cingulate cortex [14, 30, 31], subgenual cingulate [14], basal ganglia [30, 32], and superior insula [30] with variability in CBF perfusion as well as asymmetry [12].

In recent years, there has been increasing interest and understanding of CBF abnormalities on ASL in association with neurodegenerative disease. We have noticed a subset of patients with regional hypoperfusion, specifically in the parieto-occipital lobes. In this study, we investigated a potential link between regional parieto-occipital hypoperfusion and underlying common medical and neurodegenerative/psychiatric disease.

2. MATERIALS AND METHODS

2.1. Study Population

This is a single-center retrospective study, which was approved by the local Institutional Review Board with a waiver of informed consent. From March 2017 to May 2018, a total of 1026 consecutive patients who presented to our inpatient and emergency department underwent brain MRI with the inclusion of ASL (Fig. 1). One hundred and ten of these patients had regional parieto-occipital hypoperfusion (Fig. 2). We excluded patients with any perfusion defect outside of the parieto-occipital region.

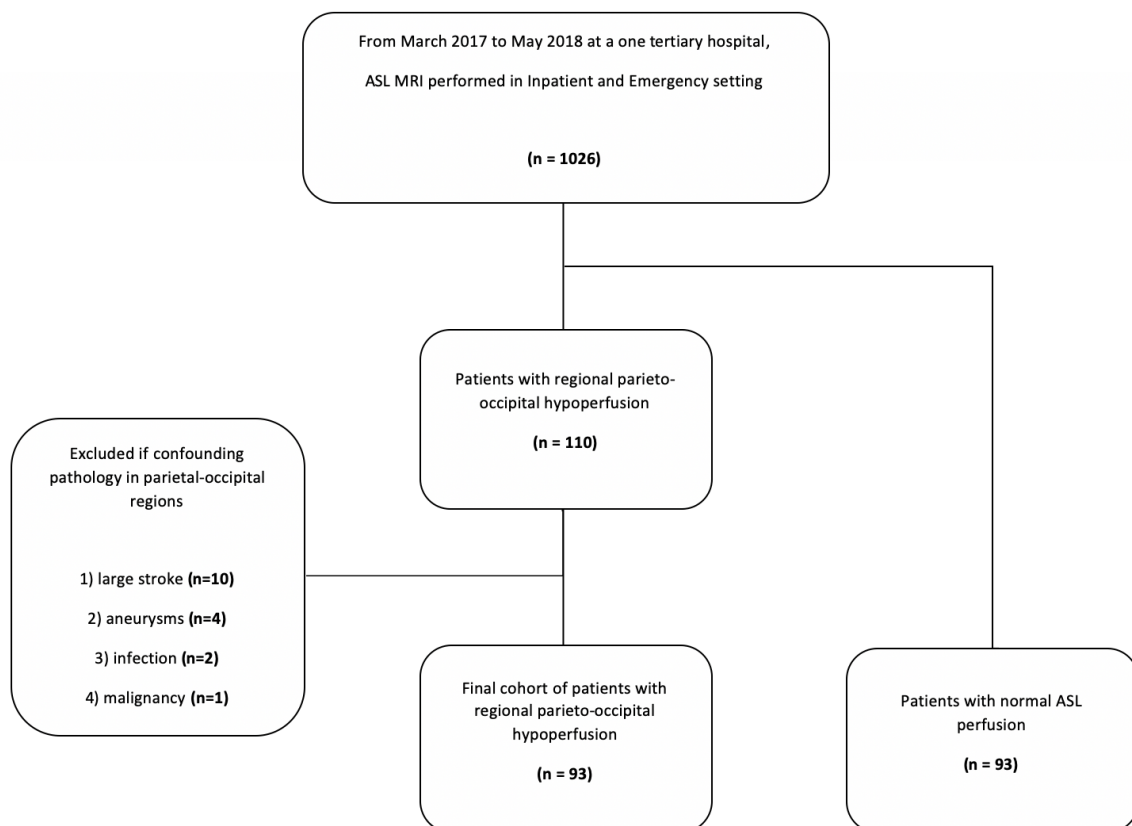


Fig. (1). Flowchart of study design with inclusions and exclusions.

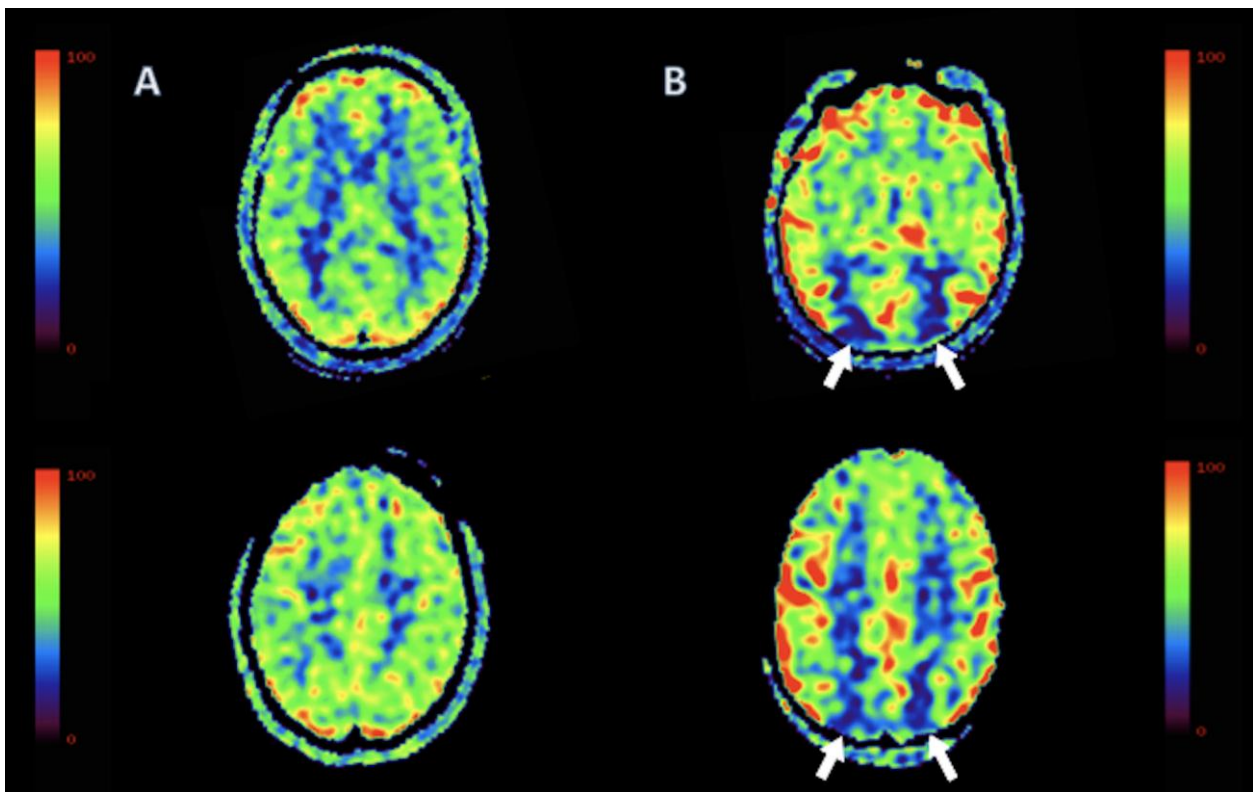


Fig. (2). Axial slices of occipital (top) and parietal (bottom) CBF from ASL perfusion. **A**, 70-year-old female without neuropsychiatric disease in control group. **B**, 70-year-old female with MDD. Note the symmetric bilateral decrease in CBF along the occipital and parietal lobes in this patient with MDD

We further excluded patients with CVA ($n=10$), aneurysm ($n=4$), infection ($n=2$), and malignancy ($n=1$) in the parieto-occipital region. Our final cohort included 93 patients. Age and gender-matched patients with no corresponding perfusion defect were concurrently collected from the same database. Comorbidity data was collected from our EMR system, including MDD, Generalized Anxiety disorder, Alzheimer's dementia, PD, Schizophrenia, hypertension, diabetes mellitus type II, coronary artery disease, and chronic kidney disease. Comorbidities were diagnosed by the primary or psychiatric team and retrospectively obtained from chart review. Neuropsychiatric conditions such as MDD, generalized anxiety disorder, and Schizophrenia were made per the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Data on cataract history, smoking history, and prior history of non-parietal-occipital strokes were also collected.

2.2. Image Acquisition and Image Analysis

Imaging protocol for brain MRI included the acquisition of sagittal T1, axial T2, axial GRE, axial FLAIR, axial DWI, and axial ASL. Image acquisition was performed using a 1.5-T clinical MR imaging unit (GE Optima MR450w; GE Medical Systems, Milwaukee) with an eight-channel head coil for signal reception. ASL was performed using a three-dimensional pseudo-continuous ASL (pCASL) with a fast spin-echo stack-of-spiral readout with eight interleaves. Each spiral arm included 512 sampling points. The following parameters were

applied: TR/TE 4525/11 ms, FOV: 24 x 24 cm, matrix size: 64 x 64, 30 slices each 4 mm thick, and NEX = 3. Pseudo-continuous spin labeling was performed for 1.5 seconds before a post-spin-labeling delay of 2 seconds. Background suppression was achieved by applying saturation pulses inferior to the labeling plane, allowing for the increase in the sharpness of the bolus [33]. This setting resulted in the acquisition of 3D voxel size of $3.8 \times 3.8 \times 4 \text{ mm}^3$ acquired in 4 minutes and 30 seconds.

Image reconstruction was performed online by the scanner software. Pairwise subtraction between label and control images was obtained and averaged to generate the mean difference and converted to CBF maps based on a previously published model [34]. After automated reconstruction by the scanner software, DICOM CBF maps along with all other anatomical imaging, were sent to PACS and available for interpretation.

One board-certified neuroradiologist reviewed the ASL-CBF MR images on PACS (Centricity, GE Healthcare, Chicago, IL). The observer was blinded to the radiological reports. If there was a subjective reduction in CBF in the parieto-occipital lobes, then the case was interpreted as hypoperfusion and included in this study.

2.3. Statistical Analysis

SAS, Version 9.4 (SAS Institute, Cary, North Carolina)

was used for statistical computations. A Pearson's Chi-Square test was performed to assess for neuropsychiatric and neurodegenerative comorbidities associated with parieto-occipital hypoperfusion.

3. RESULTS

3.1. Clinical Characteristics of Patient Population

Our patient cohorts consisted of 93 patients with bilateral hypoperfusion in the parieto-occipital lobes and 93 patients with no perfusion defect based on ASL-CBF. Demographic comparison of the two cohorts revealed no statistical difference in gender, age, or history of prior strokes (Table 1). The mean \pm standard deviation of age (years) was 75 ± 13 , with a median of 76 for the cohort with occipital hypoperfusion and 75 ± 11 with a median of 76 for the normal control.

Table 1. Demographic and evaluated comorbidity association of patient cohort.

Category	Normal CBF control (N=93)	rCBF hypoperfusion (N=93)	P value
Demographic Age (mean \pm SD; median)	75 \pm 11; 76	75 \pm 13; 76	0.87
Gender (M/F)	61/32	61/32	1
Diabetes Mellitus type II	39	40	0.88
Hypertension	71	69	0.73
Chronic Heart Failure	14	12	0.67
Coronary artery disease	36	27	0.16
Chronic kidney disease	27	20	0.24
History of malignancy	31	20	0.07
History of CVA	26	34	0.21
History of smoking	19	19	1
Neuropsychiatric Major Depressive Disorder	13	29	0.004*
Generalized Anxiety Disorder	4	9	0.15
Schizophrenia	2	2	1
Neurodegenerative Alzheimer's Dementia	11	18	0.16
Parkinson's disease	3	10	0.04*

N, sample size; Normal CBF control consisted of aged matched patients without CBF abnormalities. Parkinson's disease included with and without dementia. Chronic heart failure and chronic kidney disease included any stage as long as they were on medication.

*P<0.05 on Pearson's Chi Square test.

3.2. Association of MDD and PD to Hypoperfusion of Parieto-Occipital Lobe

Among the comorbidities assessed, there was a statistically significant association between hypoperfusion of the parieto-occipital lobes with MDD ($p= 0.004$) and with PD ($p= 0.04$) (Table 1). Compared to 13 patients in the aged-matched cohort, there were 29 patients with MDD in the cohort with parieto-occipital hypoperfusion. In our analysis of PD, there were 10 patients with PD compared to 3 in the aged-matched cohort. Of note, there were more patients with Alzheimer's disease in our cohort with parieto-occipital hypoperfusion ($n= 18$) compared to aged-matched control ($n= 11$), but the difference did not reach statistical significance ($p= 0.16$).

No significant associations were found for Schizophrenia ($p= 1.0$) or anxiety disorder ($p= 0.15$). Common inpatient comorbidities such as diabetes mellitus II ($p= 0.88$), hypertension ($p= 0.73$), coronary artery disease ($p= 0.16$), chronic kidney disease ($p= 0.24$), or malignancy ($p= 0.07$) did not yield a statistically significant difference.

4. DISCUSSION

Perfusion abnormalities in the parieto-occipital region have been extensively studied in prior ASL studies, especially in neurodegenerative disorders such as Parkinson's and Alzheimer's disease. In our single-center institution, we found a significant portion of our patients with bilateral parieto-occipital hypoperfusion as an incidental finding. To understand this CBF abnormality further, we assessed for neuropsychiatric and other neurodegenerative disorders that may associate with this perfusion defect by comparing this cohort to age and gender-matched cohort without corresponding perfusion defects.

In our study, we found that MDD and PD associate with bilateral parieto-occipital hypoperfusion. CBF abnormalities in the prefrontal cortex [13, 14, 30 - 32, 35] and anterior cingulate cortex [14, 30 - 32] have been well documented in the past in these pathologies. To our knowledge, MDD association with bilateral parieto-occipital hypoperfusion has not been described before.

The parieto-occipital cortices have numerous anatomical interconnections with cortical and subcortical pathways governing attention, spatial representation, working memory, eye movements, and guidance of action [36, 37]. Furthermore, parietal lobe dysfunction has been proposed to associate with depression [38], where they found that tactile learning problems to assess parietal lobe dysfunction was significantly impaired in patients with MDD, and rCBF using the xenon 133 inhalation technique was significantly decreased in the temporo-parietal lobes in patients with MDD [39]. Interestingly, Alosco *et al.* [40] using a Transcranial Doppler (TCD) showed a decrease in CBF in the bilateral MCA associating with significant depressive symptoms in patients with CHF. Their findings suggest a possibility that hypoperfusion of the parietal and occipital cortex may be contributing to the symptoms of depression in these patients. It has been proposed that flow reductions in these regions may correspond to impairment of temporo-parietal polymodal association area, which has strong reciprocal connectivity with prefrontal polymodal association cortex, which governs arousal, attentional, and motivational functions that are impaired in MD [36, 37]. Further analysis of the chronology of onset and progression of depression in a prospective study may be able to shed light on whether this CBF pattern may have predictive value or may correlate with disease progression.

The association of parieto-occipital CBF hypoperfusion is well documented in PD in prior ASL studies [22, 26 - 28] and observed in our current study. While frontal dysfunction is the prominent feature in PD, a posterior pattern of CBF abnormality affecting the posterior cingulate, precuneus, and occipital regions is known [26]. Furthermore, CBF perfusion reductions in posterior regions have been associated with

cognitive decline in PD [28, 41]. Firbank *et al.* [28] demonstrated that the degree of parieto-occipital lobe CBF reduction associates with cognitive assessment score (CAMCOG) in patients with PD with dementia. Furthermore, parieto-occipital CBF reduction is likely linked to developing dementia in these patients with PD. These lobes are involved in visual-spatial processing, a function that is well documented to be abnormal in PD [42 - 44].

Prior ASL studies in patients with Alzheimer's dementia have reported hypoperfusion in the parieto-occipital lobes [20, 22, 45]. Interestingly, although there were more patients with AD in our cohort with posterior hypoperfusion (n=18) compared to age-matched control (n=11), there was no statistically significant difference. Frontal and lateral temporal hypoperfusion has been documented in AD in prior studies [17, 19, 46]. As our cohort consisted exclusively of bilateral parieto-occipital hypoperfusion, there were likely cases with frontal or temporal hypoperfusion that were excluded from analysis, thus contributing to the lack of significant difference in our cohort. Additionally, prior studies have shown that CBF may be affected by several medications, including cholinesterase inhibitors, with treatment response correlating to an increase in perfusion and a relative return to baseline CBF in the frontotemporal and parieto-occipital region [47, 48]. A difference in cohorts may not be observed depending on the treatment status of these patients.

There are several limitations to our study. First, it was a retrospective study. A prospective study would have allowed us to conduct serial ASL studies to assess CBF pattern as it relates to the onset and progression of the disease. It would also allow us to structure the study design to reduce confounders, for example, including only patients with MDD without neurodegenerative disease and focusing on a single pathology at a time. Future studies may focus on prospectively recruiting patients with MDD without any other comorbidities and assessing for regional hypoperfusion. Secondly, having an objective scoring system for assessing the severity of depression, such as a Montreal Cognitive assessment or Hamilton depression scale, would have enhanced our study. Unfortunately, these were not documented in our patients. We also acknowledge that diagnosis of the assessed comorbidities, especially the underlying neuropsychiatric conditions, may vary across the diagnostic approach and specialty of the clinician.

Another limitation was that our MDD patients were treated at the time of imaging, and different SSRI/SNRI/Atypical antidepressants may have altered CBF pattern as was described in AD studies with cholinesterase inhibitors [47, 48]. Lastly, we acknowledge that this is a single-center study and our cohort consisted of patients from an inpatient and emergency setting obtaining ASL MR imaging for a variety of neurological disorders, which is not representative of the general population.

CONCLUSION

The major depressive disorder may be linked to regional parieto-occipital hypoperfusion on ASL. Future studies can focus on the evaluation of this association with other MR

perfusion or CT perfusion imaging as well as assessing CBF pattern variation with onset and progression of MDD.

LIST OF ABBREVIATIONS

ADL	=	Alzheimer's Dementia
ASL	=	Arterial Spin Labeling
MDD	=	Major Depressive Disorder
PD	=	Parkinson's Disease
pCASL	=	Pseudo-continuous Arterial Spin Labeling

AUTHORS' CONTRIBUTIONS

Study concept and design, collection of data, analysis and interpretation of data, writing of manuscript, critical revision of manuscript. CL: collection of data. KM: Study concept and design, writing of manuscript, critical revision of manuscript. PB: Study concept and design, writing of manuscript critical revision of manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Mount Sinai Hospital Institutional Review Board under consent no (IRB# MS312-789).

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

A waiver of informed consent was obtained from the Mount Sinai Hospital Institutional Review Board as this was a retrospective study.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this study are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

- [1] Detre JA, Rao H, Wang DJ, Chen YF, Wang Z. Applications of arterial spin labeled MRI in the brain. *J Magn Reson Imaging* 2012; 35(5): 1026-37. [<http://dx.doi.org/10.1002/jmri.23581>] [PMID: 22246782]
- [2] Wintermark M, Sesay M, Barbier E, *et al.* Comparative overview of brain perfusion imaging techniques. *Stroke* 2005; 36(9): e83-99. [<http://dx.doi.org/10.1161/01.STR.0000177839.03321.25>] [PMID: 16100027]
- [3] Belani P, Kihira S, Pacheco F, Pawha P, Cruciata G, Nael K. Addition of arterial spin-labelled MR perfusion to conventional brain MRI: clinical experience in a retrospective cohort study. *BMJ Open* 2020;

- 10(6)e036785
[http://dx.doi.org/10.1136/bmjopen-2020-036785] [PMID: 32532776]
- [4] Wang Z, Wang J, Connick TJ, Wetmore GS, Detre JA. Continuous ASL (CASL) perfusion MRI with an array coil and parallel imaging at 3T. *Magn Reson Med* 2005; 54(3): 732-7.
[http://dx.doi.org/10.1002/mrm.20574] [PMID: 16086314]
- [5] Alsop DC, Detre JA, Golay X, *et al.* Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: A consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. *Magn Reson Med* 2015; 73(1): 102-16.
[http://dx.doi.org/10.1002/mrm.25197] [PMID: 24715426]
- [6] D.L. T, D.G. G, R.W. H, M.F. L, R.J. O. Understanding and optimizing the amplitude modulated control for multiple-slice continuous arterial spin labeling. *Magn Reson Med* 2005.
- [7] Dai W, Garcia D, de Bazelaire C, Alsop DC. Continuous flow-driven inversion for arterial spin labeling using pulsed radio frequency and gradient fields. *Magn Reson Med* 2008; 60(6): 1488-97.
[http://dx.doi.org/10.1002/mrm.21790] [PMID: 19025913]
- [8] Wu WC, Fernández-Seara M, Detre JA, Wehrli FW, Wang J. A theoretical and experimental investigation of the tagging efficiency of pseudocontinuous arterial spin labeling. *Magn Reson Med* 2007; 58(5): 1020-7.
[http://dx.doi.org/10.1002/mrm.21403] [PMID: 17969096]
- [9] Chalela JA, Alsop DC, Gonzalez-Atavales JB, Maldjian JA, Kasner SE, Detre JA. Magnetic resonance perfusion imaging in acute ischemic stroke using continuous arterial spin labeling. *Stroke* 2000; 31(3): 680-7.
[http://dx.doi.org/10.1161/01.STR.31.3.680] [PMID: 10700504]
- [10] Oura D, Kawabori N, Niya Y, *et al.* The validity of the Acute Stroke Assessment using rapid Pseudo-continuous arterial spin labeling (ASAP-ASL) method for acute thrombectomy. *J Neurosurg Sci* 2018.
[http://dx.doi.org/10.23736/S0390-5616.18.04607-6] [PMID: 30468360]
- [11] Wolf RL, Alsop DC, McCarvey ML, Maldjian JA, Wang J, Detre JA. Susceptibility contrast and arterial spin labeled perfusion MRI in cerebrovascular disease. *J Neuroimaging* 2003; 13(1): 17-27.
[http://dx.doi.org/10.1111/j.1552-6569.2003.tb00152.x] [PMID: 12593127]
- [12] Liao W, Wang Z, Zhang X, *et al.* Cerebral blood flow changes in remitted early- and late-onset depression patients. *Oncotarget* 2017; 8(44): 76214-22.
[http://dx.doi.org/10.18632/oncotarget.19185] [PMID: 29100305]
- [13] Lui S, Parkes LM, Huang X, *et al.* Depressive disorders: Focally altered cerebral perfusion measured with arterial spin-labeling MR imaging. *Radiology* 2009; 251(2): 476-84.
[http://dx.doi.org/10.1148/radiol.2512081548] [PMID: 19401575]
- [14] Ota M, Noda T, Sato N, *et al.* Characteristic distributions of regional cerebral blood flow changes in major depressive disorder patients: A pseudo-continuous arterial spin labeling (pCASL) study. *J Affect Disord* 2014; 165: 59-63.
[http://dx.doi.org/10.1016/j.jad.2014.04.032] [PMID: 24882178]
- [15] Kaichi Y, Okada G, Takamura M, *et al.* Changes in the regional cerebral blood flow detected by arterial spin labeling after 6-week escitalopram treatment for major depressive disorder. *J Affect Disord* 2016; 194: 135-43.
[http://dx.doi.org/10.1016/j.jad.2015.12.062] [PMID: 26826533]
- [16] Colloby SJ, Firbank MJ, He J, *et al.* Regional cerebral blood flow in late-life depression: Arterial spin labelling magnetic resonance study. *Br J Psychiatry* 2012; 200(2): 150-5.
[http://dx.doi.org/10.1192/bjp.bp.111.092387] [PMID: 22194184]
- [17] Du AT, Jahng GH, Hayasaka S, *et al.* Hypoperfusion in frontotemporal dementia and Alzheimer disease by arterial spin labeling MRI. *Neurology* 2006; 67(7): 1215-20.
[http://dx.doi.org/10.1212/01.wnl.0000238163.71349.78] [PMID: 17030755]
- [18] Chao LL, Buckley ST, Kornak J, *et al.* ASL perfusion MRI predicts cognitive decline and conversion from MCI to dementia. *Alzheimer Dis Assoc Disord* 2010; 24(1): 19-27.
[http://dx.doi.org/10.1097/WAD.0b013e3181b4f736] [PMID: 20220321]
- [19] De Vis JB, Peng SL, Chen X, *et al.* Arterial-spin-labeling (ASL) perfusion MRI predicts cognitive function in elderly individuals: A 4-year longitudinal study. *J Magn Reson Imaging* 2018; 48(2): 449-58.
[http://dx.doi.org/10.1002/jmri.25938] [PMID: 29292540]
- [20] Asllani I, Habeck C, Scarmeas N, Borogovac A, Brown TR, Stern Y. Multivariate and univariate analysis of continuous arterial spin labeling perfusion MRI in Alzheimer's disease. *J Cereb Blood Flow Metab* 2008; 28(4): 725-36.
[http://dx.doi.org/10.1038/sj.jcbfm.9600570] [PMID: 17960142]
- [21] Barzgar A, Sojkova J, Maritza Dowling N, *et al.* Arterial spin labeling reveals relationships between resting cerebral perfusion and motor learning in Parkinson's disease. *Brain Imaging Behav* 2019; 13(3): 577-87.
[http://dx.doi.org/10.1007/s11682-018-9877-1] [PMID: 29744796]
- [22] Le Heron CJ, Wright SL, Melzer TR, *et al.* Comparing cerebral perfusion in Alzheimer's disease and Parkinson's disease dementia: An ASL-MRI study. *J Cereb Blood Flow Metab* 2014; 34(6): 964-70.
[http://dx.doi.org/10.1038/jcbfm.2014.40] [PMID: 24619276]
- [23] Gunning FM, Smith GS. Functional neuroimaging in geriatric depression. *Psychiatr Clin North Am* 2011; 34(2): 403-422, viii.
[http://dx.doi.org/10.1016/j.psc.2011.02.010] [PMID: 21536165]
- [24] Smith DJ, Cavanagh JTO. The use of single photon emission computed tomography in depressive disorders. *Nucl Med Commun* 2005; 26(3): 197-203.
[http://dx.doi.org/10.1097/00006231-200503000-00004] [PMID: 15722900]
- [25] Liu F, Hu M, Wang S, *et al.* Abnormal regional spontaneous neural activity in first-episode, treatment-naive patients with late-life depression: A resting-state fMRI study. *Prog Neuropsychopharmacol Biol Psychiatry* 2012; 39(2): 326-31.
[http://dx.doi.org/10.1016/j.pnpbp.2012.07.004] [PMID: 22796277]
- [26] Garcia-Garcia D, Clavero P, Gasca Salas C, *et al.* Posterior parietooccipital hypometabolism may differentiate mild cognitive impairment from dementia in Parkinson's disease. *Eur J Nucl Med Mol Imaging* 2012; 39(11): 1767-77.
[http://dx.doi.org/10.1007/s00259-012-2198-5] [PMID: 22872307]
- [27] Melzer TR, Watts R, MacAskill MR, *et al.* Arterial spin labelling reveals an abnormal cerebral perfusion pattern in Parkinson's disease. *Brain* 2011; 134(Pt 3): 845-55.
[http://dx.doi.org/10.1093/brain/awq377] [PMID: 21310726]
- [28] Firbank MJ, Colloby SJ, Burn DJ, McKeith IG, O'Brien JT. Regional cerebral blood flow in Parkinson's disease with and without dementia. *Neuroimage* 2003; 20(2): 1309-19.
[http://dx.doi.org/10.1016/S1053-8119(03)00364-1] [PMID: 14568499]
- [29] Gonul AS, Kula M, Bilgin AG, Tutus A, Oguz A. The regional cerebral blood flow changes in major depressive disorder with and without psychotic features. *Prog Neuropsychopharmacol Biol Psychiatry* 2004; 28(6): 1015-21.
[http://dx.doi.org/10.1016/j.pnpbp.2004.05.036] [PMID: 15380862]
- [30] Ho TC, Wu J, Shin DD, *et al.* Altered cerebral perfusion in executive, affective, and motor networks during adolescent depression. *J Am Acad Child Adolesc Psychiatry* 2013; 52(10): 1076-1091.e2.
[http://dx.doi.org/10.1016/j.jaac.2013.07.008] [PMID: 24074474]
- [31] Järnum H, Eskildsen SF, Steffensen EG, *et al.* Longitudinal MRI study of cortical thickness, perfusion, and metabolite levels in major depressive disorder. *Acta Psychiatr Scand* 2011; 124(6): 435-46.
[http://dx.doi.org/10.1111/j.1600-0447.2011.01766.x] [PMID: 21923809]
- [32] Duhameau B, Ferré JC, Jannin P, *et al.* Chronic and treatment-resistant depression: A study using arterial spin labeling perfusion MRI at 3Tesla. *Psychiatry Res* 2010; 182(2): 111-6.
[http://dx.doi.org/10.1016/j.psychres.2010.01.009] [PMID: 20427157]
- [33] Mani S, Pauly J, Conolly S, Meyer C, Nishimura D. Background suppression with multiple inversion recovery nulling: Applications to projective angiography. *Magn Reson Med* 1997; 37(6): 898-905.
[http://dx.doi.org/10.1002/mrm.1910370615] [PMID: 9178242]
- [34] Yoo RE, Choi SH, Cho HR, *et al.* Tumor blood flow from arterial spin labeling perfusion MRI: A key parameter in distinguishing high-grade gliomas from primary cerebral lymphomas, and in predicting genetic biomarkers in high-grade gliomas. *J Magn Reson Imaging* 2013; 38(4): 852-60.
[http://dx.doi.org/10.1002/jmri.24026] [PMID: 23390061]
- [35] Dotson VM, Beason-Held L, Kraut MA, Resnick SM. Longitudinal study of chronic depressive symptoms and regional cerebral blood flow in older men and women. *Int J Geriatr Psychiatry* 2009; 24(8): 809-19.
[http://dx.doi.org/10.1002/gps.2298] [PMID: 19484709]
- [36] Culham J, He S, Dukelow S, Verstraten FAJ. Visual motion and the human brain: What has neuroimaging told us? *Acta Psychol (Amst)* 2001; 107(1-3): 69-94.
[http://dx.doi.org/10.1016/S0001-6918(01)00022-1] [PMID: 11572900]

- 11388143]
- [37] Culham JC, Kanwisher NG. Neuroimaging of cognitive functions in human parietal cortex. *Curr Opin Neurobiol* 2001; 11(2): 157-63. [http://dx.doi.org/10.1016/S0959-4388(00)00191-4] [PMID: 11301234]
- [38] Freedman M. Frontal and parietal lobe dysfunction in depression: Delayed alternation and tactile learning deficits. *Neuropsychologia* 1994; 32(8): 1015-25. [http://dx.doi.org/10.1016/0028-3932(94)90050-7] [PMID: 7969863]
- [39] Sackeim HA, Prohovnik I, Moeller JR, *et al.* Regional cerebral blood flow in mood disorders. I. Comparison of major depressives and normal controls at rest. *Arch Gen Psychiatry* 1990; 47(1): 60-70. [http://dx.doi.org/10.1001/archpsyc.1990.01810130062009] [PMID: 2294857]
- [40] Alosco ML, Spitznagel MB, Cohen R, *et al.* Reduced cerebral perfusion predicts greater depressive symptoms and cognitive dysfunction at a 1-year follow-up in patients with heart failure. *Int J Geriatr Psychiatry* 2014; 29(4): 428-36. [http://dx.doi.org/10.1002/gps.4023] [PMID: 24022882]
- [41] Kasama S, Tachibana H, Kawabata K, Yoshikawa H. Cerebral blood flow in Parkinson's disease, dementia with Lewy bodies, and Alzheimer's disease according to three-dimensional stereotactic surface projection imaging. *Dement Geriatr Cogn Disord* 2005; 19(5-6): 266-75. [http://dx.doi.org/10.1159/000084551] [PMID: 15775716]
- [42] McKeith IG, Dickson DW, Lowe J, *et al.* Diagnosis and management of dementia with Lewy bodies: Third report of the DLB Consortium. *Neurology* 2005; 65(12): 1863-72. [http://dx.doi.org/10.1212/01.wnl.0000187889.17253.b1] [PMID: 16237129]
- [43] Mentis MJ, McIntosh AR, Perrine K, *et al.* Relationships among the metabolic patterns that correlate with mnemonic, visuospatial, and mood symptoms in Parkinson's disease. *Am J Psychiatry* 2002; 159(5): 746-54. [http://dx.doi.org/10.1176/appi.ajp.159.5.746] [PMID: 11986127]
- [44] Abe Y, Kachi T, Kato T, *et al.* Occipital hypoperfusion in Parkinson's disease without dementia: correlation to impaired cortical visual processing. *J Neurol Neurosurg Psychiatry* 2003; 74(4): 419-22. [http://dx.doi.org/10.1136/jnnp.74.4.419] [PMID: 12640053]
- [45] Alsop DC, Detre JA, Grossman M. Assessment of cerebral blood flow in Alzheimer's disease by spin-labeled magnetic resonance imaging. *Ann Neurol* 2000; 47(1): 93-100. [http://dx.doi.org/10.1002/1531-8249(200001)47:1<93::AID-ANA15>3.0.CO;2-8] [PMID: 10632106]
- [46] Wierenga CE, Hays CC, Zlatar ZZ. Cerebral blood flow measured by arterial spin labeling MRI as a preclinical marker of Alzheimer's disease. *J Alzheimers Dis* 2014; 42(Suppl. 4): S411-9. [http://dx.doi.org/10.3233/JAD-141467] [PMID: 25159672]
- [47] Chaudhary S, Scouten A, Schwindt G, *et al.* Hemodynamic effects of cholinesterase inhibition in mild Alzheimer's disease. *J Magn Reson Imaging* 2013; 38(1): 26-35. [http://dx.doi.org/10.1002/jmri.23967] [PMID: 23239554]
- [48] Li W, Antuono PG, Xie C, *et al.* Changes in regional cerebral blood flow and functional connectivity in the cholinergic pathway associated with cognitive performance in subjects with mild Alzheimer's disease after 12-week donepezil treatment. *Neuroimage* 2012; 60(2): 1083-91. [http://dx.doi.org/10.1016/j.neuroimage.2011.12.077] [PMID: 22245641]