

UCSF

UC San Francisco Previously Published Works

Title

Evaluation of 3-dimensional stereotactic surface projection rendering of arterial spin labeling data in a clinical cohort

Permalink

<https://escholarship.org/uc/item/1n6600j9>

Journal

Journal of Neuroimaging, 33(6)

ISSN

1051-2284

Authors

Andre, Jalal B
Oztek, Murat Alp
Anzai, Yoshimi
[et al.](#)

Publication Date

2023-11-01

DOI

10.1111/jon.13153

Copyright Information

This work is made available under the terms of a Creative Commons Attribution-NoDerivatives License, available at <https://creativecommons.org/licenses/by-nd/4.0/>

Peer reviewed



Evaluation of 3-dimensional stereotactic surface projection rendering of arterial spin labeling data in a clinical cohort

Jalal B. Andre¹ | Murat Alp Oztek¹ | Yoshimi Anzai² | Gregory J. Wilson¹ |
Mahmud Mossa-Basha¹ | Daniel S. Hippe¹ | Michael N. Hoff¹ | Donna J. Cross² |
Satoshi Minoshima²

¹Department of Radiology, University of Washington, Seattle, Washington, USA

²Department of Radiology, University of Utah, Salt Lake City, Utah, USA

Correspondence

Jalal B. Andre, Department of Radiology,
University of Washington, 1959 NE Pacific St,
NW 011, Seattle, WA 98195, USA.
Email: drjalal@uw.edu

Abstract

Background and Purpose: To assess the feasibility of 3-dimensional stereotactic surface projection (3D-SSP) as applied to arterial spin labeling (ASL) in a clinical pilot study.

Methods: A retrospective sample of 10 consecutive patients who underwent ASL as part of a clinically indicated MR examination was collected during this pilot study. Five additional subjects with normal cerebral perfusion served as a control group. Following voxel-wise M0-correction, cerebral blood flow (CBF) quantification, and stereotactic anatomic standardization, voxel-wise CBF from an individual's ASL dataset was extracted to a set of predefined surface pixels (3D-SSP). A normal database was created from averaging the extracted CBF datasets of the control group. Patients' datasets were compared individually with the normal database by calculating a Z-score on a pixel-by-pixel basis and were displayed in 3D-SSP views for visual inspection. Independent, two-expert reader assessment, using a 3-point scale, compared standard quantitative CBF images to the 3D-SSP maps.

Results: Patterns and severities of regionally reduced CBF were identified, by both independent readers, in the 3D-SSP maps. Reader assessment demonstrated preference for 3D-SSP over traditionally displayed standard quantitative CBF images in three of four evaluated imaging metrics ($p = .026$, $.031$, and $.013$, respectively); 3D-SSP maps were never found to be inferior to the standard quantitative CBF images.

Conclusions: Three-dimensional SSP maps are feasible in a clinical population and enable quantitative data extraction and localization of perfusion abnormalities by means of stereotactic coordinates in a condensed display. The proposed method is a promising approach for interpreting cerebrovascular pathophysiology.

KEYWORDS

arterial spin labeling, cerebrovascular disorders, magnetic resonance imaging, perfusion imaging, spin labels

INTRODUCTION

Arterial spin labeling (ASL) is an MRI technique that allows for the noninvasive visualization and quantification of cerebral blood flow (CBF).^{1,2} It provides valuable information regarding cerebral perfusion

in both normal physiological states and in the context of underlying cerebrovascular disease, including acute ischemic stroke, brain tumors, infection, demyelinating disease, dementia, moyamoya disease, and intracranial vascular malformations.²⁻¹⁴ When ASL is incorporated into serial MRI examinations, it can provide valuable clinical insights



into the hemodynamic progression of cerebrovascular disease as well as the hemodynamic response of these diseases to therapeutic interventions.²

Unlike other MR perfusion techniques that rely on the use of gadolinium-based contrast agents, ASL is a contrast-free imaging method that utilizes radiofrequency pulses to selectively label water molecules within the arterial blood pool of the neck.^{1,2,15} Once magnetically labeled, these water molecules are imaged as they flow downstream into the intracranial circulation and diffuse across the capillary bed into the extravascular (interstitial and intracellular) space of the brain parenchyma.^{15,16} Because gadolinium contrast agents are not used with this imaging technique, ASL can be safely used across a variety of patient populations, including those with difficult intravenous access and severe renal impairment. It is also suitable for use in children, especially with chronic problems, where multiple studies over a period of time might increase caregiver or physician concern for gadolinium deposition.¹⁷ Despite the many strengths of ASL, however, the visual inspection, analysis, and comparison of its perfusion maps have been criticized for their relatively poor spatial resolution and paucity of imaging aesthetic, the latter occasionally attributed to the absence of usual anatomic landmarks on the image as well as inherently low signal-to-noise ratio, which ultimately impede a traditional radiological (visual inspection) approach to their analysis. Furthermore, regional brain perfusion can vary with age, gender, and ethnicity,^{18,19} among other things, and the variability in regional anatomic and physiological CBF between and within individual cerebrovascular territories further complicates evaluation. While there are a few studies presenting normative data for the perfusion of the entire brain by age, regional differences remain unaddressed.²⁰ Additionally, in routine clinical practice, ASL perfusion maps are traditionally displayed as a 2-dimensional array of images sectioned from various levels of the brain as opposed to coherent 3-dimensional statistical parametric mapping, further complicating their evaluation and interpretation.

Intracranial PET and SPECT imaging provides information regarding brain metabolic activity and the cerebral perfusion coupled to it.^{6,9,21–26} Like ASL, the evaluation of intracranial PET and SPECT imaging and the comparison of PET and SPECT findings between subjects are challenging due to regional anatomic variations in the size and stereotactic location of brain parenchymal structures. In the field of nuclear medicine, these radiological challenges have been addressed by the incorporation of various automated 3-dimensional surface-rendered/projected visualization as typically produced by statistical parametric mapping. One such approach, 3-dimensional stereotactic surface projections (3D-SSP), has been used in metabolic PET and SPECT data and minimizes individual differences in brain contour and size by comparing the perfusion data obtained in imaged individuals to a referenced normative database.^{22,27} The process includes volumetric transformation onto a corresponding set of predefined brain surface pixels with subsequent generation of z-score maps displayed as orthogonal projection images, thereby creating the patient-specific 3D-SSP.^{22,27} These orthogonal projection images are views of the volumetric 3D image in axial, coronal, and sagittal planes as con-

ventionally used in nuclear medicine brain PET and SPECT studies (Figure 1).²⁷

We hypothesize that these same image fitting and stereotactic projection techniques can be applied to ASL perfusion imaging to improve the clinical interpretation and comparison of these perfusion studies. The purpose of this proof-of-concept pilot study was therefore to evaluate the diagnostic applicability and performance of a statistical parametric brain perfusion mapping technique (3D-SSP maps) commonly employed in the field of nuclear medicine, as applied to routine, clinical ASL perfusion data.

METHODS

Patient selection

Following institutional review board approval for a Health Insurance Portability and Accountability Act of 1996-compliant retrospective case-control imaging study, 10 consecutive patients who underwent ASL imaging as part of a clinically indicated MRI examination for known cerebrovascular pathology were identified. An additional five healthy control patients without any history of cerebrovascular disease who had normal cerebral perfusion as demonstrated on ASL imaging were also identified to serve as normal imaging comparisons. All patients were 18 years of age or older. Patients under the age of 18 or who had medical conditions prohibiting them from being scanned on a 3 Tesla (T) MRI scanner were excluded from this study. All imaging studies that were not of diagnostic quality due to imaging artifact would have been subsequently excluded (but was not relevant to the current evaluated cohort).

Imaging methods

All imaging was performed on a 3T MRI scanner (Ingenia; Philips Healthcare), using a standard clinical imaging protocol that was dependent upon the clinical indication for imaging. These standard clinical imaging protocols included a combination of the following sequences: axial diffusion-weighted imaging (repetition time [TR]/echo time [TE], 6000/70 ms; B, 1000 seconds/mm²); axial gradient echo (TR/TE, 600/30 ms); axial T2-weighted fast spin echo (TR/TE, 4717/85 ms); axial fluid-attenuated inversion recovery (TR/TE/inversion time, 8802/110/220 ms); axial T1-weighted postcontrast (TR/TE, 600/15 ms); and 3-dimensional time-of-flight MR angiography (TR/TE, 34/3.1 ms; matrix, 512 × 128; 1-mm-thick sections). Unless stated, all anatomic imaging was performed with a 5-mm slice thickness, 1.5-mm skip, and 24-cm field of view. Every imaging protocol also included a pseudocontinuous ASL (pCASL) imaging preparation using body coil transmission and SENSE 15-channel reception, with the following parameters: TE = 7.8 ms, TR = 5500 ms, flip angle = 90°, label duration = 1800 ms, postlabeling delay (PLD) = 2000 ms, matrix = 96 × 96 × 20, spatial resolution = 3.5 × 3.5 × 5 mm³, background suppression pulses at 1830 and 3370 ms, 30 control/label pairs,

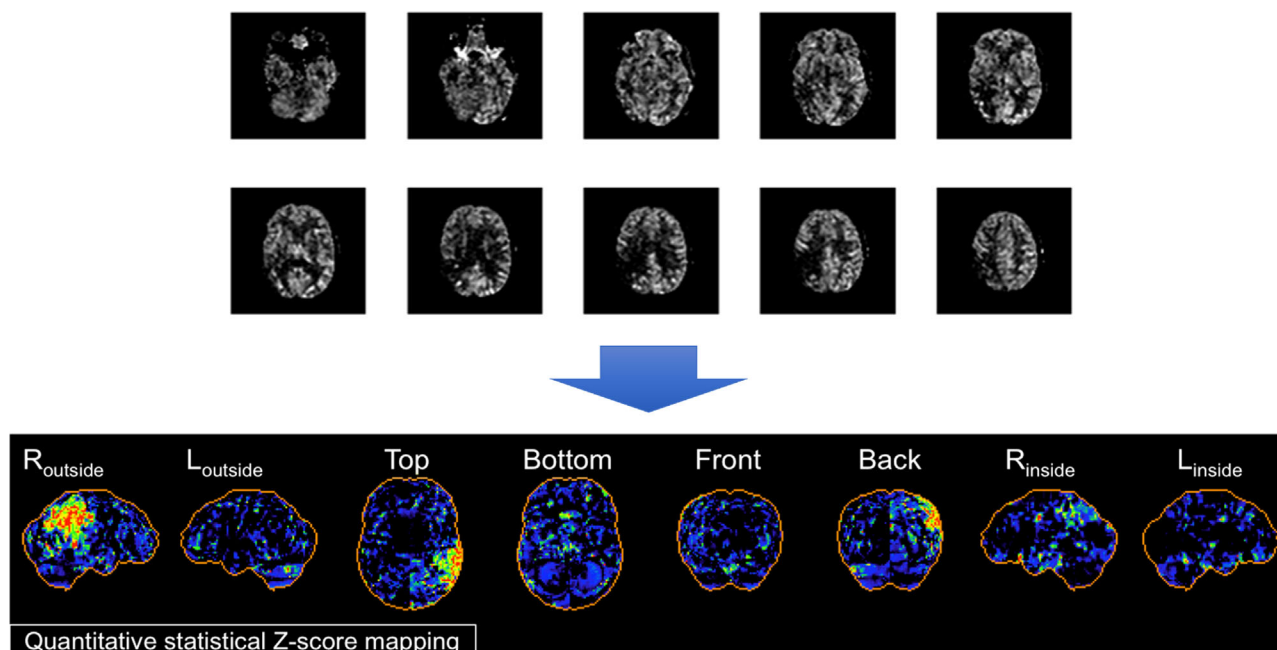


FIGURE 1 Three-dimensional SSP maps generated directly from quantitative, M0-corrected cerebral blood flow (CBF) maps (standard arterial spin labeling [ASL] data). Please note (1) only 10 of the 20 sequentially acquired ASL slices are displayed for the standard ASL data; (2) the radiological convention for sidedness is preserved for M0-corrected CBF maps, whereas the nuclear medicine convention for sidedness is preserved for the 3D-SSP maps (which appear left-right reversed, due to nuclear medicine convention, compared with the M0-corrected CBF maps from which they were derived). Colors represent the degree of hypoperfusion in that voxel, with blue = 1, green = 2, yellow = 3, and red = 4 standard deviations from mean CBF. L, left; R, right.

and $R = 2.5$. An M0 image acquisition was acquired, identical to the pCASL acquisition, but without the applied label, and $TR = 10,000$ ms. The chosen label duration and PLD allowed time for magnetically labeled arterial blood pool water molecules to flow into the intracranial circulation.³ For optimal neck vessel labeling, phase contrast angiography preceded all ASL image acquisition and was used to inform optimal ASL label slab angulation (perpendicular to neck arteries at ~ 90 mm inferior to the anterior commissure-posterior commissure line), as per International Society for Magnetic Resonance in Medicine (ISMRM) guideline.³ Readout was performed with a 2-dimensional background-suppressed echo-planar imaging comprising whole-brain coverage.

Standard ASL data processing

pCASL images were registered to the respective M0 image following motion-correction using in-house Matlab scripts (v8.6, Matlab, Mathworks, Natick, MA). Subsequently, pCASL control and label pairs underwent pairwise subtraction and CBF calculation, to generate the standard quantitative CBF images, as per the ISMRM working group recommendations.³

Image reconstruction

As described elsewhere in the literature,²⁷ stereotactic image standardization was performed first to the Talairach atlas,²⁸ requiring

both automated linear scaling to normalize patient brain size and automated nonlinear image warping to minimize regional anatomic variations among individual pCASL image sets.²⁷ Briefly, linear scaling requires the measurement of the anteroposterior length and mediolateral width of the brain from pCASL images.²⁷ The anteroposterior length is defined as the distance between the most anterior edge of the frontal cortex and the most posterior edge of the occipital cortex.²⁷ Mediolateral brain width is defined as the distance between the midsagittal plane and the most lateral edge of the parietotemporal cortex.²⁷ If there is a significant discrepancy between the right and left hemispheric brain length or width measurements, the discrepant measurement (length or width) will be averaged with that of its corresponding contralateral hemisphere.²⁷ Once the length and width dimensions of the brain are measured, linear stretching of the brain in the anteroposterior and mediolateral dimensions is performed to match the anteroposterior and mediolateral dimensions of a standard Talairach reference stereotactic brain atlas.^{27,28} The brain height contour is then derived by first identifying the midsagittal line from the pCASL images and then fitting the projected brain height contour to that of the height contour of the standard stereotactic reference brain atlas, requiring the use of axial pCASL image edge detection and a weighted least-squares algorithm to minimize height differences.²⁷

Using a technique developed by Minoshima and colleagues,²⁷ differences in anatomic variation between subjects were minimized using an automated nonlinear image warping technique to again match the anatomic contours of individual pCASL image sets to those of the standard reference stereotactic brain. Briefly, numerous reference points



are identified along the surface of the cortical gray matter and within white matter tracts of the standard reference stereotactic brain atlas and corresponding pCASL image sets.²⁷ An in-house image reconstruction algorithm then deforms the surface contour of each pCASL image set at the specified surface reference points to match the standard reference stereotactic brain atlas, while the white matter reference points remain fixed in space.²⁷ The algorithm utilizes a penalty criterion to eliminate erroneous surface landmarks that would inaccurately distort the pCASL brain surface contour.²⁷

Prior to linear scaling and nonlinear warping of the pCASL image sets, voxel-wise, whole-brain CBF quantitation was calculated from the acquired pCASL imaging data for both the control and experimental patient groups using in-house Matlab scripts, as described above. These quantitative ASL data (the standard quantitative CBF images) were then extracted to a set of predefined surface pixels corresponding to the standardized 3D-SSP for each brain and used for subsequent analysis. The extracted CBF values calculated for members of the control group were averaged together on a pixel-by-pixel basis, creating a normative dataset that each individual in the experimental patient group could be compared to. The individual dataset for each patient in the experimental patient group was then independently compared to the normative dataset by calculating Z-scores on a pixel-by-pixel basis. Z-scores for each experimental group patient were then assigned quartile color-scale values, which were subsequently mapped onto the corresponding brain 3D-SSP map, creating quantitative statistical Z-score perfusion maps, as depicted in Figure 1.

Evaluated data included two sets of images: (1) the standard quantitative CBF images, comprised of 20 consecutive slices of quantitative whole-brain ASL data ($N = 10$), derived from the M0-corrected pCASL images, displayed in their native 2-dimensional slice orientation in a single mosaic display, and (2) the corresponding 3D-SSP maps derived from these same 20 consecutive standard quantitative CBF images ($N = 10$), displayed as a mosaic of eight surface projections per subject, as per nuclear medicine convention (see Figure 1).²⁷ These two sets of images were subsequently intermixed, displayed in random order and without attention to patient succession.

Image evaluation

Two board-certified neuroradiologists, blinded to all patient clinical information and all imaging and postprocessing techniques, independently evaluated each mosaic display, composed only of either the standard quantitative CBF images (the 20 sequential slices of conventional M0-corrected pCASL CBF maps, $N = 10$) or the corresponding generated 3D-SSP maps ($N = 10$), generated directly from the same standard quantitative CBF images, without access to additional anatomic imaging. Raters were presented with images in random order, and ASL and 3D-SSP processing for the same individual was never presented sequentially. Raters were asked to evaluate all displayed images based on the following qualitative imaging metrics: (1) image quality; (2) ease of identifying abnormalities; (3) diagnostic confidence that no additional findings were present; and (4) confidence in the loca-

tion of the abnormality (specifically hypoperfusion). These variables were graded on a 3-point scale with a score of 1 corresponding to a low/poor evaluation; a score of 2 corresponding to an average/medium evaluation; and a score of 3 corresponding to a high/good evaluation. Additionally, raters were also instructed to identify the location of the perfusion abnormality, specifying the laterality, lobe, and vascular territory.

Statistical analysis

A Wilcoxon signed-rank test was used to compare the imaging metrics between the two employed techniques (standard quantitative CBF images vs. 3D-SSP maps).

RESULTS

Demographic data for the 10 consecutive subjects are presented in Table 1. Select patterns and severities of reduced CBF (hypoperfusion) were identified in tumor resection cavities, follow-up stroke regions, and in patients with notable regional hypoperfusion, as depicted in the 3D-SSP maps in Figure 2 (4 standard deviations, red color).

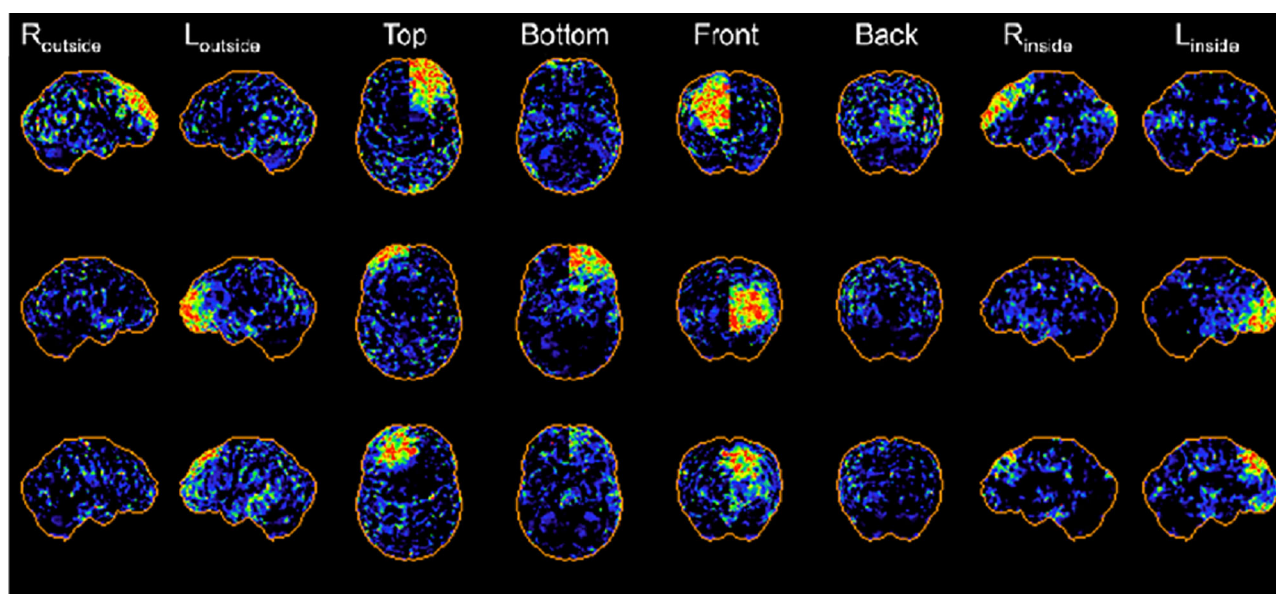
Expert neuroradiologist reader assessment demonstrated that 3D-SSP maps were preferred, in general, over the traditionally displayed standard quantitative CBF images and that 3D-SSP maps were never found to be inferior to the standard quantitative CBF images, across all assessed imaging metrics. Three-dimensional SSP maps, on average, possessed higher qualitative imaging metric scores compared with the standard quantitative CBF images. When the individual ratings for reader 1 and reader 2 were averaged together, 3D-SSP maps outperformed the standard quantitative CBF images, receiving higher scores for each qualitative imaging metric (Table 2), with three of the four score differences achieving statistical significance ($p < .05$). Reader assessment demonstrated that image quality, ease of identifying abnormalities, and confidence in identifying the exact location of hypoperfusion were all significantly higher for the 3D-SSP maps ($p = .026$, $.031$, and $.013$, respectively, calculated by paired, two-tailed t-test).

Interrater performance analysis demonstrated that imaging metric scores for the 3D-SSP maps were higher in interrater agreement than were those for the standard quantitative CBF images (Table 3); "ease of identification" of abnormalities and "confidence in location of hypoperfusion" metrics possessed the largest percent agreement between raters at 80% and 90%, respectively. Interrater analysis also demonstrated that Rater 1 consistently scored qualitative imaging metrics lower than did Rater 2 (Table 3), a trend that held true for both the standard quantitative CBF images and the 3D-SSP maps. For the standard quantitative CBF images, statistically significant differences between the scores generated by Rater 1 and Rater 2 were observed for all assessed imaging metrics except for the "ease of identification" of abnormality metric, which possessed a p -value of .15. There were fewer statistically significant differences between the scores generated by

TABLE 1 Patient demographics.

Patient number	Age (years)	Sex	Intracranial pathology	Resection cavity location
1	29	M	Oligodendroglioma (WHO 2)	Right frontal
2	62	M	Glioblastoma multiforme (WHO 4)	Right parietal
3	46	F	Oligoastrocytoma (WHO 2)	Left frontal
4	33	F	Glioblastoma multiforme (WHO 4)	Left frontal
5	61	M	Glioblastoma multiforme (WHO 4)	Left temporal
6	52	M	Anaplastic astrocytoma (WHO 3)	Left frontal
7	55	F	Glioblastoma multiforme (WHO 4)	Right parietal
8	22	F	Anaplastic astrocytoma (WHO 3)	Left frontal
9	48	F	Oligodendroglioma (WHO 2)	Right frontal
10	46	F	Glioblastoma multiforme (WHO 4)	Right parietal

Abbreviations: F, female; M, male; WHO, tumor grade according to World Health Organization CNS tumor classification.

**FIGURE 2** Exemplary 3-dimensional stereotactic surface projection maps, in which each subject is displayed per row. Colors represent the degree of hypoperfusion in that voxel, with blue = 1, green = 2, yellow = 3, and red = 4 standard deviations from mean cerebral blood flow. L, left; R, right.**TABLE 2** Comparison of quality ratings for the M0-corrected CBF maps and 3D-SSP maps (N = 10).

Metric	Average of readers 1 and 2			Reader 1			Reader 2		
	Images			Images			Images		
	CBF	3D-SSP	p-value	CBF	3D-SSP	p-value	CBF	3D-SSP	p-value
Image quality	2.1 ± 0.5	2.4 ± 0.3	.026*	1.7 ± 0.5	1.9 ± 0.6	.35	2.5 ± 0.5	3.0 ± 0.0	.037*
Ease of identification	2.4 ± 0.6	3.0 ± 0.2	.031*	2.2 ± 0.8	3.0 ± 0.0	.031*	2.5 ± 0.5	2.9 ± 0.3	.072
Confidence in not missing findings	2.1 ± 0.6	2.6 ± 0.5	.051	1.8 ± 0.9	2.4 ± 0.7	.12	2.5 ± 0.5	2.8 ± 0.4	.15
Confidence in location of hypoperfusion	2.2 ± 0.6	2.9 ± 0.2	.013*	1.8 ± 0.8	2.8 ± 0.4	.010*	2.7 ± 0.5	3.0 ± 0.0	.15

Note: Data presented as mean ± standard deviation.

Abbreviations: 3D-SSP, three-dimensional stereotactic surface projection; CBF, cerebral blood flow; N, number of cases.

*Statistically significant with p-value < .05.

**TABLE 3** Interreader agreement ($N = 10$).

Metric	M0-corrected CBF maps				3D-SSP maps			
	Reader				Reader			
	R1	R2	<i>p</i> -value	% Agree	R1	R2	<i>p</i> -value	% Agree
Image quality	1.7 ± 0.5	2.5 ± 0.5	.006*	20%	1.9 ± 0.6	3.0 ± 0.0	.006*	10%
Ease of identification	2.2 ± 0.8	2.5 ± 0.5	.15	70%	3.0 ± 0.0	2.9 ± 0.3	>.99	90%
Confidence in not missing findings	1.8 ± 0.9	2.5 ± 0.5	.042*	20%	2.4 ± 0.7	2.8 ± 0.4	.13	40%
Confidence in location of hypoperfusion	1.8 ± 0.8	2.7 ± 0.5	.008*	20%	2.8 ± 0.4	3.0 ± 0.0	.35	80%

Note: Data presented as mean ± standard deviation.

Abbreviations: 3D-SSP, three-dimensional stereotactic surface projection; CBF, cerebral blood flow; N, number of cases; R1, reader 1; R2, reader 2.

*Statistically significant with p -value <.05.

Rater 1 and Rater 2 with respect to 3D-SSP analysis. Perceived “image quality” was the only assessed metric that possessed a statistically significant difference between the scores generated by Rater 1 and those generated by Rater 2, with a p -value of .006.

DISCUSSION

In this retrospective case-control pilot study investigating the radiological applicability and performance of a novel implementation of 3D-SSP, a cerebral statistical parametric mapping technique, to ASL data, expert readers preferred 3D-SSP maps over their conventional M0-corrected brain perfusion map counterparts (standard quantitative CBF images) with respect to all assessed qualitative imaging metrics. Averaged rater scores were higher for the evaluated metrics of image quality, ease of identification of abnormalities, confidence in not missing findings, and confidence in the location of hypoperfusion abnormalities when using 3D-SSP maps compared to standard quantitative CBF images, three of which achieved statistical significance. In addition to outperforming standard quantitative CBF images, 3D-SSP maps also demonstrated greater percent agreement between raters on these qualitative characteristics of the images when compared to standard quantitative CBF images. Interrater agreement proved greatest for the ease of identification of abnormalities and the anatomic location of cerebral hypoperfusion (Table 2).

Multiple studies have demonstrated that ASL offers important insight into the hemodynamics underlying a variety of cerebrovascular pathologies.^{4,5,8,10,12–15,18,29–31} These insights prove valuable to clinical decision-making,^{10,12–15,30,32} allowing clinicians to better risk-stratify patients based on their likelihood of having an adverse cerebrovascular event as well as to better plan surgical or endovascular intervention. For example, collateral circulation pathways or vascular reserve in patients with Moyamoya disease can be evaluated in a non-invasive manner and studies report good agreement between ASL and digital subtraction angiography, PET or SPECT.^{9,10,33} In other research performed by Hendrikse and colleagues,³⁴ evaluating cerebral perfusion abnormalities underlying acute ischemic infarcts, ASL highlighted the potential variability in cerebral perfusion territories by demonstrating alterations in the classification of 11% of cortical versus border

zone infarcts, which deviated from their initially assumed textbook vascular distributions. Further advances in ASL acquisition, such as MR fingerprinting ASL and image reconstruction using machine learning approaches, which have so far been demonstrated to correlate with standard ASL results, could help overcome some of the limitations of ASL and make its utilization more widespread.^{35–37}

In the current radiological paradigm of ASL image interpretation, accurate evaluation of cerebral perfusion often proves difficult due, in part, to variations in individual brain morphology and physiological differences in regional CBF. Additionally, M0-corrected perfusion maps are traditionally displayed as an array of 2-dimensional images taken from various levels of the brain. The manner in which these images are currently displayed can impede accurate localization of perfusion abnormalities in 3-dimensional space, limiting the overall utility of this perfusion technique and other perfusion imaging modalities. The work presented here attempts to address these obstacles to improve accurate and reproducible image interpretation using 3D-SSP maps, which have proved advantageous to the interpretation of intracranial PET and SPECT imaging data.^{22,27}

In this proof-of-concept study, which retrospectively recruited sequentially imaged individuals at our institution. Our patient cohort comprised patients with prior tumor resection sites and/or chemoradiosurgically treated tumors, a few of which had documented, superimposed ischemic infarcts near the resection sites. While this cohort represents a relatively limited patient population, the results of this small study suggest that 3D-SSP maps can be routinely generated from clinically acquired ASL data using standard quantitative CBF processing, and that this technique may be applied to other cerebrovascular pathologies. Combined with the benefit of near-infinite ASL sequence repeatability during the same imaging session (due to obviation of any dependence upon an exogenous contrast agent), the use of 3D-SSP maps may represent an attractive, alternative methodology for processing ASL-derived CBF data, particularly for evaluating pathologies with subtle, regional cerebrovascular pathophysiological differences including those with mild cognitive impairment and vascular dementia. The application of 3D-SSP maps may also aid in the evaluation of other pathologies including Alzheimer's disease, Parkinson's disease, and schizophrenia and provide benefit in the evaluation of longitudinal studies of normal aging and age-related neuropathies.



It is worth noting that other statistical mapping and stereotactic anatomic standardization approaches are available and have been routinely used, although some have been utilized primarily in the research domain. The choice to generate 3D-SSP maps in the current study was informed by two features that have been previously explored with 3D-SSP: (1) PET and SPECT data have been previously shown to be transformable into a standard coordinate system (3D-SSP) without dependency on the availability of additional morphological MR images²⁷; (2) following stereotactic anatomic standardization, perfusion data are extracted to a set of predefined surface pixels via both linear scaling and nonlinear warping, to minimize regional anatomic variation among subjects.²⁷ This latter observation seemed well-suited to compliment the preferentially improved gray matter CBF quantification of the ASL technique, as previously reported.³ The addition of a referenced normative database was an additional desirable feature that is not unique to the 3D-SSP maps but has been previously explored.^{22,27,38}

Three-dimensional SSP has been used extensively in conjunction with PET and SPECT across multiple pathologies and has shown benefit as a statistical parametric technique. In one study evaluating the performance of Statistical Parametric Mapping (SPM) and 3D-SSP in statistical comparisons between healthy volunteers and AD patients, SPM was found to be more prone to residual mismatches of gray matter structures (localization, extent, and significance of estimated metabolic reductions) between these populations, as evidenced by validation using simulated PET image sets.³⁸ The authors acknowledged that both SPM and 3D-SSP maps may be prone to artifacts, particularly along the ventricular edges, although SPM was more affected by the presence of Alzheimer's disease-related atrophy,³⁸ highlighting its preferential use in this single pathology.

Our proof-of-concept pilot study, which aimed to demonstrate feasibility of 3D-SSP processing of ASL data, posed several inherent limitations and challenges. Most notably, the small sample size used in this study limits the power of our statistical results and the generalizability of our findings. As such, caution should be taken in the interpretation of our results. Additionally, a robust normal control group that is larger than the five normal control patients used in this study will be required for the development of a truly normative perfusion dataset against which patient groups with specific underlying pathologies can be compared to. A well-defined control group would require strictly screened individuals who have no clinical history of underlying conditions that would impact CBF as confirmed with relevant clinical testing and who also undergo cognitive performance assessment, neuropsychological testing, and a battery of behavioral testing, using a variety of clinical screening paradigms to confirm normal cognitive functioning. We are currently in the process of assembling a more robust normative perfusion dataset. Finally, the future application of 3D-SSP to ASL data across a broader spectrum of cerebral and cerebrovascular pathologies will be needed to fully validate this approach for quantitative CBF assessment prior to full individual and longitudinal clinical adoption.

The current pilot study results suggest that the application of statistical parametric mapping using 3D-SSP reconstruction for the evaluation and interpretation of ASL perfusion data in patients with

underlying cerebrovascular disease is clinically feasible, although further studies to validate 3D-SSP processing of ASL data are needed. In this pilot study, ASL-derived 3D-SSP maps were equally or better received by expert radiologists in terms of qualitative characteristics of images such as ease of localizing hypoperfusion or confidence in not missing an abnormality compared to standard quantitative CBF images. The use of 3D-SSP for displaying patient-specific quantitative CBF data may increase both the diagnostic confidence of the evaluating radiologist as well as the interrater agreement among radiologists compared to standard quantitative CBF images. As such, consideration should be given to the use of cerebral perfusion mapping with 3D-SSP when evaluating ASL perfusion data.

ACKNOWLEDGMENTS

This work was presented at the American Society of Neuroradiology's 2015 Annual Conference.

CONFLICT OF INTEREST STATEMENT

Jalal B. Andre has received funding from RSNA Seed Grant (Toshiba Medical) and Philips Healthcare. The other authors declare no conflicts of interest.

ORCID

Murat Alp Oztek  <https://orcid.org/0000-0002-4574-6637>

REFERENCES

1. Wong EC. An introduction to ASL labeling techniques. *J Magn Reson Imaging*. 2014;40:1–10.
2. Grade M, Hernandez Tamames JA, Pizzini FB, et al. A neuroradiologist's guide to arterial spin labeling MRI in clinical practice. *Neuroradiology*. 2015;57:1181–202.
3. 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;73:102–16.
4. Bokkers RPH, van Osch MJP, Klijn CJM, et al. Cerebrovascular reactivity within perfusion territories in patients with an internal carotid artery occlusion. *J Neurol Neurosurg Psychiatry*. 2011;82:1011–1016.
5. De Vis JB, Petersen ET, Bhogal A, et al. Calibrated MRI to evaluate cerebral hemodynamics in patients with an internal carotid artery occlusion. *J Cereb Blood Flow Metab*. 2015;35:1015–23.
6. Haller S, Zaharchuk G, Thomas DL, et al. Arterial spin labeling perfusion of the brain: emerging clinical applications. *Radiology*. 2016;281:337–56.
7. Hendrikse J, Petersen ET, Golay X. Vascular disorders: insights from arterial spin labeling. *Neuroimaging Clin N Am*. 2012;22:259–69.
8. Le TT, Fischbein NJ, André JB, et al. Identification of venous signal on arterial spin labeling improves diagnosis of dural arteriovenous fistulas and small arteriovenous malformations. *AJNR Am J Neuroradiol*. 2012;33:61–68.
9. Noguchi T, Kawashima M, Nishihara M, et al. Noninvasive method for mapping CVR in moyamoya disease using ASL-MRI. *Eur J Radiol*. 2015;84:1137–43.
10. Zaharchuk G, Do HM, Marks MP, et al. Arterial spin-labeling MRI can identify the presence and intensity of collateral perfusion in patients with moyamoya disease. *Stroke*. 2011;42:2485–91.
11. Oztek MA, Tseng YD, Mayr NA, et al. What neuroradiologists need to know about radiation treatment for neural tumors. *Top Magn Reson Imaging*. 2019;28:37–47.



12. de Havenon A, Haynor DR, Tirschwell DL, et al. Association of colateral blood vessels detected by arterial spin labeling magnetic resonance imaging with neurological outcome after ischemic stroke. *JAMA Neurol.* 2017;74:453–58.
13. Andre JB, Nagpal S, Hippe DS, et al. Cerebral blood flow changes in glioblastoma patients undergoing bevacizumab treatment are seen in both tumor and normal brain. *Neuroradiol J.* 2015;28:112–19.
14. de Havenon A, Sultan-Qurraie A, Tirschwell D, et al. Medial occipital lobe hyperperfusion identified by arterial spin-labeling: a poor prognostic sign in patients with hypoxic-ischemic encephalopathy. *AJNR Am J Neuroradiol.* 2015;36:2292–95.
15. Hartkamp NS, Petersen ET, De Vis JB, et al. Mapping of cerebral perfusion territories using territorial arterial spin labeling: techniques and clinical application. *NMR Biomed.* 2013;26:901–12.
16. Lindner T, Helle M, Jansen O. A short introduction to arterial spin labeling and its application to flow territory mapping. *Clin Neuroradiol.* 2015;25(Suppl 2):211–18.
17. Stanescu AL, Shaw DW, Murata N, et al. Brain tissue gadolinium retention in pediatric patients after contrast-enhanced magnetic resonance exams: pathological confirmation. *Pediatr Radiol.* 2020;50:388–96.
18. Bambach S, Smith M, Morris PP, et al. Arterial spin labeling applications in pediatric and adult neurologic disorders. *J Magn Reson Imaging.* 2022;55:698–719.
19. Clement P, Mutsaerts H-J, Václavů L, et al. Variability of physiological brain perfusion in healthy subjects—a systematic review of modifiers. Considerations for multi-center ASL studies. *J Cereb Blood Flow Metab.* 2018;38:1418–37.
20. Leidhin CN, McMorrow J, Carey D, et al. Age-related normative changes in cerebral perfusion: data from The Irish Longitudinal Study on Ageing (TILDA). *Neuroimage.* 2021;229:117741.
21. Tsujikawa T, Kimura H, Matsuda T, et al. Arterial transit time mapping obtained by pulsed continuous 3D ASL imaging with multiple post-label Delay acquisitions: comparative study with PET-CBF in patients with chronic occlusive cerebrovascular disease. *PLoS ONE.* 2016;11:e0156005.
22. Minoshima S, Frey KA, Koeppe RA, et al. A diagnostic approach in Alzheimer's disease using three-dimensional stereotactic surface projections of fluorine-18-FDG PET. *J Nucl Med.* 1995;36:1238–48.
23. Heijtel DFR, Mutsaerts HJMM, Bakker E, et al. Accuracy and precision of pseudo-continuous arterial spin labeling perfusion during baseline and hypercapnia: a head-to-head comparison with ¹⁵O H₂O positron emission tomography. *Neuroimage.* 2014;92:182–92.
24. Davis KM, Ryan JL, Aaron VD, et al. PET and SPECT imaging of the brain: history, technical considerations, applications, and radiotracers. *Semin Ultrasound CT MR.* 2020;41:521–29.
25. Risacher SL, Apostolova LG. Neuroimaging in dementia. *Continuum.* 2023;29:219–54.
26. Ferrando R, Damian A. Brain SPECT as a biomarker of neurodegeneration in dementia in the era of molecular imaging: still a valid option? *Front Neurol.* 2021;12:629442.
27. Minoshima S, Koeppe RA, Frey KA, et al. Anatomic standardization: linear scaling and nonlinear warping of functional brain images. *J Nucl Med.* 1994;35:1528–37.
28. Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system: an approach to cerebral imaging. Stuttgart; New York: Georg Thieme Verlag; 1988.
29. Faraco CC, Strother MK, Dethrage LM, et al. Dual echo vessel-encoded ASL for simultaneous BOLD and CBF reactivity assessment in patients with ischemic cerebrovascular disease. *Magn Reson Med.* 2015;73:1579–92.
30. Hartkamp NS, van Osch MJP, Kappelle J, et al. Arterial spin labeling magnetic resonance perfusion imaging in cerebral ischemia. *Curr Opin Neurol.* 2014;27:42–53.
31. Leoni RF, Mazzetto-Betti KC, Silva AC, et al. Assessing cerebrovascular reactivity in carotid steno-occlusive disease using MRI BOLD and ASL techniques. *Radiol Res Pract.* 2012;2012:268483.
32. van Laar PJ, Hendrikse J, Klijn CJM, et al. Symptomatic carotid artery occlusion: flow territories of major brain-feeding arteries. *Radiology.* 2007;242:526–34.
33. Zhao MY, Fan AP, Chen DY-T, et al. Using arterial spin labeling to measure cerebrovascular reactivity in moyamoya disease: insights from simultaneous PET/MRI. *J Cereb Blood Flow Metab.* 2022;42:1493–506.
34. Hendrikse J, Petersen ET, Chèze A, et al. Relation between cerebral perfusion territories and location of cerebral infarcts. *Stroke.* 2009;40:1617–22.
35. Hernandez-Garcia L, Aramendía-Vidaurreta V, Bolar DS, et al. Recent technical developments in ASL: a review of the state of the art. *Magn Reson Med.* 2022;88:2021–42.
36. Su P, Mao D, Liu P, et al. Multiparametric estimation of brain hemodynamics with MR fingerprinting ASL. *Magn Reson Med.* 2017;78:1812–23.
37. Su P, Liu P, Pinho MC, et al. Non-contrast hemodynamic imaging of moyamoya disease with MR fingerprinting ASL: a feasibility study. *Magn Reson Imaging.* 2022;88:116–22.
38. Ishii K, Willoch F, Minoshima S, et al. Statistical brain mapping of 18F-FDG PET in Alzheimer's disease: validation of anatomic standardization for atrophied brains. *J Nucl Med.* 2001;42:548–57.

How to cite this article: Andre JB, Oztek MA, Anzai Y, et al. Evaluation of 3-dimensional stereotactic surface projection rendering of arterial spin labeling data in a clinical cohort. *J Neuroimaging.* 2023;33:933–940.
<https://doi.org/10.1111/jon.13153>