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Arterial spin labeling and altered cerebral blood flow patterns in the minimally conscious state

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ABSTRACT

Objective: To use arterial spin labeling (ASL) to compare cerebral blood flow (CBF) patterns in minimally conscious state (MCS) patients with those in normal controls in an observational study design.

Methods: Subjects meeting MCS criteria and normal controls were identified. A pseudocontinuous ASL sequence was performed with subjects and controls in the resting awake state. Multiple CBF values for 10 predetermined regions of interest were sampled and average CBF was calculated and compared between controls and subjects.

Results: Ten normal controls were identified, with ages ranging from 26 to 54 years. Four subjects met the MCS criteria and received an ASL study, with one patient receiving a second study at a later date. Subjects ranged in age from 19 to 58 years and had traumatic brain injury, stroke, or hypoxic-ischemic encephalopathy. Regional CBF for controls ranged from 21.6 to 57.2 mL/100 g/min, with a pattern of relatively increased blood flow posteriorly including the posterior cingulate, parietal, and occipital cortices. CBF patterns for MCS subjects showed greater variability (from 7.7 to 33.1 mL/100 g/min), demonstrating globally decreased CBF in gray matter compared with that in normal controls, especially in the medial prefrontal and midfrontal regions. In the one subject studied longitudinally, global CBF values increased over time, which correlated with clinical improvement.

Conclusions: We identified globally decreased CBF and a selective reduction of CBF within the medial prefrontal and midfrontal cortical regions as well as gray matter in MCS patients. ASL may serve as an adjunctive method to assess functional reserve in patients recovering from severe brain injuries. *Neurology*® 2011;77:000-000

GLOSSARY

ASL = arterial spin labeling; **CBF** = cerebral blood flow; **CRS-R** = Coma Recovery Score-Revised; **DMN** = default mode network; **GM** = gray matter; **MCS** = minimally conscious state; **WM** = white matter.

Advances in intensive care have increased the number of patients surviving severe brain injury. After injury, patients typically progress from coma to varying levels of arousal and awareness. Patients who recover usually pass through an intermediate stage, the minimally conscious state (MCS), characterized by definite but inconsistent evidence of awareness of self or the environment.¹⁻³ Because of variable behavior observed at the bedside, an objective, quantitative measure of brain activity is needed.

Arterial spin labeling (ASL) is a magnetic resonance perfusion method that measures cerebral blood flow (CBF) in vivo. ASL uses a magnetic field gradient to invert existing water spins to trace blood flow.^{4,5} Unlike other comparable functional imaging modalities, ASL avoids use of a radioactive tracer or gadolinium, requires minutes to complete, and is noninvasive. ASL could therefore potentially have a wide range of clinical applications, especially in characterization of rapidly changing brain states, longitudinal follow-up, or monitoring treatment effects.⁶ CBF has been demonstrated to have a strong association with neural activity.⁷ ASL has been shown to have high interrater reliability and to be fairly stable over time.^{6,8,9} Early PET studies demonstrated a strong association

Editorial, page XXX

Supplemental data at
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between blood flow and cerebral metabolism in vegetative state patients.¹⁰ Preliminary studies suggest marked reductions in cerebral metabolism in MCS patients,¹ suggesting that CBF may also be decreased. Using ASL, global and regional perfusion differences have been reported in subjects with stroke, dementia, epilepsy, Parkinson disease, and cancer.^{11,12}

In this observational study, we sought to quantitatively measure CBF in a group of MCS patients and to follow longitudinal changes in one patient demonstrating significant functional improvement.

METHODS Patient selection. Patients who met the criteria for MCS were identified through self-referral or through discussions with physicians on the inpatient neurology and internal medicine services of the New York Presbyterian Hospital and JFK Johnson Rehabilitation Center between 2008 and 2009. Clinical subjects were adults who had sustained stroke, traumatic brain injury, or hypoxic ischemic injury and met the eligibility criteria for the larger natural history study. Subjects were included if they were between ages 18 and 75 years, had nonprogressive severe brain injury, were at least 3 months postinjury, met the Aspen Consensus Conference criteria for MCS,² and had consent provided by a legally authorized representative. Subjects were excluded if they had an intercurrent infection, were ventilator-dependent, had a history of cardiopulmonary arrest or instability, had a refractory seizure disorder, or had an MRI-incompatible device. One subject (subject 3) participated in a second ASL study. All subjects received a neurologic examination, including a Coma Recovery Scale–Revised³ assessment upon initial evaluation, before the ASL study, and on repeated assessments for one subject. Normal controls were recruited simultaneously by word of mouth and advertisement and were excluded if they had substance abuse or a major medical comorbidity.

Standard protocol approvals, registration, and patient consents. This study was conducted as part of a larger institutional review board–approved study of the natural history of recovery of consciousness. Consent for these studies was obtained for patients from a legally authorized representative. Normal controls provided their own consent.

Clinical MRI methods. Subjects and normal controls then underwent a series of structural and functional imaging studies as part of the ongoing protocol. All image data were acquired on a 3-T MRI system (GE Medical Systems, Milwaukee, WI). Conventional clinical imaging included T1-weighted, T2-weighted, and fluid-attenuated inversion recovery sequences. ASL sequences were obtained during the awake resting state. Subject and control ASL sequences with significant motion degradation were excluded from analysis.

The CBF images were acquired with a 3-dimensional pseudocontinuous ASL sequence, which uses a pseudocontinuous labeling technique.^{5,13} Pseudocontinuous ASL has been demonstrated to be both precise and reliable compared with the gold standard ¹⁵O-water PET.^{6,13}

Analysis methods. Ten regions of interest were preselected on the basis of a literature review of previous ASL studies and included the caudate, putamen, thalamus, anterior cingulate gyrus,

medial prefrontal cortex, middle frontal cortex, anterior superior temporal gyrus, posterior cingulate, parietal cortex, and occipital pole.^{14,15} We decided to omit cerebellar values from our analysis, given that imaging coverage of the cerebellum using the pulsed-continuous method is variable and subject to systematic error.¹⁶ Structures were manually selected with the guidance of an experienced neuroradiologist (L.A.H.). Multiple CBF values were sampled for each region using MRIcron 2008 software, including both left and right structures from the axial, sagittal, and coronal planes. Anatomic structures that could not be accurately identified due to distortion from traumatic injury were excluded. Average CBF, including SD, was calculated for each structure for both controls and subjects.

For a global analysis of CBF, measured values of CBF were placed in a normalized histogram of unit area. The normalized histogram was fitted with a dual Gaussian distribution function and a partial volume distribution function. The dual Gaussian distribution functions served as a model for the 2 compartments consisting of gray matter (GM) and CSF white matter (WM). The partial volume function was then modeled as a nonparametric distribution that takes account of voxels most likely consisting of a mixture of the CSF WM and GM compartments. Histogram comparisons of CSF WM and GM values are, as a result, more sensitive to changes in the underlying distributions.¹⁷ Furthermore, normalization of the histograms to account for brain volume allows for intersubject comparison, which corrects for various degrees of cerebral atrophy occurring after brain injury. Cerebral atrophy has been shown to be associated with globally decreased blood flow.¹¹

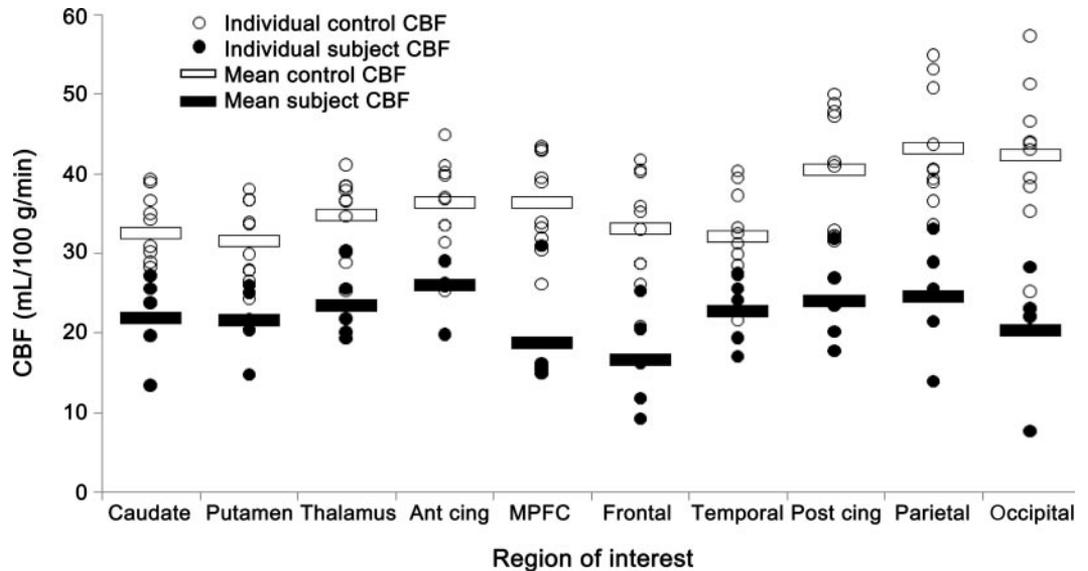
Differences in CBF in GM and WM and the GM/WM ratio between subjects and controls were calculated using a 2-sample *t* test assuming unequal variances.

RESULTS Demographics. Five subjects met MCS criteria and received an ASL study. They ranged in age from 19 to 58 years, included 4 women and 1 man and had traumatic brain injury (3), hypoxic ischemic encephalopathy (1), or stroke (1). Patients were all in the chronic phase after brain injury, with an interval from injury to evaluation ranging from 10 months to 4 years 9 months. However, the male patient was excluded from inclusion in our study because of a significant motion artifact; therefore, only 4 subjects were included in the analysis. Characteristics of the patients are shown in table e-1 on the *Neurology*[®] Web site at www.neurology.org and are described in detail in appendix e-1 case reports. Ten normal controls were identified, ranging in age from 26 to 54 years, and included 4 women and 6 men.

Subjects vs controls CBF. The regional blood flow pattern for normal controls ranged from 21.6 to 57.2 mL/100 g/min. We observed a pattern of increased blood flow in posterior structures including the posterior cingulate, parietal, and occipital cortices compared with the anterior cortical regions and subcortical structures (figure 1).

Regional blood flow patterns for the MCS subjects showed greater variability and ranged from 7.7 to 33.1 mL/100 g/min (figure 1). The majority of

Figure 1 Mean cerebral blood flow (CBF) across 10 regions of interest



Mean CBF for controls and subjects was calculated for each of the 10 structures of interest. Mean CBF for controls ranged from 33.1 to 43.2 mL/100 g/min (open bars), and mean CBF for subjects ranged from 16.6 to 26.0 mL/100 g/min (solid bars). Individual values for controls are represented by open circles, and individual values for subjects are represented by solid circles. After accounting for SD of individual measurements (not shown), mean CBF for subjects remained significantly lower than that for controls. In addition, there is again a suggestion of a relative decrease in mean CBF in the medial prefrontal cortex (MPFC) and midfrontal lobe among subjects compared with controls. Ang cing = anterior cingulate; Post cing = posterior cingulate.

subjects demonstrated decreased CBF in the medial prefrontal and midfrontal regions relative to that in other regions of interest. Mean CBF, including SD, for controls and subjects was calculated for each of the 10 structures of interest (figure 1). Mean CBF for control subjects ranged from 33.1 to 43.2 mL/100 g/min, and mean CBF for subjects ranged from 16.6 to 26.0 mL/100 g/min. After accounting for SD of individual measurements, mean CBF for subjects remained significantly lower than that for controls for all 10 regions of interest. In addition, there is again a suggestion of a relative decrease in mean CBF in the

medial prefrontal cortex and midfrontal lobe among subjects compared with controls.

In addition, in our analysis of CBF of GM vs CBF of WM histograms using partial volume modeling correction, we found that the average CBF in GM for controls was greater than that for subjects (33.7 ± 5.9 vs 17.4 ± 5.0 mL/100 g/min; $p = 0.0001$), as shown in table 1. Similarly, the GM/WM ratio was significantly different in controls vs subjects (10.4 ± 1.94 vs 6.0 ± 2.9 , $p = 0.009$).

Subject 3 underwent an initial clinical evaluation and measurement of ASL sequence approximately 13 months after experiencing a diffuse hypoxic-ischemic injury from disseminated fat emboli (see appendix e-1 for additional details). Initially, the patient was alert, could intermittently open and close her eyes to command, and smiled to family members, but was mute. Her Coma Recovery Score–Revised (CRS-R) total score was 14 (auditory 2, visual 3, motor 5, verbal 2, communication 0, and arousal 2).

A second evaluation was performed at 20 months after the initial injury. In the 7-month interval across the evaluations, the patient had regained some intermittent speech function. On examination, she more reliably produced simple verbal responses to prompts and nodded appropriately to yes/no questions but did not follow commands. She tracked objects and could reach with her right hand toward presented

Table 1 GM vs WM CBF in controls vs subjects^a

	Controls		Subjects		p Value
	Mean	SD	Mean	SD	
GM ROI	33.7	5.9	17.4	5.0	0.0001
WM ROI	3.3	0.3	3.1	0.928	0.3791
GM/WM ratio	10.4	1.94	6.0	2.90	0.00935

Abbreviations: CBF = cerebral blood flow; GM = gray matter; ROI = region of interest; WM = white matter.

^a Analysis of CBF of GM vs CBF of WM histograms. Using partial volume modeling correction, we found that the average CBF in GM for controls was greater than that for subjects (33.7 ± 5.9 vs 17.4 ± 5.0 mL/100 g/min; $p = 0.0001$). Similarly, the GM/WM ratio was significantly different in controls vs subjects (10.4 ± 1.94 vs 6.0 ± 2.9 ; $p = 0.009$). However, there was no significant difference in CBF in WM between controls and subjects (3.3 ± 0.3 vs 3.1 ± 0.928 mL/100 g/min; $p = 0.3791$).

objects. The CRS-R total score increased to 16 at this time (auditory 3, visual 3, motor 5, verbal 3, communication 0, and arousal 2). A second ASL measurement was performed (figure e-1).

On a subsequent evaluation, the patient continued to improve clinically, demonstrating reliable spoken communication and a near ceiling score on the CRS-R of 22. Notably the patient responded accurately to most simple questions and demonstrated some ability to form short-term memories. The patient clearly recognized family members and displayed a sense of humor.

In subject 3, global CBF values increased between ASL evaluations performed at 13 and 20 months, correlating with her clinical improvement and higher CRS-R score, as shown in figure e-1. Although the overall amount of CBF increased, a relative decrease in CBF was observed in the medial prefrontal and midfrontal regions and a peak was observed in the anterior cingulate region. The difference in CBF between times 1 and 2 is greater for most regions than the SD in measurement for any given region. Of note, the difference in CBF between time points is also greater than the 10% variation over time observed in other studies.^{6,8} Finally, her peak CBF in GM was increased at time 2 vs that at time 1 from 15.0 to 16.3 mL/100 g/min, which may explain the global increase in CBF (figure e-2).

DISCUSSION Our study demonstrates globally reduced ASL-measured CBF in MCS subjects compared with normal controls, particularly in the medial prefrontal cortex and midfrontal areas. In addition, as seen in one of our patients who eventually emerged from MCS with recovery of reliable spoken communication, increased global CBF, particularly within the GM, may be an indicator of physiologic recovery and therefore a quantitative method to follow patients' clinical progress over time.

Our local CBF values for normal subjects were comparable to previously published values in both young and old subjects.⁶ An exception is the posterior cingulate cortex, for which our reported CBF average of 40.5 mL/100 g/min is significantly lower than previously published values of 56.80 mL/100 g/min for elderly subjects and 60.37 mL/100 mg/min for younger subjects.⁶ This difference, however, would only lessen the evident reductions in CBF seen in controls and subjects in our measurements.

The globally decreased rate of blood flow among MCS subjects in our study is consistent with earlier observations of global reductions in cerebral flow and cerebral metabolism in vegetative state patients measured with PET.^{10,18,19} Although only a few studies have examined quantitative changes in cerebral me-

tabolism in MCS patients, similarly low metabolic rates have been observed.^{1,20,21} Human and animal studies indicate a strong linkage between CBF, glucose metabolic rate, neuronal firing rates, and related measures of oxidative metabolism.^{22,23} Our sample of MCS patients had approximately a 50% reduction in global CBF compared with controls, with a decreased GM/WM ratio, which is much larger than previously reported coefficients of variation of 10%–15%.^{6,8,9} Global depression of CBF in our patients could result from disproportionate loss of neurons in GM, such that metabolism in GM moves closer to that of WM (the latter consisting mostly of glial elements). Decreased blood flow could also reflect functional impairment of the remaining neurons,²⁴ as suggested by the partial restoration of CBF seen in our subject who was studied longitudinally.

It is of considerable interest that increased global CBF for subject 3, particularly within the GM, correlated with her clinical improvement and emergence from MCS. The overall pattern of blood flow to the various regions of the brain appears to be relatively preserved over time. Our finding of decreased relative blood flow to the medial prefrontal cortex and frontal areas in our MCS subjects is consistent with previous work highlighting the vulnerability of the anterior forebrain after severe brain injury. Various mechanisms of brain injury, whether producing widespread deafferentation or loss of excitatory neurotransmission, ultimately disrupt the corticostriatopallidal-thalamocortical projection system's ability to modulate the anterior forebrain.²⁴ Similarly, recovery of anterior forebrain metabolic activity is observed in early wakefulness as drowsiness subsides.²⁵ The activity of the mesial frontal and thalamic systems appears to be depressed early with use of various anesthetics.²⁶ Finally, the MCS patients who serve as dramatic examples as they reliably recover communication in a paradoxical response to zolpidem also demonstrate increased metabolism in the frontal cortex, striatum, and thalamus.^{27,28}

Conversely, preserved relative blood flow to the posterior portion of the default mode network (DMN) appears to be another defining characteristic of our sample of MCS patients, consistent with emerging fMRI research. The DMN consists of a set of regions, including the medial prefrontal cortex, precuneus/posterior cingulate, bilateral temporal-parietal areas, and thalamus, which are more active at rest than during attention-demanding tasks.¹⁵ The DMN has been proposed as the substrate for consciousness.²⁹ fMRI connectivity to the precuneus/posterior cingulate region, differentiating MCS patients from unconscious patients, was recently reported.³⁰ Preserved metabolism in both anterior and posterior portions of the DMN appears to characterize the locked-in syndrome,

whereas decreased metabolism in both regions defines the persistent vegetative state.^{30,31} It remains to be investigated whether locked-in, minimally conscious, and persistent vegetative states can be differentiated by different ranges of global CBF as measured by ASL.

In our study, we also used global CBF in GM to discriminate between normal controls and MCS subjects and to track recovery in one subject. Whereas the GM compartment can be well separated from the CSF WM compartment in controls, as seen in the global histogram (figure e-2), the GM compartment is less evident and therefore less easily segmented in our subjects. However, a partial volume model enabled us to segment the GM compartment and allowed us to track increased global CBF in accordance with neurologic improvement.

One of the major limitations in our study was motion artifact, a common problem in MRI examinations, including ASL. Motion artifact may produce both increases and decreases in signal intensity.⁴ Although our methods selected for data not significantly motion-degraded, even when subjects' images showed slight motion artifact, their CBF values may have been disturbed.

Another consideration in interpreting our results is the degree of intersubject variation attributed to factors other than level of consciousness, most notably characteristics such as age and gender. Previous work has demonstrated that older subjects have significantly decreased overall CBF compared with that of their younger counterparts,^{4,6,32} especially to the frontal cortex.^{32–35} Furthermore, women overall have increased global CBF, approximately 13% higher than of men.³² Given the inherent limitations of a small pilot study, we were not able to age- or gender-match our subjects and controls or correlate quantitative CBF patterns to behavioral measurements (such as CRS-R score). Further investigation in a larger population of MCS patients is needed to determine how blood flow relates to these demographic and clinical variables. Finally, our patients were all studied in the chronic phase after brain injury (although as demonstrated, a patient with a severe brain injury may still show clinical evolution in this chronic phase, making the ASL measurement useful). Whereas the appropriate timing of functional imaging is debated, there is some consensus that the late subacute phase (days 14–20) may be optimal. By this time, brain edema has subsided, and many critical decisions in medical and ethical management have been made.^{36,37} More investigation on the use of functional imaging in general, including ASL, is needed at this pivotal stage in medical decision making.

We have found that absolute differences in global cerebral flow, especially in GM, and perhaps a particular pattern of CBF (decreased to the medial prefrontal region and preserved to the posterior cingulate/precuneus region) may characterize the MCS state. Our work highlights some of the unique issues in studying patients with severe brain injury, specifically movement artifact, global brain atrophy, and traumatic distortion of neuroanatomy.

However, given these challenges in methodology and analysis, our results support the future use of ASL as an adjunctive method in diagnosis and management of patients with severe brain injuries and assessment of novel interventions at the cellular and network level. Because of its relative advantages of speed and ease of acquisition and its ability to provide precise quantitative measurements of CBF, ASL could be used efficiently in longitudinal assessments of patients with severe brain injuries.

AUTHOR CONTRIBUTIONS

Dr. Liu: drafting/revising the manuscript, analysis or interpretation of data, statistical analysis, and study supervision. Dr. Voss: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, and study supervision. Dr. Dyke: drafting/revising the manuscript, analysis or interpretation of data, statistical analysis, and study supervision. Dr. Heier: drafting/revising the manuscript and acquisition of data. Dr. Schiff: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision, and obtaining funding.

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DISCLOSURE

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Table e-1. Clinical Features of MCS Subjects.

Subject	Age	Sex	Cause	Interval*	CRS **
1	25	F	Brainstem stroke	3 yrs, 6 mo	9/14
2	27	F	Traumatic Brain Injury	4 yrs, 9 mo	15
3a	58	F	Multiple Strokes	13 mo	14
3b	59	F	Multiple Strokes	20 mo	16
4	19	F	Traumatic Brain Injury	10 mo	19

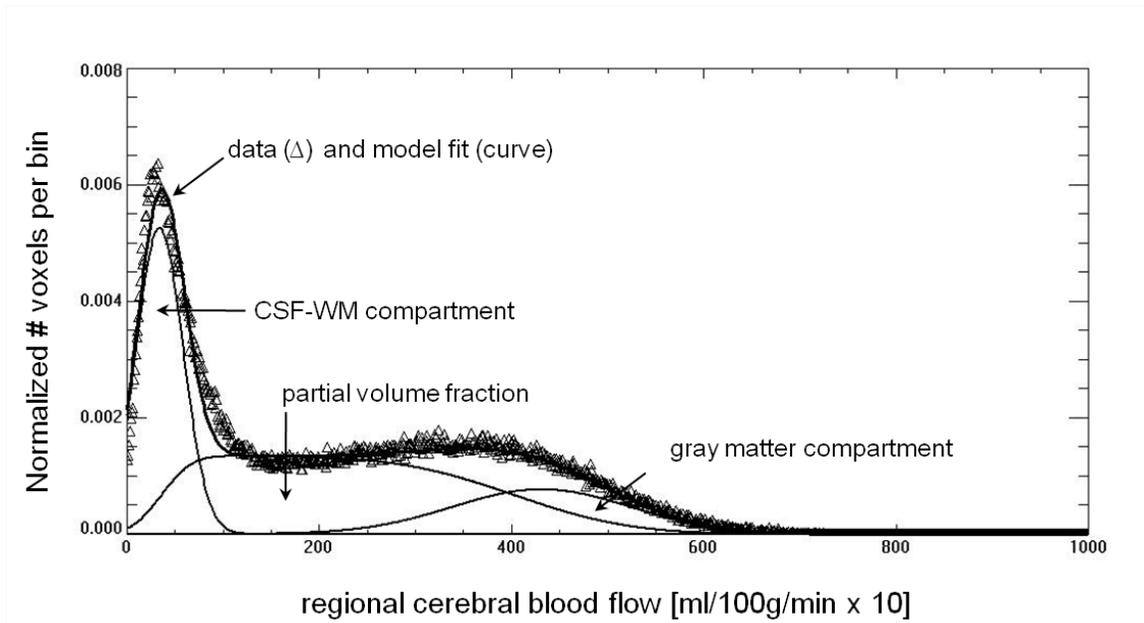
Four subjects met MCS criteria and received an ASL study. Patients ranged from ages 19 to 58; included four females; and suffered traumatic brain injury, hypoxic ischemic encephalopathy, or stroke. Patients were all in the chronic phase after brain injury, with an interval from injury to evaluation ranging from 10 months to 4 years 9 months. Subject 3, who clinically improved and gradually emerged from MCS state, received a second ASL study seven months after the initial study.

*Interval from the insult to the time of MRI-ASL Perfusion scan

**CRS=Coma Recovery Scale, based on clinician ratings of patient's level of auditory, visual, motor, and verbal function; communication; and arousal, for a total of 23 points maximum (Giacino and Kalmar 2006)

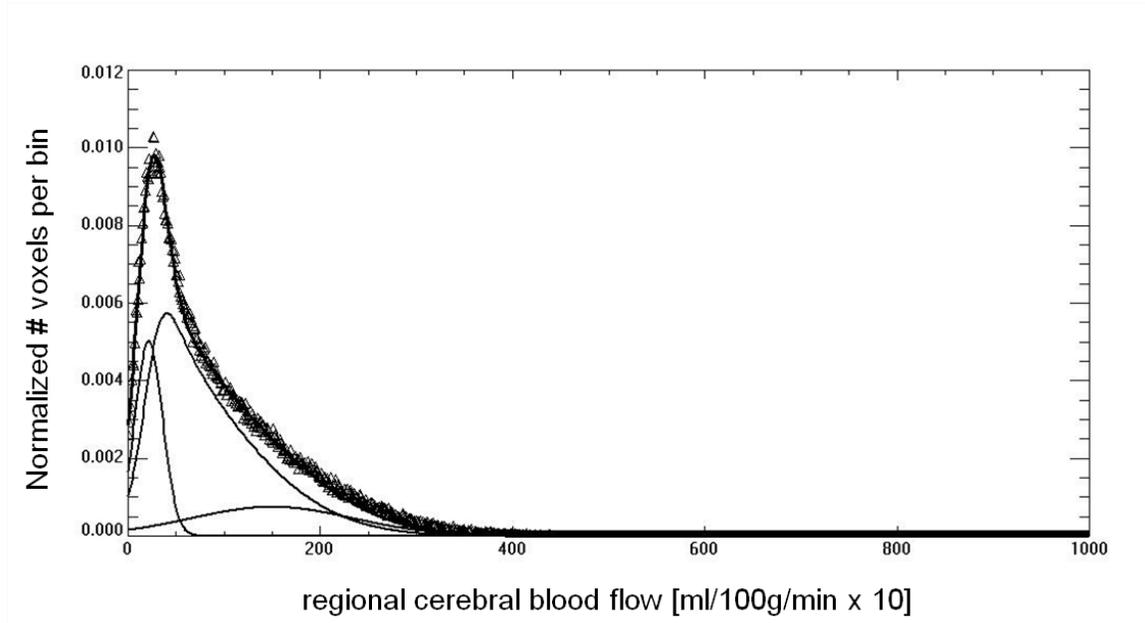
Figure e-2.

A.

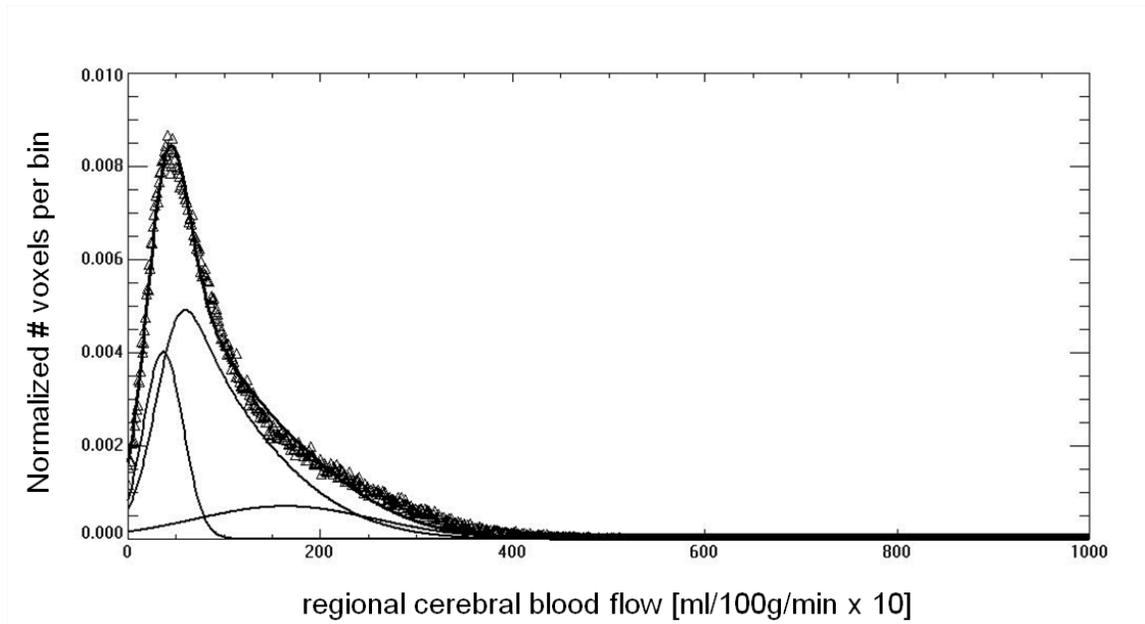


A. Normal Control Gray Matter vs. White Matter Regional Perfusion using Partial Volume Correction Modelling (female, 26 years). Shown are the histograms of CBF values (triangles), the CSF-white matter compartment Gaussian model (WM, left curve), the nonparametrically modeled partial volume fraction (middle curve), and the gray matter compartment Gaussian model (GM, right curve). In addition, the modelled histogram consisting of the three compartments CSF-WM, GM, and partial voluming between CSF-WM/GM is shown as the continuous curve close to the histogram triangles.

B.

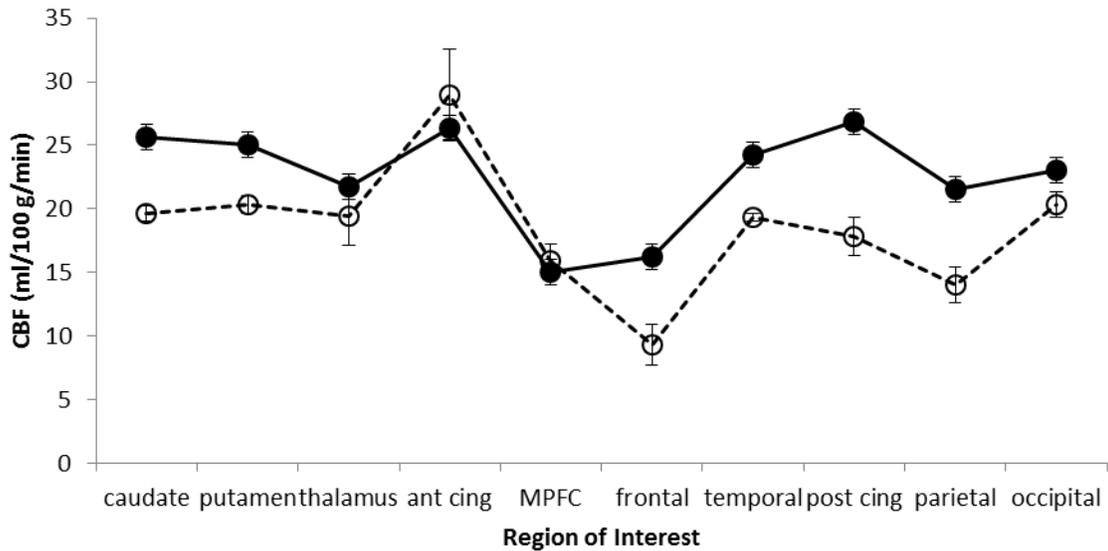


C.



B and C. Subject 3 Gray Matter vs. White Matter Regional Perfusion using Partial Volume Correction Modelling at Time of First ASL Study (13 months after injury) and Second ASL Study (20 months after injury). Her peak CBF in gray matter was increased between Time 1 and Time 2 from 15.0 to 16.3 ml/100 g/min, which likely explains the global increase in CBF. Note the overall smaller CBF values (abscissa) as compared to the control subject in A.

Figure e-1. Subject 3 CBF (ml/100 g/min) by Region of Interest at Time 1 and 2.



Subject 3 underwent an initial clinical evaluation and measurement of ASL sequence approximately 13 months after suffering diffuse hypoxic-ischemic injury from disseminated fat emboli. Initially, the patient was alert, could intermittently open and close her eyes to command, smiled to family members, but was mute. Initial CRS-R Score was 14 out of 23. Her CBF at Time 1 across the ten regions of interest, with standard error bars, is represented as the dashed line. On a subsequent evaluation at 20 months, the patient showed marked improvements in cognition and communication, demonstrating more reliable verbal responses to prompting and nodding appropriately to yes/no questions, thus scoring 16 on the CRS-R. Her CBF sampled at Time 2 is represented by the solid line. While the overall amount of CBF increased, a relative decrease in CBF was observed in the medial prefrontal and mid-frontal regions and a peak in the anterior cingulate regions. The difference in CBF between Times 1 and 2 is greater for most regions than the standard error in measurement for any given region.