Gray matter perfusion correlates with disease severity in ALS

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ABSTRACT

Objective: The goal of this study is to determine if regional brain perfusion, as measured by arterial spin labeling (ASL) MRI, is correlated with clinical measures of amyotrophic lateral sclerosis (ALS) disease severity. The presence of such a relationship would indicate a possible role for ASL perfusion as a marker of disease severity and upper motor neuron involvement in ALS.

Methods: Disease severity was assessed in 16 subjects with ALS (age 54 ± 11) using the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) and the pulmonary function measure, forced vital capacity (FVC). Upper motor neuron involvement was assessed by testing rapid tapping of the fingers and feet. Magnetic resonance perfusion images were coregistered with structural T1-weighted MRI, corrected for partial volume effects using the structural images and normalized to a study-specific atlas. Correlations between perfusion and ALS disease severity were analyzed, using statistical parametric mapping, and including age as a factor. Analyses were adjusted for multiple clusters.

Result: ALS severity, as measured by the ALSFRS and FVC, was correlated with gray matter perfusion. This correlation was predominantly observed in the hemisphere contralateral to the more affected limbs. ALSFRS scores correlated with perfusion in the contralateral frontal and parietal lobe ($p < 0.001$) and ipsilateral frontal lobe ($p < 0.02$). FVC scores correlated with gray matter perfusion in contralateral frontal lobe ($p < 0.001$). Upper motor neuron involvement, as measured by rapid finger tapping, correlated bilaterally with perfusion in the middle cingulate gyrus ($p < 0.001$).

Conclusion: Amyotrophic lateral sclerosis (ALS) severity is correlated with brain perfusion as measured by arterial spin labeling (ASL) perfusion. This correlation appears to be independent of brain atrophy. ASL perfusion may be a useful tool for monitoring disease progression and assessing treatment effects in ALS. *Neurology*® 2010;74:821-827

GLOSSARY

ALS = amyotrophic lateral sclerosis; **ALSFRS** = Amyotrophic Lateral Sclerosis Functional Rating Scale; **ASL** = arterial spin labeling; **BA** = Brodmann areas; **FDG PET** = fluorodeoxyglucose PET; **FVC** = forced vital capacity; **HMPAO SPECT** = Tc-hexamethylpropyleneamine oxime SPECT; **NAA** = N-acetylaspartate; **VBM** = voxel-based morphometry.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder that results in the loss of motor neurons both in the brain and spinal cord leading to paralysis and ultimately death. There is no definitive marker for ALS and both diagnosis and assessment of disease progression are currently based on clinical data. While lower motor neuron abnormalities can be easily evaluated by clinical electrodiagnostic examination, there is no reliable biomarker for the upper motor neuron abnormality. The development of a surrogate marker for disease progression would be useful for accurate diagnosis and for monitoring treatment effects.

Traditional MRI methods are mainly useful in ruling out diseases that mimic ALS. Several MRI techniques have helped to identify ALS-related brain changes. Two voxel-based morphometry (VBM) studies reported atrophy in ALS. One study reported global atrophy as well as regional atrophy in the right motor cortex and left precentral gyrus.¹ The other reported

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frontal lobe atrophy bilaterally in Brodmann areas (BA) 8, 9, and 10.² Magnetic resonance spectroscopy techniques have also been used to identify changes in ALS. One study found decreased *N*-acetylaspartate (NAA) both in the motor and frontal cortex³; another study reported decreased NAA and increased creatine and choline.⁴ NAA is a compound that is concentrated in neuronal cell bodies and processes, but absent from non-neuronal tissue. NAA concentration is thus considered an indicator of neuronal density. These differences were greatest in the motor cortex, but also present in other regions of the frontal and parietal lobes.

Functional imaging studies showed decreased brain glucose metabolism and perfusion in ALS using methods such as fluorodeoxyglucose PET (FDG PET) and Tc-hexamethylpropyleneamine oxime SPECT (HMPAO SPECT). One SPECT study reported bilateral frontal hypoperfusion,⁵ while a second study examining 3 related individuals with familial ALS reported frontal and parietal hypoperfusion in all 3 that was more prominent in the left hemisphere and thalamic hypoperfusion in 2.⁶ For clinical purposes, however, PET and SPECT have

several disadvantages, including injection of radioactive tracers, requirement for arterial blood sampling when performed quantitatively, and limited availability in comparison to MRI scans. Arterial spin label (ASL) perfusion is a noninvasive, rapidly repeatable method used to assess brain perfusion without exposure to radioactive tracers. Additionally, structural and perfusion images can be acquired during the same imaging session. The goal of this research was to assess ASL perfusion as a possible marker of disease severity in ALS.

METHODS Subjects. This study was approved by the Committees on Human Research at the University of California, California Pacific Medical Center, and the VA Medical Center, San Francisco, and all subjects provided written informed consent prior to MRI examination. Data were collected from 16 patients with ALS (age 54 ± 11 years). The diagnosis of ALS was established based on the El Escorial criteria (table 1).⁷ In 12 of the 16 patients with ALS, the left side of the body was identified as being more affected by clinical examination.

Clinical measurement of disease severity. ALS disease severity was assessed by the ALS Functional Rating Scale (ALSFRS) and the forced vital capacity (FVC). The ALSFRS is a measure of functional impairment in ALS. Individuals are rated using a 5-point scale (0 = cannot do, 4 = normal ability) on 10 everyday tasks (e.g., walking, writing, speaking, breathing). FVC is the total amount of air measured in liters that can be forcibly

Subject	Diagnosis	Age, y	Sex	Most affected side of body	ALSFRS	FVC	FVC %	Taps			
								More affected hand	Less affected hand	More affected foot	Less affected foot
1	Probable	49	M	Left	33	5.17	108	35	37	38	38
2	Definite	65	F	Left	19	3.57	123	15	28	0	0
3	Possible	51	M	Left	38	5.35	108	34	45	41	47
4	Probable	59	F	Right	28	2.99	105	34	33	0	12
5	Definite	62	M	Left	30	2.39	60	42	41	27	28
6	Probable	62	M	Right	33	5.32	110	36	34	0	0
7	Probable	62	M	Right	27	1.7	34	0	29	22	27
8	Probable	64	M	Left	40	4.01	95	33	38	34	32
9	Probable	36	M	Left	39	5.82	106	56	66	42	38
10	Possible	55	F	Left	40	3.41	106	38	41	33	42
11	Suspected	65	M	Left	35	3.21	90	46	60	0	37
12	Probable	59	F	Left	31	3.42	116	32	50	0	20
13	Probable	59	M	Left	37	5.76	107	38	42	32	35
14	Probable	33	M	Left	38	5.4	105	26	32	27	37
15	Possible	40	F	Right	40	4.96	124	52	51	32	31
16	Possible	41	M	Left	38	8.34	141	32	45	27	30

Abbreviations: ALSFRS = Amyotrophic Lateral Sclerosis Functional Rating Scale; FVC = forced vital capacity.

exhaled after full inhalation. Upper motor function was specifically assessed using rapid finger and foot tapping. This was the number of finger or foot taps the subject was able to complete in 10 seconds.

Image acquisition. Images were acquired using a standard 1.5 Tesla magnetic resonance system (Vision; Siemens, Erlangen, Germany) by using a circularly polarized head coil for radiofrequency transmission and reception. Labeled and reference images of ASL were collected in 6 contiguous 9-mm-thick slices along the AC/PC line with the most inferior slice at the level of the third ventricle using a pulsed arterial spin labeling sequence (postlabeling delay = 1,200 msec, repetition time/echo time = 2,500/15 msec, flip angle = 180°). The labeling delay was 1,200 msec. The field of view was 320 mm $\times$ 320 mm and the in-plane resolution was 5.0 mm $\times$ 2.5 mm. For brain tissue segmentation and for image registration to a reference brain template, a volumetric T1-weighted gradient echo MRI scan of the entire brain was acquired (echo time, 4 msec; repetition time, 10 msec; flip angle, 15° ; 1.0×1.0 mm² in-plane resolution; acquisition time, 7 minutes) that was angled perpendicular to the AC-PC line with a 1.5-mm effective slice thickness.

Image processing. Prior to processing, all images from the 4 individuals identified as having more involvement of the right side of the body were reversed, allowing group analyses of the ipsilateral and contralateral brain hemispheres relative to the more affected body side. For each subject, the perfusion image was coregistered with the T1-weighted image by using the mutual information coregistration algorithm within a statistical

parametric mapping program (SPM2; Wellcome Department of Cognitive Neurosciences, London, UK). A stepwise coregistration was used. First labeled and reference images were registered, then these images together were registered to the T1-weighted image. Once these 3 images were coregistered, the perfusion-weighted image was calculated by subtracting the labeled from the reference image. Perfusion images were corrected for inter-subject intensity variations in coil loading and signal amplification. This was done by first calculating image brightness (BR) using the following formula: $BR = FT_{scale} \times 10^{RG/20}$, where FT_{scale} accounts for coil loading and RG is the receiver gain, i.e., amplification of the signal. The T1 images were then segmented into gray matter, white matter, and CSF probabilistic masks using SPM's segmentation algorithm.

The gray matter probabilistic mask was resectioned to the same resolution as the perfusion image and converted to a binary mask thresholded at 40% probability to exclude voxels with small amounts of gray matter. The perfusion image was multiplied by the binary gray mask resulting in an image of predominantly gray matter perfusion.

A study-specific gray matter template was created by using the gray matter probability masks of all ALS and control subjects. This was accomplished by segmenting the T1-weighted images for each subject after affine normalization to the SPM T1 template, taking the mean of all gray matter probability masks, and smoothing the resultant image using an 8-mm full width at half maximum Gaussian kernel.⁸

The images were then spatially normalized, to the study-specific gray matter template, by using the normalization pa-

Figure 1 Finger tapping positive correlation with arterial spin labeling (ASL) perfusion (left = ipsilateral)

Voxels exhibiting increased ASL perfusion with increased Amyotrophic Lateral Sclerosis Functional Rating Scale. Voxels were only included if they were in clusters of at least 100 voxels ($p < 0.001$). The images in A project these voxels onto a 3-dimensional rendering of the Montreal Neurological Institute atlas. The images in B display these same data as a maximum intensity projection on a transparent "glass brain." The dashed lines indicate the extent of the brain that was covered by the ASL perfusion images.

rameters generated by spatially normalizing each subject's T1-weighted image to this template using an affine transformation.

Correcting for partial volume effects. After spatial normalization, information about the proportion of gray matter, white matter, and CSF within perfusion voxels was used to correct perfusion data for regions where gray matter atrophy has resulted in perfusion voxels with greater volume fractions of white matter and CSF. We assumed that all contributions to perfusion are from brain tissue—that is, gray matter and white matter—and CSF contributes nothing.⁹ To account for partial volumes of gray matter and white matter in perfusion voxels, we assumed that the perfusion to gray matter is 2.5 times the perfusion to white matter.¹⁰ Based on these assumptions, partial volume effects are corrected using the following formula: $I_{\text{corr}} = I_{\text{uncorr}} / (GM + 0.4 \times WM)$, where I_{corr} and I_{uncorr} are the corrected and uncorrected perfusion intensity values, GM is the probability of the voxel containing gray matter, and WM is the probability of the voxel containing white matter with $GM + WM + CSF = 1$. To avoid unreasonable high I_{corr} values due to

image misregistrations, an upper limit was set of 2 standard deviations above the mean value of I_{uncorr} for all voxels containing at least 95% gray matter.

Statistical analysis. Voxel-wise statistical analyses were conducted using SPM2. Images were smoothed with a 12-mm full width at half maximum kernel prior to statistical analysis to normalize the distribution of perfusion data. Correlations were evaluated using a multiple regression analysis with subject age included as a variable in the model. SPM's threshold masking function was used to eliminate voxels with very small intensity values (<0.5) from the analysis. Results were thresholded at $p < 0.001$ for voxel analysis and clusters were only included if they were at least 100 significant voxels large. Analyses were conducted on the entire subject group. Clusters were only reported if they were significant after correcting for multiple clusters using SPM's cluster-level analysis. Reported correlation coefficients were calculated by using the transform extension from the SPM2 VBM2 toolbox (<http://dbm.neuro.uni-jena.de>).

Table 2 Regions of significant correlation

	Corrected p value	Uncorrected p value	Cluster size	Cluster location	MNI coordinates of local maxima	Correlation coefficients at local maxima
ALSFRS and ASL perfusion	<0.001	<0.001	2,295	Contralateral inferior frontal cortex (pars triangularis and pars opercularis) and inferior parietal cortex (posterior to the supramarginal gyrus)	46, -66, 26	0.85
					46, 16, 8	0.83
					62, -16, 16	0.83
	0.018	0.010	507	Ipsilateral inferior frontal cortex (pars opercularis) extending into a portion of the precentral gyrus	-48, 14, 12	0.79
					-54, 4, 10	0.77
					-52, 8, 20	0.67
	0.018	0.010	443	Bilateral middle cingulate	12, -28, 44	0.80
					-8, -18, 32	0.79
	0.024	0.013	404	Bilateral cuneus and superior occipital gyrus	-14, -82, 24	0.78
					-22, -88, 28	0.77
					10, -76, 26	0.77
Absolute FVC and ASL perfusion	<0.001	<0.001	1308	Contralateral inferior frontal cortex (pars triangularis and pars opercularis)	50, 14, 10	0.84
					48, 22, 10	0.83
					44, -12, 16	0.82
Hand taps and ASL	<0.001	<0.001	1611	Bilateral middle cingulate and the ipsilateral precuneus	-8, -30, 24	0.84
Perfusion (more affected body side)					-12, -48, 44	0.63
					-5, -30, 40	0.69

Abbreviations: ALSFRS = Amyotrophic Lateral Sclerosis Functional Rating Scale; ASL = arterial spin labeling; MNI = Montreal Neurological Institute.

Details for all clusters identified as significant using SPM's cluster-level analysis. p Values were corrected for comparisons. Both corrected and uncorrected p values are presented. Cluster size is the number of contiguous perfusion voxels that contribute to each cluster. Cluster location is a list of the cortical structures involved in each cluster. The location of each local maxima within each cluster is listed using the MNI atlas coordinate system. Correlation coefficients are listed for each cluster's local maxima.

Voxels exhibiting increased ASL perfusion with increased absolute FVC. Voxels were only included if they were in clusters of at least 100 voxels ($p < 0.001$). The images in A project these voxels onto a 3-dimensional rendering of the Montreal Neurological Institute atlas. The images in B display these same data as a maximum intensity projection on a transparent "glass brain." The dashed lines indicate the extent of the brain that was covered by the ASL perfusion images.

RESULTS **Perfusion and ALS severity.** *ALSFRS.* A linear regression analysis of motor functioning as measured by score on the ALSFRS (and age as a covariate) reveals that motor functioning increases with ASL brain perfusion in several cortical areas. This correlation was predominantly observed in the hemisphere contralateral to the more affected limbs. One very large cluster was observed in the hemisphere contralateral to the more affected body side. One cluster was observed in the ipsilateral hemisphere and 2 clusters traversed the interhemispheric fissure. The contralateral cluster extended from pars triangularis in the inferior frontal lobe to the supramarginal gyrus in the inferior parietal lobe. The ipsilateral cluster mirrored the prefrontal local maxima of the contralateral cluster but was smaller in extent. One bilateral cluster was located in the middle cingulate and the other was located in the cuneus and superior occipital cortex (figure 1, table 2).

FVC. A linear regression analysis of lung capacity as measured by FVC (and controlling for age) reveals a cluster in the contralateral inferior frontal cortex (figure 2, table 2).

Tapping. Significant correlations between tapping of the hand on the more affected side of the body were observed bilaterally in the middle cingulate ex-

tending into the ipsilateral precuneus (figure 3, table 2). No clusters reached criteria when looking at the less affected hand or either foot.

DISCUSSION Increased ALS severity was correlated with a regional pattern of decreased gray matter perfusion. Decreased perfusion was primarily observed in the frontal cortex, but also in medial cortex, middle cingulate, and precuneus; these results have been corrected for atrophy and thus do not appear to be the result of correlations between cortical atrophy and disease severity. Correlations were more extensive in the hemisphere contralateral to the side of the body more affected by ALS.

These correlations are consistent with atrophy that has been observed by using both voxel-based morphometry¹¹ and volumetric analysis.¹²

The frontal cluster in the ipsilateral hemisphere, and to a lesser extent the frontal cluster in the contralateral hemisphere, included a portion of motor cortex, which corresponds to the upper motor neuron degeneration that occurs in ALS. The full extent of motor cortex involvement cannot be assessed as the superior regions of motor cortex were outside of the perfusion image. Moreover, these frontal lobe ab-

Figure 3 Amyotrophic Lateral Sclerosis Functional Rating Scale positive correlation with arterial spin labeling (ASL) perfusion (left = ipsilateral)

Voxels exhibiting increased ASL perfusion with increased number of finger taps. Voxels were only included if they were in clusters of at least 100 voxels ($p < 0.001$). The images in A project these voxels onto a 3-dimensional rendering of the Montreal Neurological Institute atlas. The images in B display these same data as a maximum intensity projection on a transparent "glass brain." The dashed lines indicate the extent of the brain that was covered by the ASL perfusion images.

normalities are consistent with the presence of executive function deficits in ALS.¹³⁻¹⁵

The asymmetric distribution of the correlations between ALSFRS and ASL perfusion are similar to recently reported results. One SPECT study reports correlations between the ALSFRS and perfusion that are more prominent in the left hemisphere.¹⁶ The authors of that study did not categorize subjects by affected body side so it is not possible to directly compare this to the current findings. It is important to note that while ALSFRS and FVC measure complex bilateral behavior, the correlations with ALS perfusion display hemispheric asymmetry. The correlated brain regions are not necessarily directly affecting performance on the clinical measures but it is likely that the affected brain regions are being influenced by the same disease processes responsible for the clinical deficits observed.

While degeneration of the frontal lobe is more frequently reported in ALS than are changes in posterior regions, the correlations we found in parietal cortex are consistent with the findings of MRS changes^{4,17} in ALS and atrophy in both ALS and primary lateral sclerosis.^{18,19}

To determine the usefulness of this measure, longitudinal studies are needed to determine how perfu-

sion changes over time in ALS. Additionally, future research should use a perfusion sequence with fuller coverage of regions known to be affected by ALS (e.g., motor cortex and prefrontal cortex). No cognitive testing was conducted with this group of patients with ALS. Given the presence of correlations between disease severity and perfusion in extramotor cortical regions, further research is needed into the relationship of disease severity, perfusion, and cognitive function.

This study has a number of limitations. First, there is no control group. Therefore the relationship between imaging and functioning observed in ALS cannot be compared to the relationship, if any, in individuals without ALS. Second, in the current implementation of ASL, brain coverage was limited to superior brain regions and coverage of the superior brain was incomplete. Portions of the brain implicated in other studies of ALS, including primary motor cortex and prefrontal cortex, were only partially covered. Finally, perfusion measurements were based on a simple model of water perfusion, in which instantaneous exchange of water from intravascular to extravascular space was assumed. In addition, variable arterial transit times and variations in T1 relax-

ation of the water labels were not considered. To the extent that these factors systematically vary with ALS severity, perfusion may have been overstated or understated.

The current findings, while preliminary, are promising. The relationship between ALS severity and brain perfusion suggests that brain perfusion decreases with ALS severity. Therefore brain perfusion may be a useful tool for monitoring disease progression and assessing treatment effects in ALS.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. R.R. Rule.

DISCLOSURE

Dr. Rule served on a scientific advisory board and served as a consultant for Posit Science Corporation and received research support from the NIH (NHLBI K01 HL73152 [PI]). Dr. Schuff has received travel expenses for educational activities not funded by industry and receives research support from Synarc Inc., the NIH (P41 RR 023953 [Co-I], R01 AG032306 [Co-I]), the US Department of Defense (W81XWH-05 [PI]), and the Michael J. Fox Foundation. Dr. Miller serves on the editorial board of the *ALS Journal*; received a speaker honorarium from the AANEM; served as a consultant to Celgene, Knopp Neurosciences Inc., Teva Pharmaceutical Industries Ltd., Taiji Biomedical, Inc., Sanofi-Aventis, Novartis, and Neuraltus; and receives research support from the NIH (R01 NS 44887 [PI]) and the Muscular Dystrophy Association (PI). Dr. Weiner serves on scientific advisory boards for Bayer Schering Pharma, Eli Lilly and Company, CoMentis, Inc., Neurochem Inc, Eisai Inc., Avid Radiopharmaceuticals Inc., Aegis Therapies, Genentech, Inc., Allergan, Inc., Lippincott Williams & Wilkins, Bristol-Myers Squibb, Forest Laboratories, Inc., Pfizer Inc, McKinsey & Company, Mitsubishi Tanabe Pharma Corporation, and Novartis; has received funding for travel from Nestlé and Kenes International and to attend conferences not funded by industry; serves on the editorial board of *Alzheimer's & Dementia*; has received honoraria from the Rotman Research Institute and BOLT International; serves as a consultant for Elan Corporation; receives research support from Merck & Co., Radiopharmaceuticals Inc., the NIH (U01AG024904 [PI], P41 RR023953 [PI], R01 AG10897 [PI], P01AG19724 [Co-I], P50AG23501 [Co-I], R24 RR021992 [Co-I], R01 NS031966 [Co-I], and P01AG012435 [Co-I]), the US Department of Defense (DAMD17-01-1-0764 [PI]), the Veterans Administration (MIRECC VISN 21 [Core PI]), and the State of California; and holds stock in Synarc and Elan Corporation.

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