Impaired corticopontocerebellar tracts underlie pseudobulbar affect in motor neuron disorders

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ABSTRACT

Objective: The objectives of the study were (1) to determine the prevalence and characteristics of pseudobulbar affect (PBA) in patients with primary lateral sclerosis (PLS) and amyotrophic lateral sclerosis (ALS) in an outpatient clinic population, and (2) to test the hypothesis that damage of inputs to the cerebellum, leading to cerebellar dysmodulation, is associated with PBA.

Methods: Chart review of all patients with PLS and ALS seen between 2000 and 2013. The examining neurologist documented the presence or absence of PBA in 87 patients. Forty-seven patients also had diffusion tensor imaging (DTI) studies. Tract-based spatial statistics were used to compare DTI of patients with and without PBA to identify altered white matter tracts associated with PBA.

Results: Thirty-one of 50 patients with PLS and 12 of 37 patients with ALS had PBA. Psychiatric/emotional assessment found congruence between mood and affect during episodes, but excessive magnitude of the response. DTI studies of 25 PLS and 22 ALS patient brains showed reduced fractional anisotropy of the corticospinal and callosal white matter tracts in all patients. Patients with PBA additionally had increased mean diffusivity of white matter tracts underlying the frontotemporal cortex, the transverse pontine fibers, and the middle cerebellar peduncle.

Conclusions: PBA is common in PLS. Imaging findings showing disruption of corticopontocerebellar pathways support the hypothesis that PBA can be viewed as a "dysmetria" of emotional expression resulting from cerebellar dysmodulation. ***Neurology*® 2014;83:620–627**

GLOSSARY

ALS = amyotrophic lateral sclerosis; **ALSbi** = amyotrophic lateral sclerosis with mild behavioral impairment; **ALSci** = amyotrophic lateral sclerosis with mild cognitive impairment; **ALSFRS-R** = Amyotrophic Lateral Sclerosis Functional Rating Scale–revised; **BDI-II** = Beck Depression Inventory–II; **DRS-2** = Mattis Dementia Rating Scale–2; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **FSL** = FMRIB's Software Library; **PBA** = pseudobulbar affect; **PLS** = primary lateral sclerosis; **TFCE** = threshold-free cluster enhancement; **UCLA** = University of California Los Angeles.

Pseudobulbar affect (PBA) is a syndrome of involuntary emotional expression dissociated from one's true emotional experience.[1] It occurs in several neurologic disorders, including amyotrophic lateral sclerosis (ALS).[2,3] In one retrospective series, PBA occurred in 50% of patients with ALS.[4] There have been case reports of PBA in patients with primary lateral sclerosis (PLS), a motor neuron disorder variant with relatively selective degeneration of upper motor neurons.[5] However, the prevalence of PBA in PLS has not been evaluated in a large patient series.[2,6] To assess the occurrence of PBA in PLS, we reviewed the charts of all patients seen in an upper motor neuron disorder clinic.

Two hypotheses have been proposed regarding the neural circuits that produce PBA. Wilson[7] proposed that brainstem centers controlling laughter and crying were separately controlled by volitional and emotional pathways, and that lesions of the volitional pathway led to disinhibition of the involuntary emotional pathway. Parvizi et al.,[8] who observed PBA in patients with cerebellar lesions, hypothesized that PBA results from loss of frontal cortex inputs that normally provide the cognitive, emotional, and social context that the cerebellum uses to modulate the

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duration and intensity of the facial and respiratory muscle activity producing emotional expression.[9] The loss of such inputs would result in impaired cerebellar modulation, leading to a "dysmetria" of emotional expression. To distinguish between these hypotheses, we compared diffusion tensor imaging (DTI) between patients with and without PBA to identify white matter tracts with reduced integrity in patients with PBA.

METHODS

Standard protocol approvals, registrations, and patient consents. All subjects gave written informed consent for protocols approved by the NIH CNS Institutional Review Board, in accord with the Declaration of Helsinki. Every patient was enrolled in a natural history study (NCT00015444); healthy controls and a subset of patients were enrolled in imaging or cognitive testing protocols (NCT00071435, NCT01517087).

Subjects. This is a retrospective report. Ninety-eight patients evaluated in the National Institute of Neurological Disorders and Stroke upper motor neuron disorder clinic between 2000 and 2013 fulfilled a clinical diagnosis of PLS[5] or ALS.[10] Their charts were reviewed for clinical findings. Twenty-eight healthy controls underwent DTI scanning, neurologic examination (assessment of cranial nerves, motor strength, reflexes, tone, coordination, and sensation), and measures of finger-tapping and timed gait. All subjects were examined by a neurologist, and all healthy controls had normal neurologic examinations.

The examining neurologist had asked patients and caregivers whether symptoms of PBA were present in 87 patients (50 PLS, 37 ALS). The neurologist's classification of whether patients had PBA was used for the chart review and DTI analysis. Clinical findings of dysarthria, facial muscle weakness, brisk jaw jerk, hyperactive gag reflex, frontal release signs (suck, snout, or palmomental reflexes), Myerson sign (persistent blinking to glabellar taps), history of bladder urgency, and measures of finger-tapping rate and timed gait were tallied from the charts. Beginning in 2006, the ALS Functional Rating Scale–revised (ALSFRS-R) and Beck Depression Inventory–II (BDI-II) scores were routinely obtained in patients. DTI scans were performed in all patients without contraindications seen after 2006. Forty-seven patients (25 PLS, 22 ALS) and 28 healthy controls had DTI studies. The demographic features of the imaging subset of patients were similar to the full cohort (table 1).

Between 2006 and 2010, 32 of the 47 patients who had DTI also had cognitive testing as part of a previously reported study.[11] The testing battery included the Mattis Dementia Rating Scale–2 (DRS-2),[12] the Delis-Kaplan Executive Function System,[13] the Frontal Systems Behavioral Evaluation,[14] and the University of California Los Angeles (UCLA) Neuropsychiatric Index.[15] None of the patients met criteria for frontotemporal dementia.[16] The Delis-Kaplan Executive Function System was used to classify patients as having ALS with mild cognitive impairment (ALSci), and the Frontal Systems Behavioral Evaluation and UCLA Neuropsychiatric Index were used to classify patients as having ALS with mild behavioral impairment (ALSbi) using consensus criteria.[17] After 2010, patients were screened for cognitive deficits with the ALS Cognitive Behavioral Screen,[18] the Montreal Cognitive Assessment (www.mocatest.org), or the Mini-Mental State Examination.

Although the neurologist's assessment of PBA was used for analyses, a substudy performed during this period provided additional confirmation. During 2006–2008, 30 patients had a full emotional/psychiatric evaluation that included administration of the Structured Clinical Interview for DSM Disorders (I/P)[19] and prospective evaluation of symptoms of PBA by a geriatric psychiatrist with experience working with patients with motor neuron disease (E.D.H.). The psychiatric portion of the data from these evaluations has been previously published.[20] Patients received the psychiatric/emotional evaluation based only on whether they were seen during this time period and were not selected on the basis of any patient characteristics. In the psychiatric interview, a diagnosis of PBA was defined as recurrent episodes of excessive or inappropriate emotional expression. All evaluations were corroborated with an informant. Congruence between mood and affect (i.e., crying triggered by sad stimuli and laughing by happy or funny stimuli), and relative magnitude of mood and affect changes were assessed (i.e., Are the changes in affect excessive compared with mood or are both mood and affect disproportionately increased?). The emotional/psychiatric evaluation of PBA was performed blinded to the results of the neurologist's evaluation.[20]

Imaging acquisition and processing. MRI studies were performed on two 3T scanners (Philips Achieva, Best, the Netherlands; and GE Medical Systems, Milwaukee, WI) using a receive-only, 8-channel head coil. Multislice diffusion-weighted imaging was acquired using a single-shot echo-planar sequence with 55 to 64 contiguous axial slices (slice thickness = 2.5 mm, field of view = 240 × 240 mm). Diffusion weighting was performed along either 32 noncollinear directions with b = 0 and b = 1,000 (Philips) or 80 noncollinear directions with multiple b values: b = 0 s/mm^2, b = 300 s/mm^2, and b = 1,100 s/mm^2 (GE). The diffusion sequence was repeated 4 times to increase the signal-to-noise ratio. The average scan time for each diffusion sequence was 4 to 6 minutes. Axial T2-weighted images were also acquired for echo-planar imaging distortion correction. Processing of diffusion-weighted images, including coregistration, correction for eddy currents and subject motion using a 12-mode affine transformation,[21] skull stripping, and normalization to the ICBM-DTI-81 coordinates,[22] was performed using TORTOISE (http://www.nitrc.org/projects/tortoise)[23] and MRI Studio[24] (www.MriStudio.org) software packages. The 6 elements of the diffusion tensor, the fractional anisotropy (FA), the eigenvectors, and the eigenvalues were calculated for each voxel. Voxel-wise statistical analysis of the FA skeletons was performed using tract-based spatial statistics (version 1.2; http://www.fmrib.ox.ac.uk/fsl/),[25] with methods previously described.[26]

Imaging analysis. A 2-step process was used to identify white matter tracts associated with PBA. First, each patient group was compared with healthy controls to identify motor neuron disease–related changes in white matter tracts. The Randomise tool in FSL (FMRIB's Software Library; version 2.1, 5,000 permutations), which conducts permutation-based inference on *t*-statistic maps,[27] was used to identify clusters of voxels that differed between controls and each patient group in pairwise comparisons. The FSL TFCE (threshold-free cluster enhancement) with $p < 0.05$ with family-wise error correction for multiple comparisons was used. Age and scanner type (GE or Philips) were regressed as covariates. The second step of the analysis assessed changes associated with PBA, comparing PBA+ and PBA− patients only within white matter voxels that differed from controls. For this analysis, age, scanner type, ALSFRS-R, and disease diagnosis (ALS vs PLS) were analyzed as covariates, using $p < 0.05$ with TFCE as the threshold for significance. Voxel-wise comparisons of the mean

Table 1 Demographic and clinical features of imaging study participants

	PLS (n = 25)		ALS (n = 22)			
	PBA+	PBA−	PBA+	PBA−	Healthy controls	*p* Value
No. of subjects	15	10	7	15	28	
M:F, n	9:6	6:4	4:3	7:8	21:7	NS
Age, y	56.9 ± 7.1	62.2 ± 7.8	57.3 ± 11.4	55.5 ± 10.4	54.8 ± 8.5	NS
Disease duration, mo	125.4 ± 66.6	116.9 ± 63.4	38.2 ± 38.1	39.2 ± 24.2		A
ALSFRS-R	35.3 ± 5.5	39.3 ± 5.8	32.3 ± 4.2	37.1 ± 5.9		B
Finger taps/s[a]	2.7 ± 0.7	3.9 ± 1.2	2.2 ± 1.6	3.8 ± 1.8		B
20-ft timed walk, s	18.2 ± 12.2	14.0 ± 10.5	21.7 ± 25.6	21.3 ± 32.5		
No. with clinical signs						
Dysarthria	15	4	7	6		
Facial weakness	9	1	5	2[b]		
Hyperactive gag	10	2	2	3[c]		
Myerson sign	12	3	7	6		
Cognitive testing	n = 9	n = 6	n = 5	n = 12		
DRS-2 <133	0	0	2	6		A
BDI-II ≥17	2	0	1	2		NS
ALSci	0	1	1	6		A
ALSbi	3	0	1	5		NS
Patients without cognitive battery	n = 6	n = 4	n = 2	n = 3		
MMSE <28	0	1	0	0[d]		
GE scanner, n	5	4	2	0	11	
Philips scanner, n	10	6	5	15	17	

Abbreviations: ALS = amyotrophic lateral sclerosis; ALSbi = ALS with mild behavioral impairment; ALSci = ALS with mild cognitive impairment; ALSFRS-R = ALS Functional Rating Scale-revised; BDI-II = Beck Depression Inventory-II; DRS-2 = Mattis Dementia Rating Scale-2; MMSE = Mini-Mental State Examination; NS = not significant; PBA = pseudobulbar affect; PLS = primary lateral sclerosis.
Data are no. or mean ± SD. A, $p < 0.05$: significant effect only of diagnosis (ALS vs PLS); B, $p < 0.05$: significant effect only of PBA status (PBA+ vs PBA−).
[a] Mean of right and left sides.
[b] Data missing 4 patients.
[c] Data missing 5 patients.
[d] Data missing 2 patients.

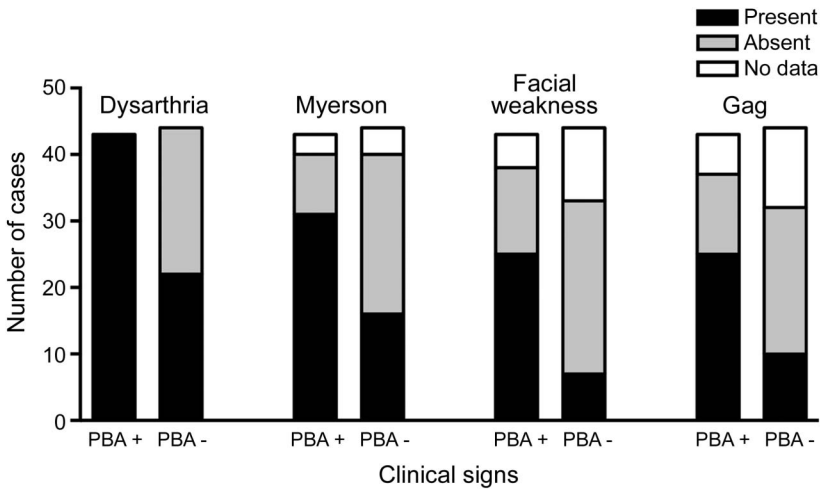
diffusivity were conducted using the same approach. Certain computationally intensive processes, such as choosing the registration target and the permutation testing, were accelerated by the high-performance computational capabilities of the Biowulf Linux cluster (NIH, Bethesda, MD).

Statistical analysis of clinical data. Continuous demographic and clinical data are presented as means ± SDs in the text and tables. In the chart review study, 2-sample *t* tests were used to test differences in continuous demographic data between patients with and without PBA. Variables were checked for normality and log transformation was applied to disease duration and an inverse square-root transformation was applied to measures of timed gait. Logistic regression was used to determine the association of clinical variables with PBA status. The first step consisted of selecting covariates to use in the regression model, using a low threshold of $p < 0.1$ in order to include variables with small or possible effects. The diagnosis (PLS vs ALS) was significant and was used as a covariate. Age and sex were not significant and were not included as covariates in the regression model. An exact *p* value was computed, and $p < 0.01$ was used to test the significance of association between PBA and clinical variables, adjusting for diagnosis. In the imaging substudy, Fisher exact test was used to determine the association between PBA (PBA+ vs PBA−) and clinical variables, DRS-2 (≥133 vs <133), the BDI-II (<17 vs ≥17), ALSci (present vs absent), and ALSbi (present vs absent), using $p < 0.05$ to determine significance. A 2-factor analysis of variance was used to assess the effect of disease diagnosis (ALS vs PLS) and PBA status on continuous clinical variables.

RESULTS

Chart review. Among the 87 patients in the chart review, 43 had PBA (PBA+) and 44 did not have PBA (PBA−). Thirty-one of the 50 patients with PLS and 12 of 37 patients with ALS were PBA+. There were no significant differences in age (58.7 ± 8.7 vs 57.4 ± 9.8 years) or sex between PBA+ and PBA− groups. However, patients with PBA had slightly worse motor function as evidenced by slower finger-tapping rates (PBA+: 2.6 ± 1.1 taps/s; PBA−: 3.7 ± 1.6 taps/s; $p < 0.001$), although there was no difference in timed gait

Figure 1 Clinical findings associated with pseudobulbar affect in the chart review of 87 patients



The clinical finding is noted above a pair of bars, one indicating patients with pseudobulbar affect (PBA+) and the other indicating patients without pseudobulbar affect (PBA−). Black bars indicate the number of patients in whom the clinical finding was present, gray bars indicate the number in whom the finding was absent, and open bars indicate patients for whom no documentation of the finding was recorded in the chart.

(PBA+: 27.8 ± 36.1 seconds; PBA−: 23.5 ± 33.1 seconds; $p = 0.195$). All PBA+ patients had upper motor neuron signs on clinical examination. Dysarthria was present in all PBA+ patients and half of the PBA− patients (figure 1). A logistic regression analysis, controlling for diagnosis of PLS or ALS, showed that facial muscle weakness, hyperactive gag reflex, and Myerson sign were associated with PBA+, but that brisk jaw jerks, frontal release signs, and bladder urgency were not associated with PBA+ (table 2).

In the prospective emotional/psychiatric evaluation, 12 of the 17 patients with PLS had PBA, and 2 of the 13 patients with ALS had PBA. The psychiatrist's determination of PBA agreed with the neurologist's assessment in all but 2 of the 30 subjects. In both discrepant cases, the patient met criteria for current major depressive disorder, suggesting that an active mood disorder may make the assessment of PBA more difficult. However, there was no significant difference in the proportion of subjects with PBA with active depressive symptoms (Fisher exact test, $p = 0.2602$), suggesting that, in this small sample, PBA did not affect the incidence of mood disorder diagnoses and vice versa. In all subjects with PBA, symptoms were mood-congruent. That is, excessive crying was triggered by sad stimuli and excessive laughing by happy or funny stimuli. In all but one subject with PBA, affect/emotional expression was increased out of proportion to mood changes. Several subjects mentioned the experience of laughing and crying excessively while internally noting that they no longer felt happy or sad.

Imaging study. ***Clinical findings.*** In the subset of 47 patients in the imaging study, there were no significant differences in age or sex between PBA+ and PBA− patients (table 1). A higher proportion of patients with PLS than patients with ALS had PBA, similar to the full cohort in the chart review. As expected, patients with PLS had longer disease durations than patients with ALS, but there was no significant interaction between diagnosis (ALS vs PLS) and PBA status (PBA+ vs PBA−). However, the ALSFRS-R score and finger-tapping rates were significantly lower for PBA+ patients compared with PBA− patients, suggesting more impaired motor function in PBA+.

Table 2 Clinical variables associated with pseudobulbar affect

	Crude odds ratio			Adjusted odds ratio[a]			
Clinical sign	No.	Estimate	*p* Value	Estimate	95% CI		*p* Value
Dysarthria	87	57.2	<0.0001[b]	51.8	10.6	∞	<0.0001[b]
Facial weakness	71	6.9	0.0003[b]	9.6	2.6	45.8	0.0001[b]
Hyperactive gag	69	4.5	0.0053[b]	3.9	1.3	12.8	0.0164
Myerson sign	80	5.1	0.0013[b]	7.8	2.3	32.0	0.0003[b]
Abnormal jaw jerk	83	1.1	1.0000	1.4	0.5	3.9	0.6934
Frontal release signs	79	2.4	0.0905	2.5	0.9	7.4	0.0839
Bladder urgency							
PLS[c]	46	3.3	0.1246				
ALS[c]	26	3.2	0.3378				

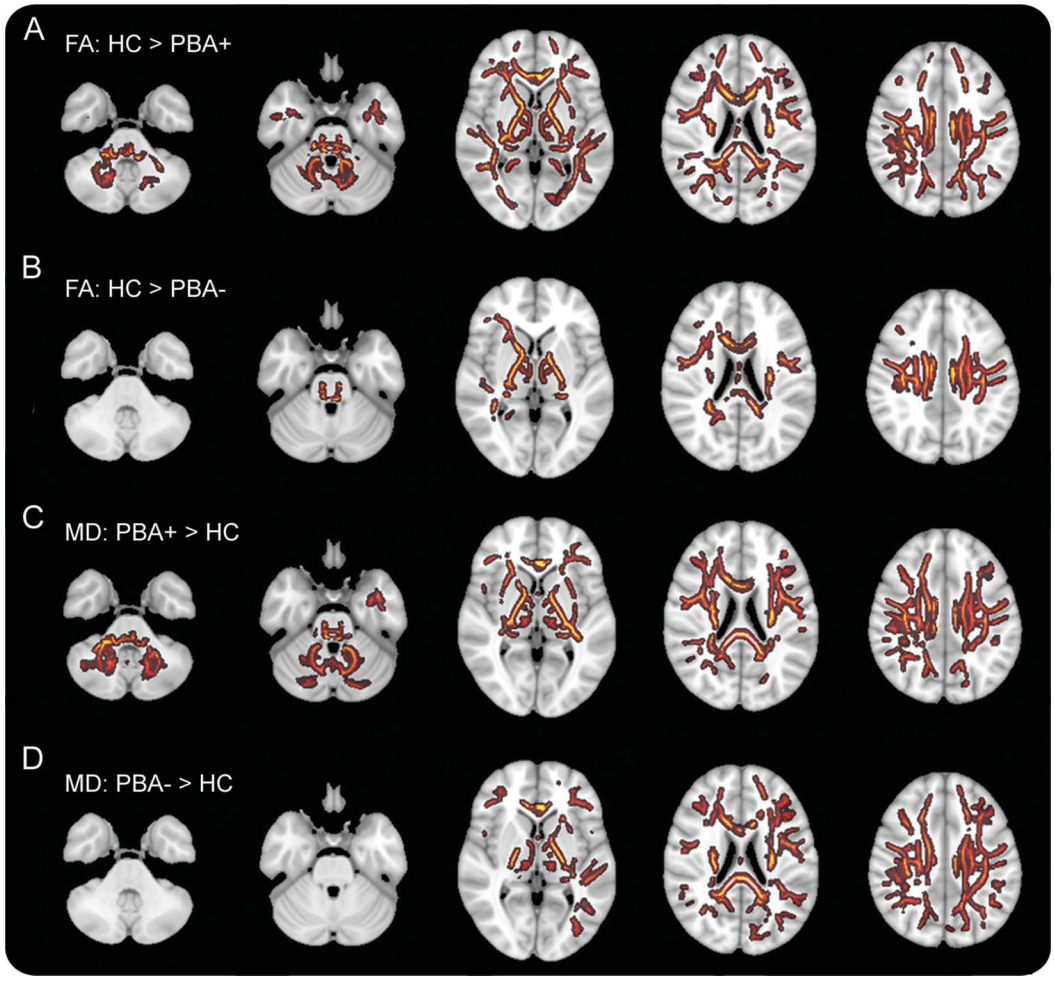
Abbreviations: ALS = amyotrophic lateral sclerosis; CI = confidence interval; PLS = primary lateral sclerosis.
[a] Adjusted for diagnosis (ALS vs PLS). No interaction between diagnosis and clinical variables.
[b] Significant values.
[c] Separate analyses of ALS and PLS, because bladder urgency was significantly associated with diagnosis.

Of the 32 patients who had cognitive testing batteries, 8 of 17 patients with ALS scored below 133 on the DRS-2, but there was no difference in the proportions of ALS and PLS patients that were PBA+ and PBA− (Fisher exact test, $p > 0.05$). No patient with PLS in this subset had an abnormal DRS-2 score. The proportions of patients who met criteria for ALSci or ALSbi, or had BDI-II >17 did not differ between the PBA+ and PBA− patient groups. In the 15 patients who did not have full cognitive testing, the Mini-Mental State Examination did not differ.

Imaging findings. In the first step of the tract-based spatial statistics analysis, both PBA+ and PBA− patients were found to have reduced FA and increased mean diffusivity in multiple white matter areas compared with healthy controls (figure 2). The affected regions included the subcortical white matter, internal capsule, and the corpus callosum, consistent with other studies.[26,28,29] In the second step, to identify white matter regions associated with PBA, white matter voxels that differed from controls were compared between PBA+ and PBA− patients, with ALSFRS-R and diagnosis (ALS vs PLS) as covariates. This analysis revealed a small region of white matter underlying the left motor cortex with reduced FA in PBA+ compared with PBA− patients (figure 3, row A). In addition, PBA+ patients had increased mean diffusivity in several white matter regions compared with PBA− patients (figure 3, row B). Notably, there was greater mean diffusivity in the right middle cerebellar peduncle, transverse pontine fibers, and white matter tracts underlying the frontotemporal cortex in PBA+ patients compared with PBA− patients.

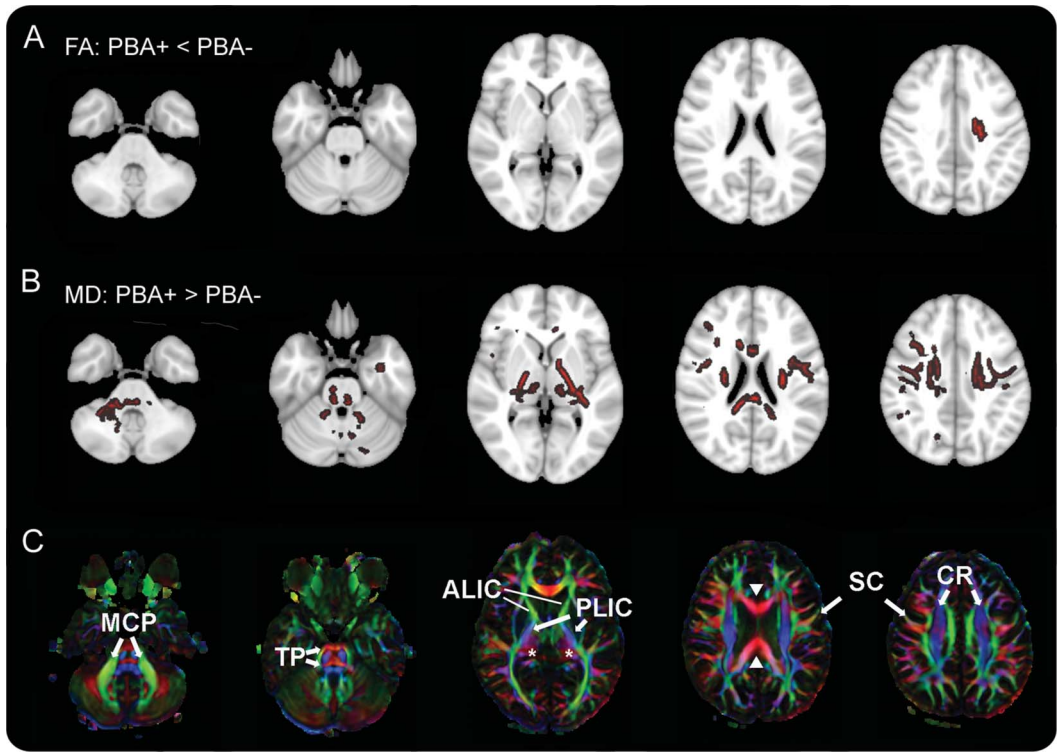
DISCUSSION Two-thirds of the patients with PLS in our clinic had PBA, a frequency higher than

Figure 2 **Differences in diffusion tensor imaging between patients and healthy controls**



Tract-based spatial statistics showing differences in diffusion properties between white matter skeletons of healthy controls (HC) and patients with pseudobulbar affect (PBA+, rows A and C) and between healthy controls and patients without pseudobulbar affect (PBA−, rows B and D) projected on axial sections. White matter areas shown in color were significantly different between patients and healthy controls (threshold-free cluster enhancement with $p < 0.05$, correction using family-wise error rate). (A, B) Differences in fractional anisotropy (FA) maps. (C, D) Differences in mean diffusivity (MD) maps. Axial sections are shown in radiologic convention with right brain on the left side.

Figure 3 Differences in diffusion tensor imaging between patients with and without pseudobulbar affect



(A, B) Color indicates white matter regions where diffusion properties differ between patients with pseudobulbar affect (PBA+) and patients without pseudobulbar affect (PBA−) (tract-based spatial statistics, threshold-free cluster enhancement, $p < 0.05$). (C) Directionally encoded color map providing labels for selected structures. (A) Fractional anisotropy (FA) was reduced in PBA+ patients only in a small region underlying the left motor cortex. (B) Mean diffusivity (MD) was greater in PBA+ patients in multiple white matter areas, including the middle cerebellar peduncles (MCP), transverse pontine fibers (TP), bilateral posterior limbs of the internal capsule (PLIC), left anterior limb of the internal capsule (ALIC), thalamus (asterisks), frontotemporal subcortical white matter, corona radiata (CR), white matter underlying the motor cortex (SC), and corpus callosum (solid arrowheads). Axial sections are shown in radiologic convention with right brain on the left side.

published reports in ALS.[4] All PBA+ patients had dysarthria and upper motor neuron signs. PBA was associated with other clinical findings, such as hyperactive gag and Myerson sign. Although all patients in the DTI study had abnormalities in the corticospinal tract and corpus callosum typical for motor neuron disease, patients with PBA also had increased mean diffusivity in white matter tracts underlying frontotemporal regions, the pons, and cerebellum. Increased mean diffusivity is thought to signify the loss of integrity of myelinated axons.[30] The altered white matter tracts associated with PBA connect the frontal cortex to the cerebellum via the anterior limb of the internal capsule and through the pontine nuclei. Affected axons are likely to arise from neurons of cortical regions projecting to brainstem structures that have been implicated in emotional processing, including periaqueductal gray neurons projecting to medullary premotor interneurons,[31] and from pontine nuclei, in regions where spectroscopy studies indicate neuronal loss.[32] Functional imaging studies suggest that the network for emotional processing includes the prefrontal and orbitofrontal cortex, insula, anterior cingulate cortex, and regions of the cerebellum.[1,33,34] Clinical observations of stroke patients who developed emotional facial paresis in the setting of preserved volitional expression also implicate the frontal cortex.[7,35] The cerebellum has been shown to have a modulatory role in behavioral and cognitive control, receiving input from frontal and paralimbic cortex through pontine relay nuclei.[34,36] In the hypothesis proposed by Parvizi et al.[9] to explain PBA, inputs from the frontal and association cortex to the cerebellum are used to modulate the duration and intensity of facio-respiratory muscle activation in emotional expression. Our imaging data support this hypothesis, and suggest that PBA can be considered a "dysmetria" of emotional expression[1,8] that results from loss of corticopontine inputs. However, it is important to note that diffusion changes were also seen in white matter tracts from the motor cortex. The combination of impaired volitional motor control and cerebellar dysmodulation may be necessary to produce PBA. Impairment of pathways for volitional expression of emotion, central to Wilson's[7] proposal that disinhibition of pontine

centers for emotional expression caused PBA, may be contributory.

PBA is one of a number of terms that have been used in the literature to describe disorders with paroxysmal outbursts of emotional expression. Emotional lability is the term applied to a subset of PBA in which episodes are congruent to mood but disproportionate to the triggering stimulus, and unable to be fully suppressed.[1,9] The emotional/psychiatric interviews conducted in our study showed that affect was generally mood-congruent with a triggering stimulus, but out of proportion to mood. This fits with emotional lability, in agreement with previous studies of PBA in patients with ALS.[37] The psychiatric/emotional data support the idea that the initiation of the emotional response arises from the areas normally involved in emotional processing and the motor expression of emotion.[1,33,34] PBA in our subjects was also independent of mood disorders. As one subject with major depressive disorder and PBA said, "I can tell the difference between when I'm crying because I'm feeling depressed and when I'm crying inappropriately." Clinical measures of cognitive status were not associated with PBA. Although previous studies found alterations in extramotor cortical areas associated with cognitive dysfunction in ALS or PLS,[11,38] the primary structural correlates seem to be interhemispheric long association tracts. However, an association between oral naming and integrity of portions of cerebellar white matter was reported in one recent study[39] that defined cognitive impairment in PLS less stringently than consensus criteria and did not assess for concurrent PBA.[17] In our study, PBA was independent of cognitive impairment, and thus cognitive impairment seems unlikely to account for diffusivity changes observed in pontocerebellar tracts.

This retrospective study has several limitations. First, classification of patients as PBA+ or PBA− was based on a neurologist's clinical assessment, rather than using an instrument specific for measuring PBA.[40] Nevertheless, there was good agreement of the neurologist's classification with the independent emotional/psychiatric evaluation. Another limitation is the likelihood of sample selection bias toward stable patients who are willing to travel to NIH to participate in research and are able to tolerate imaging studies. This may account for the relatively low proportion of patients with cognitive impairment.

The main finding of our chart review is that PBA is common among patients with PLS. PBA adversely affects the quality of life, leading to social isolation and housebound status in many different diseases, including ALS.[6] Treatment can ameliorate symptoms of PBA and improve ratings of the quality of life in patients with ALS.[3] Such treatment may be of benefit to patients with PLS as well. Our imaging study found white matter differences associated with PBA that implicate corticopontocerebellar circuits in its origin, supporting the view that PBA is a dysmetria of emotional expression.

AUTHOR CONTRIBUTIONS

Dr. Floeter was responsible for study concept and design, acquisition of clinical data, overall analysis and interpretation, writing and revising the manuscript, and study supervision. Mr. Katipally was responsible for analysis and interpretation of imaging data. Ms. Kim was responsible for analysis and interpretation of chart review data. Ms. Schanz was responsible for acquisition of imaging data and initial data analysis and interpretation. Mr. Stephen was responsible for acquisition of clinical data and initial data analysis and interpretation. Ms. Danielian was responsible for acquisition of imaging data and analysis and interpretation. She trained the postbaccalaureate students in imaging analysis methods and performed quality checks of the imaging data analyses. She critically read the manuscript. Dr. Wu was responsible for statistical analysis and interpretation, and critical revision of the manuscript for important intellectual content. Dr. Huey was responsible for acquisition of psychiatric/emotional data and their analysis and interpretation, and for critical revision of the manuscript for important intellectual content. Dr. Meoded was responsible for designing MRI sequences for acquisition of imaging data, for analysis and interpretation of imaging data, critical revision of the manuscript for important intellectual content, and for study supervision.

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DISCLOSURE

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