

Structural brain abnormalities in adult males with clefts of the lip and/or palate

Peg Nopoulos, MD¹, Stephanie Berg, BA¹, John Canady, MD², Lynn Richman, PhD³, Duane Van Demark, PhD², and Nancy C. Andreasen, MD, PhD¹

Purpose: To evaluate brain morphology of adult males with nonsyndromic clefts of the lip and/or palate (NSCLP) in comparison to a matched healthy control group. **Methods:** Brain structure was measured using quantitative analysis of magnetic resonance images. **Results:** Subjects with NSCLP had significant abnormalities in brain morphology consisting of abnormally enlarged anterior regions of the cerebrum, and decreased volumes of the posterior cerebrum and cerebellum. Overall, the most severely affected region was the left temporal lobe. Furthermore, these structural abnormalities were directly related to cognitive dysfunction. **Conclusions:** These findings highlight the important relationship and interplay between face and brain development. *Genet Med* 2002; **4(1):1–9.**

Key Words: magnetic resonance imaging, brain structure, oral clefts, brain development

Oral clefts compose a significant component of morbid human birth defects. These oral clefts are developmental craniofacial abnormalities that result, at least in part, from a failure of neural crest cells to migrate properly. As a group, 70% of clefting disorders are composed of those that are isolated to facial clefts only (nonsyndromic), and 30% are those in which the facial cleft is part of a well-defined syndrome of additional anomalies.¹ Nonsyndromic clefts of the lip and/or palate (NSCLP) occur in approximately 1 per 1,000 livebirths among Caucasians and are further divided anatomically into clefts of the lip and/or palate (CLP) and clefts of the palate only (CPO).

In addition to the facial cleft, many patients also suffer from cognitive impairment. In syndromic clefts, this impairment is often severe. In NSCLP, the cognitive impairment is less severe but the functional consequences of these deficits should not be underestimated. Specifically, children with NSCLP have been shown to have a lower IQ compared with matched controls.² In addition to this generalized deficit, many patients also have abnormalities in language function.^{3,4} This language deficit is severe enough to be designated as a reading disability in as many as 35% of this population.⁵

Many have considered these cognitive abnormalities as “secondary” to factors such as hearing deficits, speech deficits, or both.^{6,7} Yet other reports have shown that cognitive skills are not significantly affected by peripheral deficiency in speech and hearing.^{8,9} More likely is the notion that abnormal brain function (cognitive impairment) is *not* secondary to external

factors but primary to abnormal brain structure. In the case of NSCLP, this most likely would be due to abnormalities in brain development.

The development of the brain and face are intimately related in both normal and pathologic conditions.^{10,11} This relationship is such a well-known phenomenon that dysmorphologists have coined the phrase “the face reflects the brain.” Therefore, that there may be abnormal brain development accompanying an abnormality in facial development should not be surprising. However, the systematic study of structural brain abnormalities in patients with NSCLP (and the functional consequences thereof) has been almost completely overlooked.

Advances in neuroimaging techniques using magnetic resonance imaging (MRI) allows for sophisticated methods in quantifying human brain structure. Using state of the art post-processing procedure, the current study is the first to evaluate brain morphology in subjects with NSCLP. A published preliminary analysis on the first 30 subjects in the study (15 patients vs. 15 controls) indicated significant abnormalities in brain morphology with enlargement of anterior regions of the cerebrum and decrement in size of the posterior cerebrum and of the cerebellum.¹² The current report documents the result of the entire sample of 92 (46 subjects vs. 46 controls) with more extensive regional analysis as well as evaluation of tissue type (gray matter and white matter volumes).

METHODS

Subjects

A total of 46 adult males with NSCLP were recruited from the University of Iowa Cleft Lip and Palate Registry. Medical records were reviewed to verify and document cleft status, including cleft region (lip only, cleft lip and palate, palate only), side of the cleft (right, left, median, or bilateral), and the degree

From the ¹Departments of Psychiatry, ²Otolaryngology, and ³Pediatrics, University of Iowa Hospitals and Clinics, Iowa City, Iowa.

Peg Nopoulos, MD, 1-180 MEB, Department of Psychiatry, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

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of clefting (complete, partial, microform). All patients had been previously examined by a trained medical geneticist to rule out congenital syndromes. Three subjects were found to have lip pits in addition to oral clefts. The occurrence of lip pits and isolated clefts of the lip and/or palate is referred to as Van der Woude syndrome. However, because this syndrome is manifested only in oral clefts and lip pits (no other congenital defects), these three patients were retained in the sample. There were a total of 32 subjects with CLP (11 with bilateral clefting, 18 with left unilateral clefting, 3 with right unilateral clefting) and 14 subjects with CPO.

The comparison group was obtained through a registry of healthy controls (recruited from the community) from the University of Iowa Mental Health Clinical Research Center (MH-CRC). This control group was designed to be equivalent to the clefting subjects on sex, age, parental socioeconomic status, and level of education. Reflective of the population in Iowa, all of the subjects and controls were Caucasian. After complete description of the protocol, both subject groups signed informed consent as directed by the local institutional review board. Table 1 displays the demographic data for both study groups.

Both groups were administered a battery of cognitive tests, including measures of Full Scale IQ (FSIQ), Performance IQ (PIQ), and Verbal IQ (VIQ) using the Wechsler Adult Intelligence Scale-Revised.¹³ A previous study details the results of the comparative analysis of cognitive tasks.¹⁴

Imaging methods

Images were obtained on a 1.5 Tesla GE Signa MR scanner. Three different sequences were acquired for each subject. T1 weighted images, using a spoiled grass sequence, were acquired with the following parameters: 1.5-mm coronal slices, 40-degree flip angle, 24-msec TR, 5-msec TE, 2 NEX, 26-cm field of view (FOV), and a 256 × 192 matrix. The PD and T2 weighted images were acquired with the following parameters: 3.0-mm coronal slices, 36-msec TE (for PD) or 96-msec TE (for T2), 3,000-msec TR, 1 NEX, 26-cm FOV, 256 × 192 matrix, and an echo train length = 1.

Processing of the images after acquisition was done using a locally developed family of software programs called BRAINS (acronym for Brain Research: Analysis of Images, Networks, and Systems). Details of the image analysis are published elsewhere.^{15–18} Briefly, a three-dimensional data set is created and the images are realigned, re-sampled, and transformed into Talairach Atlas space.¹⁹

Brain volume measures

Within the stereotactic space, boxes are assigned to specific brain regions. Intracranial volume is subdivided into brain tissue and cerebral spinal fluid (CSF). Total volume of CSF is broken down into internal CSF (includes ventricles and cisterns) and surface CSF. Brain tissue is subdivided into the cerebrum and cerebellum. The cerebrum is then divided further into its four lobes. Volumes of tissue are obtained from each region in an automated manner (see Fig. 1). This method of automated measures using a stereotactically based method has been reported by our lab and others to be efficient and accurate for cerebral lobe measures.^{20,21}

Tissue classification

To break down the tissue volumes described above into the component parts, we used our newest method for segmentation, a fully automated method based on discriminant function analysis. This method uses data from the T1 and the proton density (PD)/T2 sequences (see Fig. 2). The details of this method are published elsewhere.²² Measures obtained for analysis included total cerebral gray matter volume and cerebral white matter volume. In addition, each cerebral lobe is segmented into components of gray and white matter volume.

Statistical analysis

All analyses were performed by using the SAS language with SAS STAT procedures. All brain tissue measures were analyzed using the General Linear Models Procedure. A systematic study of brain measures was used starting with the analysis of more general measures and moving through increasingly smaller portions or regions of the brain. In addition, each tissue measure was then broken down into its components of gray matter and white matter. This method created a “hierarchy” of variables, beginning with the general measures of intracranial volume, cerebral tissue volume, and cerebellar tissue volume. These were further broken down into total cerebral spinal fluid (CSF), further divided into ventricle volume and surface CSF; cerebral gray matter, further divided into surface gray matter (reflecting the volume of the cortex) and subcortical gray matter (reflecting the volume of the subcortical nuclei); cerebral white matter; cerebellar gray matter; and cerebellar white matter. Next, the cerebrum was divided into an anterior/superior region (frontal and parietal lobes) and a posterior/inferior region (temporal and occipital lobes). These regions were further divided into gray and white matter volumes.

Table 1
Demographics of sample

		Age Mean (SD)	Parental SES ^a Mean (SD)	Ratio left-handers/ right-handers	Education (years) Mean (SD)
NSCLP subjects	(n = 46)	30.1 (7.04)	3.13 (0.71)	4/42	13.8 (2.09)
Controls	(n = 46)	28.8 (7.60)	2.97 (0.33)	8/38	14.5 (1.97)

^aParental socioeconomic status (SES) based on a modified Hollingshead scale of 1–5 with the higher the number, the lower the status.

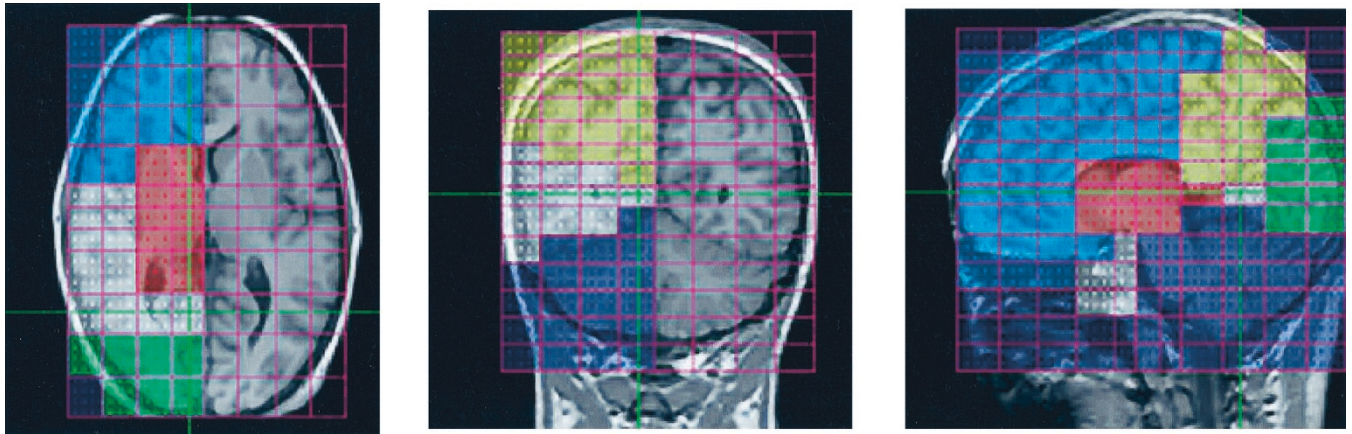


Fig. 1 Talairach Atlas-based method for automated measures of general and regional brain tissue. First image in the left is an axial section, the image in the middle is a coronal section, and the image on the right is a sagittal section. Blue, frontal lobe; yellow, parietal lobe; white, temporal lobe; green, occipital lobe; purple, cerebellum; red, subcortical tissue.

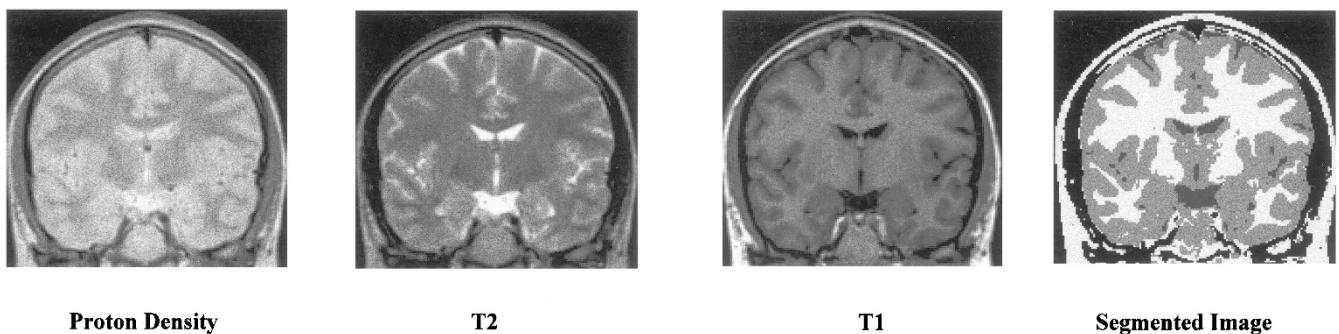


Fig. 2 Tissue classification method using three separate imaging sequences (proton density, T2 and T1) to classify tissue into gray matter, white matter, and cerebral spinal fluid.

Finally, each lobe of the cerebrum (frontal, parietal, temporal, and occipital) was individually analyzed as a whole and as their component gray and white matter volumes.

The covariates used in the analyses varied with the size of the measure. That is, for the general measures, height was used as a covariate. For the tissue segmentation of the general measures and the anterior and posterior cerebral volumes analysis, intracranial volume was used as the covariate. Finally, for the smallest regions (the four cerebral lobes), total cerebral tissue volume was used as the covariate. All possible interaction terms were entered into the model but were dropped if not significant. An alpha level of 0.05 was used for significance tests, except for tests for assumptions within the general linear model, in which case an alpha of 0.10 was used. That is, if an interaction term was found to be significant at $P < 0.10$, it was maintained within the model.

To investigate laterality of regional measures, repeated measures analysis of covariance (total cerebral tissue covariate) was used. To limit number of analysis and possible type I error, only those regions that had significant structural abnormalities were entered. Significant laterality was identified by a side-by-diagnosis interaction with a $P < 0.05$.

RESULTS

Table 2 outlines the findings of the analysis of general measures, tissue segmentation of general measures, regions of the cerebrum, and cerebral lobes. To help gauge the magnitude of difference, effect sizes are shown in the last column. Effect size is a way of showing the size of difference between two groups based on the average intersubject variability. Effect sizes of 0.2 are considered small, of 0.5 are moderate, and those of 0.8 or greater are large.^{2,3}

General measures

Subjects with NSCLP showed no significant difference from controls on measures of intracranial volume, total brain volume, or cerebral volume. Total volume of CSF was significantly decreased in subjects with NSCLP. This finding was true for both the ventricular volume as well as the volume of surface CSF. In addition, there was a significant difference between the two groups in the volume of the cerebellum with the NSCLP subjects having smaller volumes compared with controls.

Tissue segmentation of general measures

The NSCLP group showed significant differences compared with controls in regard to volumes of specific tissue types:

Table 2
Results of analysis on general and regional brain measures

	NSCLP subjects (<i>n</i> = 46)			Controls (<i>n</i> = 46)			F	P	Effect size
	Mean	SD	Adjusted mean ^a	Mean	SD	Adjusted mean ^a			
General measures ^b (cc's)									
Intracranial volume	1,449	141	1,448	1,490	117	1,491	2.67	0.105	0.342
Total brain tissue	1,360	134	1,359	1,384	118	1,385	1.02	0.315	0.215
Total CSF	88.6	34.1	88.7	106.2	40.8	106	4.91	0.025	0.461
Ventricles	13.4	6.49	13.8	16.3	6.70	16.3	4.56	0.035	0.437
Surface CSF	50.3	27.3	50.4	63.7	33.0	63.6	4.36	0.039	0.437
Cerebral volume	1,190	123	1,189	1,201	108	1,201	0.27	0.602	0.108
Cerebellar volume	133	17.7	133	146	16.9	146	11.3	0.001	0.747
Tissue segmentation of general measures ^c (cc's)									
Cerebral gray matter	706	71.9	715	706	62.5	696	5.78	0.018	0.530
Surface gray matter (cortex)	652	67.2	660	649	59.7	640	7.41	0.007	0.579
Subcortical gray matter	54.0	7.00	54.5	56.8	6.13	56.2	2.07	0.153	0.308
Cerebral white matter	484	59.4	492	494	61.8	486	0.088	0.351	0.191
Cerebellar gray matter	97.6	13.9	98.6	110	14.3	109	15.5	0.0002	0.825
Cerebellar white matter	36.3	7.96	36.7	35.8	6.20	35.4	0.083	0.364	0.195
Regions of cerebrum ^c (cc's)									
Anterior cerebrum	727	82.1	738	720	73.3	709	13.0	0.0005	0.775
Gray matter	418	47.1	423	409	43.8	404	10.3	0.001	0.659
White matter	309	40.2	314	310	40.0	305	3.45	0.066	0.393
Posterior cerebrum	351	34.7	356	369	33.8	364	9.05	0.003	0.655
Gray matter	224	22.1	227	229	19.4	226	0.11	0.735	0.084
White matter	127	16.0	129	140	20.3	138	14.3	0.0003	0.841
Cerebral lobes ^d (cc's)									
Frontal lobe	463	55.9	465	460	49.7	458	4.88	0.029	0.451
Gray matter	275	32.3	276	270	30.0	269	4.97	0.028	0.460
White matter	188	27.3	189	190	26.5	188	0.00	0.981	0.070
Parietal lobe	264	28.0	265	260	26.7	258	10.5	0.001	0.736
Gray matter	143	15.6	143	139	15.3	139	7.86	0.006	0.486
White matter	120	14.1	121	120	15.4	119	0.09	0.330	0.251
Temporal lobe	227	22.9	228	238	20.6	237	18.3	<0.0001	0.891
Gray matter	153	14.4	154	159	12.9	158	9.41	0.002	0.526
White matter	74.0	10.3	74.3	78.9	10.8	78.6	8.11	0.005	0.603
Occipital lobe	124	14.3	124	131	17.2	130	7.63	0.007	0.571
Gray matter	70.7	9.92	71.0	69.5	9.92	69.2	0.97	0.328	0.213
White matter	53.2	7.39	53.5	61.6	7.39	61.3	23.8	<0.0001	1.015

^aMean adjusted by covariate.

^bCovariate used = height.

^cCovariate used = intracranial volume.

^dCovariate used = total cerebral tissue volume.

NSCLP subjects relative to controls had significantly less total CSF, and a significant *increase* in the amount of cerebral gray matter. Breaking down the volume of cerebral gray matter into surface volume (cortex) and subcortical gray, the increase appears to be accounted for by larger volumes of cerebral cortex as volumes of subcortical gray matter were not different between the two groups. There was no difference between the groups in volume of cerebral white matter. In regard to the cerebellum, when the tissue types were broken down, the volume reduction of this region seen in the subjects with NSCLP was most likely accounted for by a reduction in gray matter volume with sparing of the white matter.

Regions of the cerebrum

With frontal and parietal lobes combined, the region of the anterior cerebrum showed robust differences between the two groups, with the NSCLP subjects having larger volumes compared with controls. This difference was accounted for by increases in both gray and white matter volume; however, the increase in gray matter volume was robust, whereas the increase in white matter was only at a trend significance level ($P = 0.066$).

In contrast to the anterior cerebrum, the volume of the posterior cerebrum (temporal and occipital lobe) was significantly *smaller* in subjects with NSCLP compared with controls. This reduction in total tissue was accounted for primarily by a reduction in white matter volume as the gray matter volume in this region was equal in both groups.

Cerebral lobes

Evaluation of the individual cerebral lobes showed results similar to the regional analysis above, but with important differences. As expected, both the frontal and parietal lobes were significantly increased in volume in the NSCLP group with elevated gray matter volumes accounting for the majority of the effect. With regard to the posterior section, both the temporal lobe and the occipital lobe showed significant reduction of overall volume in the subjects with NSCLP. However, although the posterior cerebrum measure showed no overall gray matter reduction, when this region was further divided into the temporal lobe and occipital lobe, there were robust reductions of gray matter found in the temporal lobes of the NSCLP group. The temporal lobe also showed significant reductions in white matter volume as well. The occipital lobe showed no differences in gray matter volumes between the two study groups, but did have a robust reduction of volume of white matter in the NSCLP group.

Laterality

Measures of the cerebral lobes and cerebellum that showed significant group volume discrepancies included frontal lobe gray matter, parietal lobe gray matter, temporal lobe gray and white matter, occipital lobe white matter, and cerebellar gray matter. These regions were evaluated for abnormalities in laterality, comparing right-sided measures to left-sided measures (see Table 3). The enlargement of the anterior regions (frontal

and parietal gray matter) did not show significant differences in laterality. However, most of the posterior measures showed significant side by diagnosis interactions with the left-sided volumes being more robustly reduced compared with the right. This finding was the case for temporal lobe gray matter, occipital lobe white matter, and cerebellar gray matter. Although the temporal lobe white matter also showed greater left than right volume reduction, this did not manifest as a significant interaction ($F = 0.19$; $P = 0.662$).

Cleft lip/palate comparison to cleft palate only

Epidemiologic, phenomenologic, and genetic data support the notion that CLP patients are etiologically distinct from patients with CPO.²⁴ Therefore, we believed it would be useful to compare these two subgroups of the NSCLP sample. The same analysis was conducted, as described above, for general measures, regional measures, and cerebral lobes comparing the CLP group ($N = 32$) with the healthy controls ($N = 46$) and again comparing the CPO ($N = 14$) group with the healthy controls. Results are shown in Table 4. In general, the results of the CPO versus control analysis are not as robust as the findings in the CLP versus control analysis, and some of this finding may be due to lower power secondary to the small CPO sample of only 14 subjects. Given that preface, both subgroups of the NSCLP sample appeared to have the *same pattern* of abnormal brain morphology. Both CLP and CPO subjects had significant increases in the anterior cerebral gray matter volumes and concomitant decrements in volumes of the posterior cerebral white matter volumes. The most robust findings for the CLP group were the volume decrements in the cerebellum, occipital lobe, and temporal lobe, in that order. Conversely, the most robust findings for the CPO group were the decrements in temporal lobe tissue (white matter more than gray matter), and volume increases in the anterior cerebral gray matter, in that order.

DISCUSSION

General and regional brain measures

Brain structure in subjects with NSCLP is altered. In all quantitative measures of regional brain volume, and tissue composition, the subjects with NSCLP were significantly different than the control group. With regard to regional brain tissue volume, the NSCLP group had an increase in volume of the anterior portion of the cerebrum with a concomitant decrement in volume of the posterior cerebrum and of the cerebellum. With regard to tissue composition, the increase in anterior regions was accounted for by an increase in cortical gray matter volume. The posterior regions had both white and gray matter decrement in volume with the temporal lobe having significantly decreased white *and* gray matter, the occipital lobe having decreased white matter, and the cerebellum having decreased gray matter. The temporal lobe appeared to be the region that was most severely affected as it was the only region that had decrement in volume of *both* gray and white matter. Finally, CSF volume was decreased in the NSCLP group, both

Table 3
Results of lateralization analysis

Regional brain volume measure ^a	Subjects (<i>n</i> = 46) adjusted means ^b	Controls (<i>n</i> = 46) adjusted means ^b	ANCOVA		Repeated measures side by diagnosis	
			F	<i>P</i>	F	<i>P</i>
Frontal lobe gray matter					3.12	0.080
Right	142	137	6.65	0.011		
Left	133	131	2.45	0.121		
Parietal lobe gray matter					0.20	0.652
Right	73.2	70.7	8.25	0.005		
Left	70.6	68.3	5.56	0.019		
Temporal lobe gray matter					5.60	0.020
Right	77.1	78.9	4.65	0.033		
Left	76.9	80.0	13.1	0.0005		
Temporal lobe white matter					0.19	0.662
Right	37.2	39.2	5.74	0.018		
Left	37.1	39.3	8.50	0.004		
Occipital lobe white matter					11.61	0.001
Right	25.9	28.8	11.8	0.0009		
Left	27.6	32.5	32.8	<0.0001		
Cerebellum gray matter					4.58	0.035
Right	49.0	53.5	11.47	0.001		
Left	49.6	55.6	17.98	<0.0001		

ANCOVA, analysis of covariance.

^aCovariate = total cerebral tissue volume.

^bMean adjusted by covariate.

internally (ventricle volume) and externally (CSF on the cortical surface).

Although no other studies have evaluated brain structure in NSCLP, two studies have reported on brain structure in velocardio-facial syndrome.^{25,26} This condition is a genetic syndrome manifested by heart defects, cognitive impairment, and craniofacial abnormalities, including cleft palate. Although these studies showed these patients had significantly smaller total brain size, both studies found a relative *increase* in the size of the frontal lobe volume, similar to the current findings. Whether or not this phenomenon is related to the oral cleft in this syndrome is unclear, however.

Laterality

The decrement in the size of the posterior cerebrum in NSCLP subjects was lateralized to the left side. That is, although both sides of the cerebrum and cerebellum were smaller in this group, the left side was more robustly affected than the right. The brain is known to have asymmetry in its representation of cognitive processes. For example, receptive and expressive aspects of language are predominantly represented and more efficiently processed by the left cerebral hemisphere, and in particular, the left temporal lobe. Moreover, there is a substantial amount of literature on the gender differ-

ences of cerebral lateralization (for review see Nopoulos and Andreasen and Nopoulos et al.^{27,28}). In general, the male brain appears to be more unilateral (left sided) in its processing of language function, whereas females have more bilateral representation.²⁹ This sex difference in the lateralization of language function is most likely related to differences in early brain development, for which it is theorized that the presence of testosterone either promotes the development of the right hemisphere or conversely delays the development of the left hemispheres.^{30,31} It is this particular pattern of male brain development that may be responsible for their vulnerability (compared with females) for neurodevelopmental syndromes, and in particular language disorders such as dyslexia.³²

Early studies of brain morphology on subjects with language disorders such as dyslexia found that temporal lobe structures such as the planum temporale (PT) have shown “anomalous dominance” in which the normal asymmetry of this region is lost.^{33–35} More recent studies have shown that not just the PT are affected but that the entire left temporal lobe has reduced volume in subjects with dyslexia.^{36,37} In a related group of patients, subjects with the genetic syndrome of XXY (Klinefelter syndrome) have language-based cognitive dysfunction similar to that of dyslexia.³⁸ Supportive of the reports of left temporal lobe gray matter reduction in dyslexia, subjects with Klinefelter

Table 4
Comparison of CLP group, CPO group, and healthy controls

	CLP (N = 32) adjusted mean ^a	CPO (N = 14) adjusted mean ^a	Controls (n = 46) adjusted mean ^a	CLP vs. control		CPO vs. control	
				F	P	F	P
General measures ^b (cc's)							
Intracranial volume (ICV)	1,437	1,487	1,491	4.16	0.049	0.06	0.814
Total brain tissue	1,345	1,395	1,385	2.53	0.116	0.16	0.686
Total CSF	91.6	82.1	106	2.44	0.122	4.18	0.042
Ventricles	12.3	16.0	16.3	7.26	0.008	0.020	0.890
Surface CSF	54.4	41.0	64.1	1.50	0.224	5.87	0.018
Cerebral volume	1,178	1,219	1,201	1.18	0.281	0.041	0.526
Cerebellar volume	131	139	146	13.26	0.0005	1.31	0.257
Tissue segmentation of general measures ^c (cc's)							
Cerebral gray matter	712	727	696	2.96	0.089	4.48	0.038
Surface gray matter (cortex)	656	674	640	3.48	0.066	6.56	0.013
Subcortical gray matter	55.5	52.8	56.2	0.31	0.579	5.43	0.023
Cerebral white matter	494	496	486	1.2	0.277	0.11	0.742
Cerebellar gray matter	96	103	109	17.09	<0.0001	2.81	0.099
Cerebellar white matter	36.8	37.1	35.4	0.77	0.383	0.69	0.410
Regions of the cerebrum ^d (cc's)							
Anterior cerebrum	737	747	709	9.42	0.003	6.72	0.012
Gray matter	421	433	404	5.80	0.018	7.16	0.009
White matter	316	314	305	4.01	0.049	0.56	0.458
Posterior cerebrum	355	363	364	9.40	0.003	1.74	0.192
Gray matter	226	230	226	0.01	0.927	0.44	0.509
White matter	129	132	138	10.75	0.001	3.92	0.05
Cerebral lobes ^d							
Frontal lobe	465	466	458	5.00	0.028	1.06	0.307
Gray matter	274	280	269	2.72	0.103	3.42	0.069
White matter	190	186	188	0.43	0.515	0.90	0.345
Parietal lobe	264	268	258	7.25	0.008	6.28	0.015
Gray matter	142	146	139	4.25	0.042	5.19	0.026
White matter	121	122	119	1.00	0.320	0.35	0.555
Temporal lobe	229	227	237	10.55	0.001	12.87	<0.001
Gray matter	154	154	158	7.14	0.009	4.34	0.041
White matter	75.2	72.6	78.6	3.38	0.069	8.61	0.004
Occipital lobe	122	129	130	11.34	0.001	.022	0.640
Gray matter	70.1	72.7	69.2	0.24	0.625	1.41	0.239
White matter	52.0	57.0	61.3	24.41	<0.001	3.16	0.081

^aMean adjusted by covariate.

^bCovariate = height.

^cCovariate = intracranial volume.

^dCovariate = total cerebral tissue volume.

syndrome were found to have reductions in the volume of their left temporal lobe gray matter as well.³⁹

In reference to the current sample, all the subjects are male. In addition, this sample has been shown to have significant cognitive deficit with a mild decrement in IQ accompanied by specific deficits in language function.¹⁴ Therefore, the findings of decreased left temporal lobe gray matter volume in this sample of adult males with NSCLP and language deficits are strikingly similar to the brain morphologic findings of other developmental language disorders.

Structure/function relationship

Are these morphologic changes related to function? The notion that the anterior cerebrum was actually enlarged was somewhat unexpected. One possibility was that it was a compensatory overgrowth, not a primary abnormality. Although the notion that the larger the cerebral volume, the greater the cognitive function, has been documented in normal brains,⁴⁰ there is also evidence to suggest that pathologic enlargement is associated with decreased cognitive function. This finding has been reported in both autism^{41,42} and neurofibromatosis.^{43,44} To investigate this suggestion in the current NSCLP sample, a Spearman's correlation (chosen to decrease the influence of outliers) was calculated between volumes of cerebral regions and IQ, controlling for total brain tissue volume. Table 5 shows the correlations and indicates that the anterior cerebral enlargement was pathologic, with significant inverse correlation with Full Scale IQ (FSIQ)—the larger the anterior cerebrum, the lower the IQ. In addition, there was the reverse finding for the posterior cerebrum—significant positive correlation with FSIQ, indicating that the smaller this region, the lower the FSIQ. These correlations were significant for FSIQ and for Verbal (IQ) but were nonsignificant for Performance IQ (PIQ; non-language-based skills).

Etiology

The development of the brain and that of the face is intimately entwined. Therefore, it is likely that the abnormalities in brain morphology seen in the current sample are a manifestation of aberrant brain development, just as the facial cleft is a manifestation of aberrant craniofacial development. A previous *qualitative* study of the MRI scans obtained on the current sample of adult males with NSCLP showed an elevated incidence of a midline brain developmental anomaly, enlarged cavum septi pellucidi (CSP), supporting the notion that the abnormalities seen in the current study are developmental in

nature.⁴⁵ In addition, the *decreased* volume of CSF in the NSCLP sample compared with controls would speak against some type of degenerative process, which would instead manifest as regions of decreased tissue volume accompanied by *increases* in CSF.

The etiology of NSCLP is complex, with both genetic and environmental factors having a role. Genetic epidemiologic studies have shown that several interacting loci, including a major gene, are involved in the etiology of NSCLP, possibly accounting for approximately half of the familial occurrences.⁴⁶ Several candidate genes have been identified as being involved in NSCLP, based on expression, phenotype in transgenic animal, mutations, and linkage/associations in mice or humans. As brain and face development are so closely related, it seems likely that the genetic determinants involved in NSCLP may also be related to formation of abnormal brain structure and function.

As an example of one specific possibility, one particular gene, transforming growth factor (TGF β 3), has been shown to have a strong relationship to the etiology of NSCLP.^{47,48} In addition, TGF β 3 has a significant role in both early AND late (maturational) brain development. TGF β 3 proteins have been shown to play an important role in neuronal development in both invertebrates and vertebrates.⁴⁹ With regard to early brain development, these proteins are involved in proliferation and dorsal-ventral patterning. Clearly, the abnormalities in brain morphology outlined above have a distinct pattern consistent with abnormal dorsal-ventral tissue distribution. In addition, TGF β 3 has been shown to be involved in a late step in the pathways that specify asymmetry in the embryo.⁵⁰ Once again, the abnormal brain morphology demonstrated in this study of adults with NSCLP shows significant asymmetry with the left-sided regions being more severely affected than right-sided regions. Finally, a very recent report outlines the key role that TGF β 3 plays in neurogenesis and apoptosis, mechanisms directly linked to etiology of neuronal tissue morphology.⁵¹

In summary, subjects with NSCLP show significant alterations in brain morphology. Moreover, these changes are directly related to cognitive function. These findings highlight the intimate relationship between growth and development of the brain and that of the face. Aberrant craniofacial development may manifest in brain abnormalities and vice versa, suggesting that facial clefting may be the result of a primary problem in facial growth, a primary problem in brain growth, or both.

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Table 5

Spearman correlations^a between regional brain volume measures and intelligence quotients

	Full Scale IQ r (P)	Performance IQ r (P)	Verbal IQ r (P)
Anterior cerebrum volume	−0.316 (0.034)	−0.199 (0.189)	−0.342 (0.021)
Posterior cerebrum volume	0.409 (0.005)	0.169 (0.265)	0.456 (0.001)

^aControlling for total brain tissue volume.

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