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Period of Susceptibility for Cross-Modal Plasticity in the Blind

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Cross-modal plasticity in blind subjects contributes to sensory compensation when vision is lost early in life, but it is not known if it does so when visual loss occurs at an older age. We used $H_2{}^{15}O$ positron emission tomography to identify cerebral regions activated in association with Braille reading, and repetitive transcranial magnetic stimulation to induce focal transient disruption of function during Braille reading, in 8 subjects who became blind after age 14 years (late-onset blind), after a lengthy period of normal vision. Results were compared with those previously reported obtained from congenitally and early-onset blind subjects. As shown by $H_2{}^{15}O$ positron emission tomographic scanning, the occipital cortex was strongly activated in the congenitally blind and early-onset blind groups but not in the late-onset blind group. Occipital repetitive transcranial magnetic stimulation disrupted the Braille reading task in congenitally blind and early-onset blind subjects but not in late-onset blind subjects. These results indicate that the susceptible period for this form of functionally relevant cross-modal plasticity does not extend beyond 14 years.

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Visual deprivation early in life results in various physiological and behavioral effects involving the developing cortex.[1] Cross-modal plasticity associated with visual deprivation has been described in animals[2,3] and humans.[4–7] In general, areas activated in sighted subjects by performance of visual tasks become activated in association with tactile[7] or auditory discrimination tasks. These studies have been done mostly in individuals who were congenitally blind or became blind very early in life.[8]

A clear link between specific measures of plasticity (electrophysiological or neuroimaging) and functional relevance in terms of sensory compensation is not always clear.[9] In at least one form of cross-modal plasticity, this link has been demonstrated. Activation of the occipital cortex by tactile discrimination tasks like Braille reading in early blind subjects[7] appears to play a role in sensory processing.[10] Our goal in this study was to determine if this particular form of useful plasticity can take place later in life or if it is only a property of the developing nervous system.

Transcranial magnetic stimulation (TMS) is a noninvasive technique that can induce focal and transient disruption of function in the cortical regions under the magnetic coil.[11–13] Disruption of specific cognitive tasks by focal cortical stimulation has been interpreted as a sign that the region stimulated is functionally engaged and useful for task performance.[14] $H_2{}^{15}O$ positron emission tomography ($H_2{}^{15}O$ PET) and repetitive transcranial magnetic stimulation (rTMS) are therefore complementary in that although $H_2{}^{15}O$ PET can identify areas activated in association with task performance, rTMS allows the noninvasive study of the behavioral consequences of focal transient disruption of the activated cortical regions. The combination of both techniques provides a powerful tool to identify networks activated in association with Braille reading and to test behavioral effects of reversible disruption of specific cortical regions.

In this study we tested 8 subjects blind after age 14 by using a combination of $H_2{}^{15}O$ PET and rTMS. The results in patients with late-onset blindness (LOB) were compared with results reported previously in subjects who became blind earlier in life[7,10] and support the existence of a period of susceptibility for functionally relevant cross-modal plasticity in human blind subjects.

Subjects and Methods

Subjects

Eight subjects participated in this study (Table 1). Four right-handed LOB subjects underwent PET scanning, and 5

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Table 1. Clinical Characteristics of the Patients

	Age/Sex	Age at Onset of Blindness	Cause	Age when Started Braille Reading	Years Reading Braille	Hours per Day Reading Braille	Visual Perception	Reading Hand	PET	rTMS
A Late-onset blind subjects										
1	31/F	15	Retinal detachment	16	15	1	None	R	+	
2	64/M	17	Glaucoma	20	44	0.5	None	R	+	+
3	34/F	25	Diabetes	25	9	2	None	R	+	
4	48/M	44	Retinitis pigmentosa	45	3	0.5	Light	R	+	
5	38/F	35	Glaucoma	36	2	1	Bright light	R		+
6	56/M	16	Trauma	16	40	1	None	L		+
7	62/F	58	Glaucoma	60	2	1.7	Bright light	L		+
8	53/F	33	Glaucoma	39	14	1.5	None	R		+
Mean	48.25	30.37		32.13	16.13	1.15				
SD	12.68	15.25		15.69	16.8	0.54				
B Congenital blind, PET										
1	43/M	Birth	Retinolental fibroplasia	5	38	1.5	None	R	+	
2	49/F	Birth	Anophthalmos	6	43	2	None	R	+	
3	45/M	Birth	Optic nerve dysplasia	6	39	4	None	R	+	
4	45/F	Birth	Retinolental fibroplasia	6	39	1	None	L	+	
Mean	45.5			5.8	39.8	2.1				
SD	2.5			0.5	2.2	1.3				
C Early blind, PET										
1	60/M	4	CNS infection	5	55	3	None	R	+	
2	58/M	5	CNS infection	7	51	1	None	L	+	
3	55/F	13	Retinolental fibroplasia	8	47	3	None	R	+	
4	42/F	12	Congenital glaucoma	5	37	2	None	R	+	
Mean	53.8	8.5		6.3	47.5	2.3				
SD	8.1	4.7		1.5	7.7	1.0				
D Congenital early blind, rTMS										
1	44/M	3 mo	Glaucoma	5	39	2	None	L		+
2	38/M	Birth	Premature retinitis	4	29	4	None	R		+
3	63/M	4 yr	Meningitis	6	57	6	None	R		+
4	47/F	Birth	Premature retinitis	6	41	2	Bright light	L		+
5	44/F	Birth	Glaucoma	5	39	2	None	R		+
Mean	47.2			5.2	41	3.2				
SD	9.42			0.84	10.1	1.79				

PET = positron emission tomography; rTMS = repetitive transcranial magnetic stimulation; CNS = central nervous system.

LOB subjects underwent rTMS (1 of the subjects underwent both PET and rTMS). The PET and rTMS experiments were performed as previously described.[7,10] All our subjects lost their vision after age 14 years and started to read Braille daily soon afterward. The protocols were approved by the Institutional Review Board of the National Institute of Neurological Disorders and Stroke, all subjects gave informed consent, and rTMS was used under a US Food and Drug Administration investigational device exemption. The blind subjects had normal brain magnetic resonance imaging scans and no progressive neurological disease.

PET Methodology

There were 3 PET conditions—mostly "word," mostly "nonword" Braille reading, and an unconstrained rest condition. Under the word condition, 41 words and 3 nonwords were presented. Under the nonword condition, 41 nonwords and 3 words were presented. Subjects were asked to utter "num" when they encountered the infrequent word or nonword.[7] Letters were presented in strings of 8 letters. The rate of presentation was one string every 2.4 seconds. Subjects read by using the right hand. All subjects were scanned with their eyes closed and patched to minimize blinking. The lights of the PET room were dimmed. Each subject underwent six (two per condition) sequential regional cerebral blood flow (rCBF) PET scans with $H_2{}^{15}O$, using a Scanditronix (Uppsala, Sweden) PC 2048-15b PET camera with an axial field of view of 9.75 cm and an in-plane resolution at the center of the field of view of 6.1 mm. A bolus of 30 mCi of $H_2{}^{15}O$ was injected for each scan, and data were collected in two-dimensional acquisition mode with a 10-minute interscan interval. The attenuation corrected emission data were reconstructed as 15 contiguous axial planes of slice thickness 6.5 mm.

Statistical Analysis of PET Data

All head images were analyzed with statistical parametric mapping (Wellcome Department of Cognitive Neurology, London, UK).[15] After realignment, all images were transformed into standard stereotactic space.[16] Each image was smoothed with an isotropic Gaussian filter of 10 mm. To explore the effect of the onset of blindness on the activation patterns during Braille reading, the 12 blind subjects were categorized into three groups. Four subjects who never had vision were categorized as the congenitally blind (CB) group, 4 who lost their sight before the age of 14 as the early-onset blind (EOB) group (mean onset of complete blindness was 8.5 years), and the other 4 who lost their sight after the age

of 14 as LOB group. The following general linear model was then applied. Let Y^k_{iqjt} denote the rCBF at voxel k for the jth measurement in condition q of subject i in group t (j = 1,2; q = 1,2,3; i = 1,. . . ,12; t = 1,2,3).

$$Y^k_{iqjt} = \alpha\phi^k_{qt} + \gamma^k_i + \zeta^k_i(g_{iqj} - g_{i\cdot\cdot}) + \varepsilon^k_{iqjt}$$

where $\alpha\phi^k_{qt}$ is the interaction effect for condition q of group t (the condition-by-group effect), γ^k_i is the subject effect, ζ^k_i is the global regression effect of subject i, g_{iqj} is the global CBF of subject i in jth replication of condition q, and g_i is the mean of the gCBF over q conditions and j replications of subject i, and ε^k_{iqjt} is an error term that is an independent, normally distributed random variable with zero means. The tested contrasts are summarized in Table 2. As mostly word and mostly nonword tasks produced identical results,[7] the contrasts representing the averaged effect of these two task conditions were used. Contrasts 1, 2, and 3 represent the averaged task effects within the group, and contrasts 4 through 9 represent the difference of the task effects among the groups (simple effects).

The effect of the onset of blindness on the regional activation patterns by Braille reading was evaluated as group × condition interaction by using conjunction analysis.[17] With this approach, several hypotheses or simple effects described by the contrasts (see Table 2) were tested, asking whether all the effects are jointly and equally significant. In other words, the main effect we were interested in was the conjoint expression of the series of simple effects. The conjunction analysis has two processes.[17] First is the elimination of the regions that show significant differences among the simple effects, by F test with an appropriate threshold ($p < 0.05$, uncorrected for multiple comparisons). Second is the statistical inference test for the main effect, using the standard procedure based on the theory of Gaussian random fields.[15] To depict the task-related neuronal activities common to three groups, contrasts 1, 2, and 3 were tested with conjunction analysis (see Table 2). This comparison shows the neuronal activities unaffected by the onset of the blindness. To depict the regions that show the task-related activation in both CB and EOB but no activation in LOB, the same procedure was applied to the different combination of contrasts, namely, 1, 2, and 6. Contrast 1 indicates the task-related activation in CB, 2 indicates that in EB, and 6 indicates the difference of task-related activation between EB and LOB. The elimination step of the conjunction analysis discounts the areas where the effects of contrasts 1, 2, and 6 are significantly different. Through this process, 2 and 6 are equally significant only when the task-related neuronal change in LOB is null, because contrast 6 indicates the difference between task effect of EB, which is represented by contrast 2, and that of LOB. This comparison shows the task-related neural activities specific for congenital and early blind groups but not for late-onset group, hence the onset-dependent plastic change in Braille reading. In a similar manner, activations by congenital and late, early and late, congenital only, early only, and late only were assessed. A statistical threshold of $p < 0.05$, with correction for multiple comparisons at voxel level,[15] was considered significant. The simple analysis protects against false positives; the conjunction analysis protects against false negatives.

TMS Methodology

TMS was delivered with a magnetoelectric stimulator (Cadwell Laboratories, Kennewick, WA) and a figure 8–shaped[18] water-cooled coil. The coil was held tangentially to the scalp with the intersection of both loops oriented sagittally. Trains of stimuli were used because they are more effective than single stimuli in disrupting cognitive tasks.[19] rTMS was delivered to three occipital positions (midline, contralateral, and ipsilateral to the reading finger, overlying Brodmann areas 17, 18, and 19; O_z, O_1, and O_2 of the international 10-20 system of electrode placement), two parietal positions (contralateral and ipsilateral, approximately overlying Brodmann area 7; P_3 and P_4), a midfrontal position (F_z), and to the contralateral sensorimotor area (overlying Brodmann areas 4, 3, 1, and 2).[20] As a control condition, rTMS was also delivered into the air (the sound of the stimulator was as loud as in actual brain stimulation, but no stimulation reached the brain). Each train of rTMS was triggered by the reading finger crossing a laser beam[10] and had a fixed frequency of 10 Hz and a duration of 3 seconds. The stimulus

Table 2. Contrasts for Simple Effects

	Congenital			Early			Late		
No.	Rest	Word	Nonword	Rest	Word	Nonword	Rest	Word	Nonword
1	−2	1	1	0	0	0	0	0	0
2	0	0	0	−2	1	1	0	0	0
3	0	0	0	0	0	0	−2	1	1
4	−2	1	1	2	−1	−1	0	0	0
5	−2	1	1	0	0	0	2	−1	−1
6	0	0	0	−2	1	1	2	−1	−1
7	2	−1	−1	−2	1	1	0	0	0
8	2	−1	−1	0	0	0	−2	1	1
9	0	0	0	2	−1	−1	−2	1	1

Main effects of conjoint expression of simple effects by conjunction analysis: 1 & 2 & 3: common to congenital, early, and late; 1 & 2 & 6: common to congenital and early, without change in late; 2 & 3 & 7: common to early and late, without change in congenital; 1 & 3 & 4: common to congenital and late, without change in early; 2 & 6 & 7: early only, without change in congenital or late; 3 & 8 & 9: late only, without change in congenital or early. The ampersand (&) denotes conjunction analysis.[17]

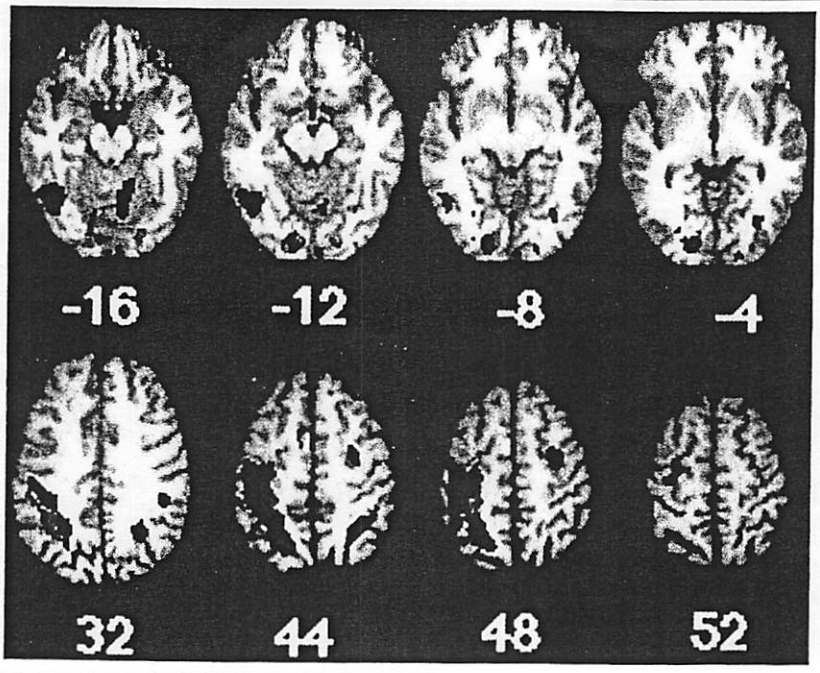

Fig 1. Conjunction analysis of activation by Braille discrimination tasks by congenital (n = 4), early (n = 4), and late (n = 4) blind groups, superimposed on typical magnetic resonance images unrelated to the study's subjects. Eight transaxial images of 16, 12, 8, and 4 mm below the anterior–posterior commissural line and 32, 44, 48, and 52 mm above are shown. The pixels show levels of statistical significance above $p < 0.05$ with correction for multiple comparisons at voxel level. Colors were not scaled for the Z magnitude. Areas commonly activated by congenital, early, and late blind (violet), congenital and early but not late blind (red), congenital and late blind but not early blind (yellow), early and late blind but not congenital blind (green), early blind only (light blue), and late blind only (pink) are shown. The primary visual cortex is commonly activated by congenital and early blind, but not by late blind.

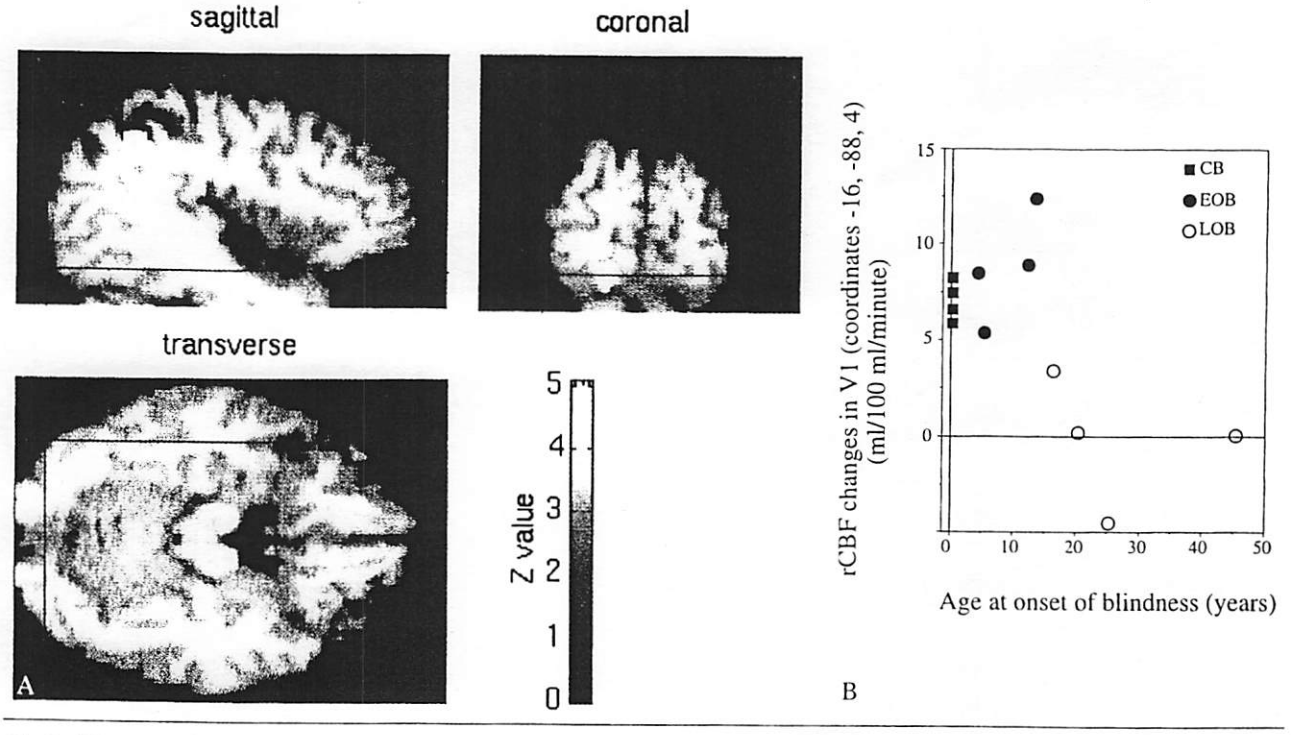

Fig 2. (A) A statistical parametric map of the t statistic (after transformation to an SPM) projected onto an anatomical coregistered representative magnetic resonance imaging scan. Comparison between late-onset early blind (n = 2; onset of blindness at 12 and 13 years of age) and the late blind group (see Table 1) in reference to activation by Braille reading with the right index finger $[(A_{ear} - R_{ear}) - (A_{late} - R_{late})]$. *The anatomical space corresponds to that of the conventional stereotactic atlas of Talairach.*[16] *The SPM has been thresholded at Z > 3.09 with a correction for multiple comparisons. (B) Regional cerebral blood flow changes in* V_1 *as a function of age at onset of blindness.*

intensity (normalized across subjects) was 10% above the minimal output of the stimulator required to induce a 50-μV electromyographic response from the relaxed first dorsal interosseous muscle. Parameters of stimulation were within those considered to be safe in recent publications.[21,22] rTMS can transiently suppress visual perception of letters[11] and extrafoveal targets,[23] probably by interference with visual calcarine[11] and association cortical areas at depths of 1.5 to 2.25 cm below the scalp surface.[24] Reading was also done in the absence of rTMS. The subjects identified 25 Braille letters presented in five strings of five letters (all nonwords) each for each scalp position stimulated. The order of string presentations and stimulated positions were randomized across subjects. Errors were defined as wrong identification or inability to identify letters. Subjects were encouraged to report sensations and subjective experiences felt after each rTMS train. Results from subjects in the LOB group (n = 5) were compared with those in a combined CB + EOB group already reported (see Table 1).

Statistical Analysis of rTMS Data

Overall errors in the LOB group and the CB + EOB groups were compared by using the Fisher exact test. The effects of repetition and letter were evaluated in individual logistic regressions. To evaluate the error rate by stimulated position, a logistic regression model with the seven stimulated positions (+ no stimulation + air stimulation) as a categorical factor was derived for each of the two groups (LOB and CB + EOB) separately.

Results

Cortical Regions Activated in Association with the Braille Reading Task

Irrespective of the onset of blindness, performance of the Braille discrimination task with the right index finger activated the left primary sensorimotor cortex (SM1), superior and inferior parietal lobule, prefrontal cortex, fusiform gyrus and cerebellum bilaterally, right dorsal premotor cortex, left fusiform gyrus, right inferior occipital lobe, and anterior cingulate gyrus (Fig 1, Table 3).

CB and EOB blind subjects, but not LOB subjects, activated the primary visual cortex bilaterally, the right inferior occipital gyrus, and the left superior parietal lobule extending to the angular gyrus and supramarginal gyrus on the left (see Table 3). EOB subjects activated the primary visual cortex slightly more extensively than subjects in the CB group. The percentage of increase in rCBF in the primary visual cortex was similar in both groups (see Table 3 and Fig 2B). EOB and LOB subjects, but not subjects in the CB group, activated the cerebellar vermis bilaterally adjacent to the areas of cerebellar activation common to all groups and right lingual gyrus. The CB and LOB groups, but not the EOB group, activated the anterior cingulate gyrus close to the supplementary motor area, the right inferior parietal lobule, the right fusiform gyrus, and the right inferior occipital gyrus, all of which were adjacent to the activated areas common to all groups. Only the EOB group activated the primary visual cortex adjacent to the commonly activated area. Only the LOB group activated the left dorsal premotor cortex and left precuneus. There was no region activated by the CB group only.

The 2 subjects who became blind at ages 12 and 13 (see Table 1) after a protracted period of partial vision[25] showed clear activation of the left primary visual cortex and left supramarginal gyrus, where there was no activation in LOB subjects (see Fig 2A and Table 4).

Effects of Disruption of Cortical Activity

In unstimulated trials, subjects in the LOB group identified letters 1 through 5 in 1.4 ± 0.6, 2.4 ± 0.5, 3.3 ± 0.5, 4 ± 0.5, and 4.3 ± 0.3 seconds after reading began. Therefore, the 3-second duration of the rTMS trains covered approximately 75% of the reading time. Accuracy level in unstimulated trials before the rTMS session was 85.4 ± 8.1% in the LOB group, lower than in the CB ± EOB group (94.8 ± 4.6%).[10] In a similar manner, accuracy level during intervention was lower in the LOB group (81.3 ± 1.2%) than in the CB + EOB group (87.5 ± 1.0%) ($p < 0.0001$, Fisher's test). Neither repetition nor letter affected error rates in either group. Based on logistic regressions, the LOB group showed no significant effect of stimulated position on error rate (likelihood ratio test, χ^2 with 8 $df = 4.83$, $p = 0.78$) whereas the CB + EOB group did, because of the higher rate of errors with midoccipital stimulation (likelihood ratio test, χ^2 with 8 $df = 30.56$, $p < 0.001$). The only single position where the CB + EOB group showed more errors than the LOB was O_z (25.6% vs 16.8%) (Fig 3A). The difference in error rates between stimulation of midoccipital regions (O_z) and Air was larger in subjects in the CB + EOB group than in those in the LOB group (see Fig 3B).

Subjects in the LOB group did not report distorted somatosensory perceptions with stimulation at any site as subjects in the CB + EOB group did.[10]

Discussion

Effects of Deafferentation on Visual Function

Individuals blind since early age because of cataracts can regain function to variable degrees after corrective surgeries.[26] However, if this correction takes place later in life, patients do not learn to use their vision normally.[27] Thus, the probability of success in visual rehabilitation relates to the degree of visual competence during a sensitive period,[28] which in cats and monkeys is limited to the first weeks or months of life[1,29–31] but in humans lasts substantially longer, approximately to the beginning of the second decade.[35–37] Therefore, the visual cortex undergoes functionally significant plasticity when changes in visual input take place early

Table 3. Activation by Braille Discrimination with Right Index Finger

Location[a]		Coordinates			Z	p^b	%ΔCBF		
		x	y	z			Congenital	Early	Late
Congenital, early, and late blind									
SM1	Left	−36	−24	52	7.81	<0.01	14.2	6.3	16.2
LPs (7)	Left	−28	−54	44	7.94	<0.01	14.8	9.9	7.0
	Right	30	−56	44	6.78	<0.01	7.6	8.4	9.7
LPi (40)	Left	−44	−38	36	7.22	<0.01	12.3	8.2	7.5
	Right	42	−40	36	7.14	<0.01	10.0	4.2	9.8
Cerebellum	Left	−14	−82	−20	6.25	<0.01	4.4	8.7	9.5
	Right	16	−50	−28	7.70	<0.01	14.3	15.5	11.1
GF (37)	Left	−42	−62	−20	6.92	<0.01	9.8	8.4	7.2
	Right	50	−50	−24	4.85	0.01	3.7	5.7	7.1
PMd (6)	Right	24	−8	48	7.00	<0.01	11.1	7.5	7.6
GFi (44)	Left	−50	−2	24	4.73	0.01	5.7	3.5	6.0
	Right	40	0	24	5.66	<0.01	8.4	2.7	8.6
ACG	Left	−10	6	44	5.20	<0.01	11.0	2.9	6.4
GOi (18)	Right	32	−72	−4	4.56	0.03	13.1	8.9	4.1
Congenital and early blind, not late blind									
Cu (17)	Left	−16	−88	4	5.41	<0.01	7.7	9.8	0.0
	Right	16	−98	−4	4.67	0.02	6.8	12.5	−0.1
Ga (39)	Left	−38	−56	36	6.57	<0.01	8.1	14.9	−3.7
Gsm (40)	Left	−48	−40	32	5.44	<0.01	7.6	8.8	0.4
GOi (18)	Right	28	−76	−4	5.49	<0.01	7.5	15.6	−1.4
LPs (7)	Left	−28	−38	44	5.31	<0.01	7.6	11.6	−1.2
Early and late blind, not congenital blind									
Cerebellum	Left	−8	−76	−16	5.03	<0.01	−1.5	7.4	9.8
	Right	4	−64	−8	6.59	<0.01	−4.0	14.3	12.4
GL (18)	Right	20	−88	−20	5.26	<0.01	0.5	13.4	4.7
Congenital and late blind, not early blind									
ACG	Left	−8	2	48	5.31	<0.01	12.4	1.7	5.1
LPi (40)	Right	40	−40	44	5.11	<0.01	8.3	−1.3	10.7
GF (37)	Right	48	−56	−28	4.84	<0.01	7.5	−0.5	8.2
GFi (44)	Right	38	2	24	4.83	0.01	8.5	1.1	8.2
GOi (18)	Right	36	−68	0	4.67	0.01	10.1	−0.6	4.5
Early blind only									
Cu (17)	Left	−14	−96	−16	6.58	<0.01	2.0	15.7	−0.3
	Right	12	−92	−12	4.81	0.01	0.3	11.1	−0.7
Late blind only									
PMd (6)	Left	−38	−6	52	5.89	<0.01	−0.1	−1.7	14.6
PCu (7)	Left	−14	−78	44	5.53	<0.01	1.1	1.5	17.2

All foci were defined as the local maxima of the Z scores, within the clusters thresholded by the predefined statistical significance ($p < 0.05$, with correction for multiple comparisons).

[a]Brodmann area, in parentheses, according to Talairach and Tournoux.[16]
[b]With correction for multiple comparisons at voxel level.[15]

ACG = anterior cingulate gyrus; Cu = cuneus; Ga = angular gyrus; GF = fusiform gyrus; GFi = inferior frontal gyrus; GL = lingual gyrus; GOi = inferior occipital gyrus; Gsm = supramarginal gyrus; LPi = inferior parietal lobule; LPs = superior parietal lobule; PCu = precuneus; PMd = dorsal premotor cortex; SM1 = primary sensorimotor cortex.

in life. The influence of age at the time of deafferentation in the development of plasticity across sensory modalities has been less well documented.[38–41]

Plasticity Across Sensory Modalities in the Blind

In subjects with congenital and early blindness, a distributed network is activated in association with Braille reading. These areas include the inferior parietal lobule, primary visual cortex, inferior occipital gyri, fusiform gyri, ventral premotor area, superior parietal lobule, cerebellum, and primary sensorimotor cortex bilaterally, right dorsal premotor cortex, right middle occipital gyrus, and right prefrontal area.[7,25] It has been proposed that tactile processing pathways usually linked in SII in sighted subjects, are rerouted in blind subjects to ventral occipital areas.[25] This activation of "visual" brain regions by a tactile discrimination task represents an important example of cross-modal plasticity.[9] Furthermore, it is now known that this occipital activity plays an important role in terms of sensory compensation. That is, disruption of occipital function during Braille reading in subjects blind at an early age, using

Table 4. Comparison Between Early Blind[a] and Late Blind[b] with Regard to Activation by Braille Discrimination with Right Index Finger

Location[c]	Coordinates					%ΔCBF	
	x	*y*	*z*	*Z*	*p*[d]	Early	Late
Early > late blind							
Gsm (40), left	−40	−58	36	5.09	<0.01	14.4	−4.6
Cu (17), left	−14	−94	−16	4.97	<0.01	16.5	−1.2

[a]n = 2; onset of blindness was 12 and 13 years of age.
[b]n = 4.
[c]Brodmann area, in parentheses, according to Talairach and Tournoux.[16]
[d]With correction for multiple comparisons at voxel level.[15]
Cu = cuneus; Gsm = supramarginal gyrus.

TMS, results in accuracy errors in the reading task and in induction of phantom dots and distorted tactile perceptions.[10]

Cross-modal plasticity in blind humans has been described in association with a variety of tasks,[4,5,42–45] but so far it has been demonstrated to be important in terms of sensory compensation only when associated with performance of tactile discrimination tasks.[10] Therefore, identification of a period of susceptibility (or lack of it) would be of interest in a model of cross-modal plasticity known to play a compensatory role.

Period of Capability for Cross-Modal Plasticity in the Blind

The cortical areas activated during Braille reading by all three groups were widely distributed. At the periphery of these areas, there were small foci that lacked activation by one group; ie, the cerebellar vermis was activated in EOB and LOB but not CB, and anterior cingulate gyrus, right inferior parietal lobule, right fusiform gyrus, right inferior frontal gyrus, and right inferior occipital gyrus were activated in CB and LOB but not EOB. Although this may indicate subtle fluctuations of the extent of the activation because of the different onset of blindness, these areas represent the neural substrates for Braille reading by blind subjects irrespective of the onset of their blindness.

Our study in a group of subjects who lost their vision after age 14 (LOB) shows that the occipital cortex, except for small regions in the right inferior occipital gyrus and lingual gyrus with weak activation, does not activate in association with the tactile discrimination task. These two areas were detected only by conjunction analysis, which is more sensitive than the conventional subtraction approach because of reduced search volume.[17] Comparison within each group with a more conservative approach[15] showed strong activation in the CB and EOB groups, as reported previously.[7,25] Furthermore, the present study shows that most of the

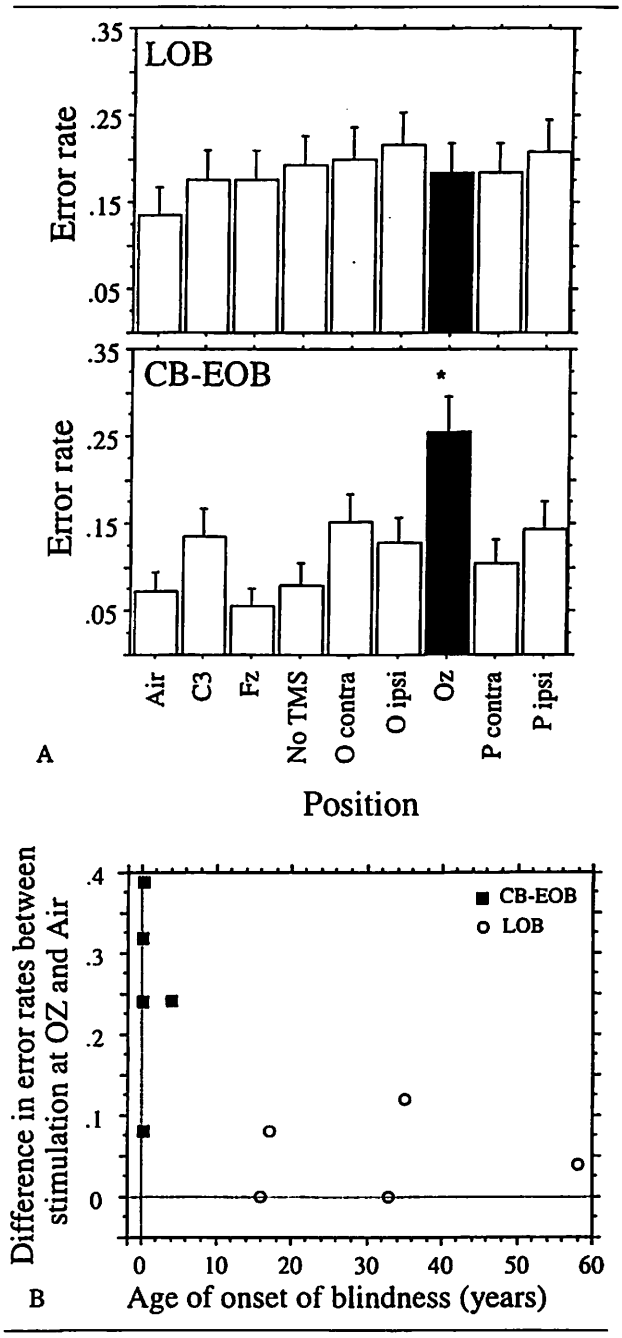

*Fig 3. (A) Error rates (mean ± SE) for stimulation of different scalp positions in the late-onset blind (LOB) group (A, top) and in the congenitally blind (CB) + early-onset blind (EOB) group (displayed here for comparison) (A, bottom). Solid columns indicate error rates induced by stimulation of the midoccipital position. Note that in the CB + EOB group, stimulation of midoccipital positions elicited the largest error rate. In the LOB group, there are no differences in error rates by stimulation position. * = scalp positions where significantly more errors occurred than control (air). TMS = transcranial magnetic stimulation; Air, no brain stimulation (control); C3, sensorimotor cortex; contra, contralateral; ipsi, ipsilateral. (B) Difference in error rates with stimulation over the midoccipital region (O_z) and control (Air) as a function of age of onset of blindness.*

visual cortex, including the primary visual cortex, was activated in the CB and EOB groups but not in the LOB group. In addition, disruption of occipital activity by TMS points to a functionally relevant occipital cortex in the CB and EOB groups but not in the LOB group. Therefore, the occipital cortex appears to play a fundamentally different role in LOB subjects in comparison with the other two groups. It is noteworthy that only the LOB group activated the left precuneus, a medial parietal region considered to be involved in visual imagery as part of conscious memory recall paradigms[46,47] and spatial aspects of visual perception.[48,49] Because several LOB subjects started to learn Braille before complete blindness, it is possible that Braille reading after vision loss uses regions similar to those involved in visual imagery in the sighted.[50] In addition, LOB subjects activated the left dorsal premotor cortex whereas CB or EOB subjects did not. The premotor cortex is involved in learning of associations between movements and external cues[51] and is active as task difficulty increases.[52] Because subjects in the LOB group were less experienced readers than those in the CB or EOB groups, this activation may be a reflection of the increased effort required to perform the task. Buchel and colleagues[50] have also demonstrated activation of extrastriatal visual areas in the blind, but primary visual cortex was activated only in those subjects with blindness after puberty. This apparently paradoxical result is actually difficult to interpret, because the Braille reading was contrasted with auditory word processing rather than rest.

The rTMS results show that disruption of neuronal processing in the occipital areas does not significantly affect Braille reading when visual deprivation started later in life, as it did in subjects blind since very early age.[10] Stimulation of contralateral sensorimotor areas induced similar error rates in both groups (see Fig 3A). Taken together, neuroimaging and neurophysiological results provide evidence supporting the concept of a window of opportunity for this form of functionally relevant cross-modal plasticity.

The mean age of onset of blindness in a previous PET study was 4.3 years,[7] and in the previous rTMS study all subjects became blind even before that age.[10] In the present study all subjects in the LOB group had vision up to at least 14 years. The differential activation of occipital cortex in the 2 subjects who became blind at ages 12 and 13 (in the EOB group) and the LOB group (including a subject blind at age 15) (see Fig 2 and Table 4) suggests that the age boundary for the susceptible period of this form of cross-modal plasticity ranges between 13 and 15 years, close to that described for effective treatment of strabismic amblyopia in humans.[36] The upper limit of the critical period for starting effective learning of a language is also considerably higher[53] than previously estimated.[54,55] These findings are compatible with the proposition that puberty may mark a milestone for the facility in language acquisition[56,57] and other plastic processes in the brain.

Thus, the development of functionally relevant cross-modal plasticity in visual cortex would seem to require the onset of blindness before adolescence, during a sensitive period of life. If plastic changes that occurred during this period of susceptibility underlie the improved abilities of blind individuals in sensory modalities other than visual,[58–60] it is understandable why subjects who acquired blindness late in life appear to read Braille with higher error rates than those with early blindness (despite a relatively similar range of daily practice hours). It is also possible that where tactile discrimination failed to elicit functionally relevant cross-modal plasticity in blind human adults, other tasks could succeed. For example, a pitch discrimination task elicited similar electrophysiological changes in both early and late blind subjects.[61] One interpretation given to these changes was that they could reflect coactivation of occipital areas in blind individuals during attentional processing.[6] That is, it is likely that some electrophysiological or neuroimaging patterns associated with visual deafferentation represent specific engagement of the occipital cortex in task performance (PET activation of occipital cortex during Braille reading in congenital and early blind[10]), whereas others may represent less specific attentional components equally present in early or late blind (N_2, P_3 scalp distribution of auditory event–related potentials in a pitch discrimination task).[61]

These considerations underline the need to identify to which extent each electrophysiological or neuroimaging measures of plasticity play a compensatory role in a behavioral sense. In our paradigm, we know that the activation of the occipital cortex contributes behaviorally to the Braille reading task.[10] We do not exclude the possibility that plasticity across sensory modalities could play a compensatory role in tasks other than tactile discrimination in blind human adults.

In summary, the present experiment indicates that there is a window of opportunity for the development of functionally relevant cross-modal plasticity in the blind. This observation may have implications for ongoing studies of the feasibility of visual prostheses[62] and rehabilitation programs in the blind.[63]

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References

1. Hubel DH, Wiesel TN. The period of susceptibility to the physiological effects of unilateral-eye closure in kittens. J Physiol (Lond) 1970;206:419–436
2. Hyvarinen J, Carlson S, Hyvarinen L. Early visual deprivation alters modality of neuronal responses in area 19 of monkey cortex. Neurosci Lett 1981;26:239–243
3. Rauschecker JP, Korte M. Auditory compensation for early blindness in cat cerebral cortex. J Neurosci 1993;13:4538–4548
4. Uhl F, Franzen P, Podreka I, et al. Increased regional cerebral blood flow in inferior occipital cortex and cerebellum of early blind humans. Neurosci Lett 1993;150:162–164
5. Kujala T, Alho K, Kekoni J, et al. Auditory and somatosensory event-related brain potentials in early blind humans. Exp Brain Res 1995;104:519–526
6. Roder B, Rosler F, Henninghausen E. Different cortical activation patterns in blind and sighted humans during encoding and transformation of haptic images. Psychophysiology 1997;34:292–307
7. Sadato N, Pascual-Leone A, Grafman J, et al. Activation of the primary visual cortex by Braille reading in blind subjects. Nature 1996;380:526–528
8. Rauschecker JP. Compensatory plasticity and sensory substitution in the cerebral cortex. Trends Neurosci 1995;18:36–43
9. Pons T. Novel sensations in the congenitally blind. Nature 1996;380:479–480
10. Cohen LG, Celnik P, Pascual-Leone A, et al. Functional relevance of cross-modal plasticity in the blind. Nature 1997;389:180–183
11. Amassian VE, Cracco RQ, Maccabee PJ, et al. Suppression of visual perception by magnetic coil stimulation of human occipital cortex. Electroencephalogr Clin Neurophysiol 1989;74:458–462
12. Day BL, Rothwell JC, Thompson PD, et al. Delay in the execution of voluntary movement by electrical or magnetic brain stimulation in intact man. Brain 1989;112:649–663
13. Cohen LG, Bandinelli S, Sato S, et al. Attenuation in detection of somatosensory stimuli by transcranial magnetic stimulation. Electroencephalogr Clin Neurophysiol 1991;81:366–376
14. Ojemann GA. Brain organization for language from the perspective of electrical stimulation mapping. Behav Brain Sci 1983;6:190–206
15. Friston KJ, Holmes AP, Worsley KJ, et al. Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapping 1995;2:189–210
16. Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. New York, NY: Thieme Medical, 1988
17. Price CJ, Friston KJ, Friston KJ. Cognitive conjunction: a new approach to brain activation experiments. Another neural code? Neuroimage 1997;5:261–270
18. Cohen LG, Roth BJ, Nilsson J, et al. Effects of coil design on delivery of focal magnetic stimulation: technical considerations. Electroencephalogr Clin Neurophysiol 1990;75:350–357
19. Luders H, Lesser RP, Dinner DS, et al. Commentary: chronic intracranial recording and stimulation with subdural electrodes. In: Engel J, ed. Surgical treatment of the epilepsies. New York: Raven Press, 1987:297–321
20. Homan RW, Herman J, Purdy P. Cerebral location of international 10-20 system electrode placement. Electroencephalogr Clin Neurophysiol 1987;66:376–382
21. Chen R, Gerloff C, Classen J, et al. Safety of different intertrain intervals for repetitive transcranial magnetic stimulation and recommendations for safe ranges of stimulation parameters. Electroencephalogr Clin Neurophysiol 1998;105:415–421
22. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the international workshop on the safety of repetitive transcranial magnetic stimulation. Electroencephalogr Clin Neurophysiol 1998;108:1–16
23. Epstein CM, Zangaladze A. Magnetic coil suppression of extrafoveal visual perception using disappearance targets. J Clin Neurophysiol 1996;13:242–246
24. Epstein CM, Verson R, Zangaladze A. Magnetic coil suppression of visual perception at an extracalcarine site. J Clin Neurophysiol 1996;13:247–252
25. Sadato N, Pascual-Leone A, Grafman J, et al. Neural networks for Braille reading by the blind. Brain 1998;121:1213–1229
26. von Senden M. Raum und Gestalt: Auffassung bei operierten Blindgeborenen vor und nach del Operation. Leipzig: Barth, 1932
27. Hyvarinen J, Hyvarinen L. Blindness and modification of association cortex by early binocular deprivation in monkeys. Child Care Health Dev 1979;5:385–387
28. Carlson S, Hyvarinen L. Visual rehabilitation after long lasting early blindness. Acta Ophthalmol (Copenh) 1983;61:701–713
29. von Noorden GK. Experimental amblyopia. Isr J Med Sci 1972;8:1496–1499
30. Regal DM, Boothe R, Teller DY, Sackett GP. Visual acuity and visual responsiveness in dark-reared monkeys (*Macaca nemestrina*). Vis Res 1976;16:523–530
31. Crair MC. The role of visual experience in the development of columns in cat visual cortex. Science 1998;279:566–570
32. Banks MS, Aslin RN, Letson RD. Sensitive period for the development of human binocular vision. Science 1975;190:675–677
33. Hohmann A, Creutzfeldt OD. Squint and the development of binocularity in humans. Nature 1975;254:613–614
34. von Noorden GK, Crawford MLJ. The sensitive period. Trans Ophthalmol Soc UK 1979;99:442–446
35. Vaegan, Taylor D. Critical period for deprivation amblyopia in children. Trans Ophthalmol Soc UK 1979;99:432–439
36. Epelbaum M, Milleret C, Buisseret P, Dufier JL. The sensitive period for strabismic amblyopia in humans. Ophthalmology 1993;100:323–327
37. Keech RV, Kutschke PJ. Upper age limit for the development of amblyopia. J Pediatr Ophthalmol Strabismus 1995;32:89–93
38. Rebillard G, Carlier E, Rebillard M, Pujol R. Enhancement of visual responses on the primary auditory cortex of the cat after an early destruction of cochlear receptors. Brain Res 1977;129:162–164
39. Sur M, Pallas SL, Roe AW. Cross-modal plasticity in cortical development: differentiation and specification of sensory neocortex. Trends Neurosci 1990;13:227–233
40. Rauschecker JP, Kniepert U. Auditory localization behaviour in visually deprived cats. Eur J Neurosci 1994;6:149–160
41. Neville HJ. Developmental specificity in neurocognitive development in humans. In: Gazzaniga MS, ed. The cognitive neurosciences. Cambridge, MA: MIT Press, 1995:219–231
42. Kujala T, Huotilainen M, Sinkkonen J, et al. Visual cortex activation in blind subjects during sound discrimination. Neurosci Lett 1995;183:143–146
43. Pascual-Leone A, Torres F. Plasticity of the sensorimotor cortex representation of the reading finger in Braille readers. Brain 1993;116:39–52
44. Pascual-Leone A, Cammarota A, Wassermann EM, et al. Modulation of motor cortical outputs to the reading hand of braille readers. Ann Neurol 1993;34:33–37
45. Uhl F, Kretschmer T, Lindinger G, et al. Tactile mental imagery in sighted persons and in patients suffering from peripheral blindness early in life. Electroencephalogr Clin Neurophysiol 1994;91:249–255
46. Fletcher PC, Frith CD, Baker SC, et al. The mids eye-

precuneus activation in memory-related imagery. Neuroimage 1995;2:195–200
47. Buckner RL, Raichle ME, Miezin FM, Petersen SE. Functional anatomic studies of memory retrieval for auditory words and visual pictures. J Neurosci 1996;16:6219–6235
48. Mishkin M, Ungerleider LG, Macko KA. Objects vision and spatial vision: two cortical pathways. Trends Neurosci 1983;6: 414–417
49. Haxby JV, Grady CL, Horwitz B, et al. Dissociation of object and spatial visual processing pathways in human extrastriate cortex. Proc Natl Acad Sci USA 1991;88:1621–1625
50. Buchel C, Price C, Frackowiak RSJ, Friston K. Different activation patterns in the visual cortex of late and congenitally blind subjects. Brain 1998;121:409–419
51. Passingham R. Functional organization of the motor system. In: Frackowiak RSJ, et al., eds. Human brain function. San Diego: Academic Press, 1997:243–274
52. Winstein CJ, Grafton ST, Pohl PS. Motor task difficulty and brain activity: investigation of goal-directed reciprocal aiming using PET. J Neurophysiol 1997;77:1581–1594
53. Vargha-Khadem F, Carr LJ, Isaacs E, et al. Onset of speech after left hemispherectomy in a nine-year-old boy. Brain 1997; 120:159–182
54. Skuse DH. Extreme deprivation in early childhood. In: Bishop D, Mogford K, eds. Language development in exceptional circumstances. Edinburgh: Churchill Livingstone, 1988:29–46
55. Johnson JS, Newport EL. Critical period effects in second language learning: the influence of maturational state on the acquisition of English as a second language. Cogn Psychol 1989; 21:60–99
56. Lenneberg EH. Biological foundations of language. New York: Wiley, 1967
57. Lenneberg EH. On explaining language. Science 1969;164: 635–643
58. Niemeyer W, Starlinger I. Do the blind hear better? Investigations on auditory processing in congenital or early acquired blindness. II. Central functions. Audiology 1981;20:510–515
59. Starlinger I, Niemeyer W. Do the blind hear better? Investigations on auditory processing in congenital or early acquired blindness. I. Peripheral functions. Audiology 1981;20:503–509
60. Bagdonas AP, Kodryunas RB, Lynyauskaite AI. Psychoacoustic functions in visually normal and impaired and blind subjects. Hum Physiol 1980;6:108–113
61. Kujala T, Alho K, Huotilainen M, et al. Electrophysiological evidence for cross-modal plasticity in humans with early- and late-onset blindness. Psychophysiology 1997;34:213–216
62. Schmidt EM, Bak MJ, Hambrecht FT, et al. Feasibility of a visual prosthesis for the blind based on intracortical microstimulation of the visual cortex. Brain 1996;119:507–522
63. Carlson S, Hyvarinen L, Raninen A. Persistent behavioural blindness after early visual deprivation and active visual rehabilitation: a case report. Br J Ophthalmol 1986;70:607–611