Brain SPECT Evaluation of the Visual Cortex in Amblyopia

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In amblyopia, the number of visual cortical neurons are reduced and abnormal or absent sensitivity to retinal light stimulation of the amblyopic eye is demonstrated. Ten amblyopic patients were studied to evaluate the response of the visual cortex to visual stimulation. **Methods:** All patients with unilateral amblyopia received 500–550 MBq ^{99m}Tc-HMPAO during visual stimulation. Strobe light flashing was used as the stimulus for five patients and a checkerboard pattern reversal was used in the other five patients, closing one eye. For both groups a 2-Hz frequency was used. One week later, the same procedure was repeated with the opposite eye closed. SPECT images were reconstructed with prefiltering techniques and sliced along the orbitomeatal line. **Results:** For all patients, the amblyopic eye demonstrated less radioactivity in the visual cortex than in the normal eye. The mean cerebral-to-cerebellar ratios were 0.95 ± 0.05 and 1.09 ± 0.07 for amblyopic and normal eyes, respectively ($p < 0.0001$). **Conclusion:** Visual cortex response of the amblyopic eye to light stimulation was severely reduced when compared to the normal eye.

Key Words: visual cortex; amblyopia; brain single-photon emission computed tomography; visual neuroactivation; visual-evoked potentials

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Amblyopia is classically defined as a unilateral or bilateral decrease of visual acuity in the absence of ophthalmologically visible abnormalities (*1,2*). Amblyopia occurs in 2% of the general population. The most common types of amblyopia are those secondary to strabismus and unequal refractive errors. Early diagnosis and onset of treatment are essential to a favorable outcome and management of amblyopia and other associated serious conditions (*1,2*). Diagnostic techniques for amblyopia vary according to patient age. A satisfactory method, however, for reliably measuring monocular visual acuities in infants and young children is still lacking (*1–6*).

Experimental studies have demonstrated that the size and number of visual cortical neurons are reduced in amblyopia (*7*). Cortical cells receiving input from affected cell layers of the lateral geniculate is known to show abnormal or absent sensitivity to retinal light stimulation of the amblyopic eye (*8,9*). PET studies in amblyopic humans, using $H_2{}^{15}O$ as an indicator of cerebral blood flow and ^{18}F-fluorodeoxyglucose as an indicator of glucose metabolism, have disclosed that the neuronal activity is reduced in the part of the visual cortex connected to the amblyopic eye (*10*). Other studies using PET have demonstrated increased metabolism of the visual cortex during ictal visual hallucinations and decreased perfusion in cases of visual cortex ischemia (*11–14*).

Recently, Woods et al. showed that SPECT can detect regional cerebral blood flow (rCBF) increase in the visual cortex with visual stimulation (*15*). The clinical utility of brain SPECT has also been documented in patients with cortical visual loss, even in those patients who had normal or nondiagnostic MRI (*16,17*).

This study evaluates visual cortex response to visual stimulation with brain SPECT in amblyopic patients and its usefulness in the diagnosis of amblyopia.

MATERIALS AND METHODS

Patients

Ten patients (4 men, 6 women; age range, 8–14 yr) with unilateral amblyopia strabismus secondary to refractive errors were studied. The visual acuity of the amblyopic eye ranged from 3 m counting fingers (mcf) to 20/100 as measured with the Snellen acuity testing (*18*) and did not improve with treatment.

Stimulation

All patients had two separate studies. Before each study, patients were placed in a dark, silent room for 10 min to adjust to the darkness. After closing one eye, visual stimulation was performed in five patients for 2 min using a black-and-white checkerboard pattern reversal with a frequency of 2 Hz. The other five patients were stimulated with a 2-Hz strobe light flash. For stimulation, a 2-Hz frequency was used because it was the routine rate for the visual-evoked potential (VEP) recordings of the pediatric patients in our ophthalmology department. The strobe light and pattern reversal screen were placed 50 cm from the patients who were asked to look directly at the stimulus and stay motionless. While the patients were under visual stimulation, 500–550 MBq ^{99m}Tc-HMPAO (Ceretec Amersham, Inc., Amersham, UK, prepared

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according to the manufacturer's instructions) was injected via a two-way venous catheter inserted previously and stimulation continued for an additional 2 min after the injection. The same procedure was repeated 1 wk later with the opposite eye closed.

Acquisition

SPECT scans were acquired 20–30 min after injection using a single-head, rotating gamma camera (Siemens, Orbiter 75 ZLC, Hoffman Estates, IL) fitted with a low-energy, high-resolution collimator. Images were obtained in a circular step-and-shoot mode, at 360° for 128 15-sec views in a 64 × 64 frame matrix. Image reconstruction was performed with Butterworth filter (0.45 Nyquist frequency, 10th order). Chang attenuation correction and reorientation of the slices parallel to the orbitomeatal line were performed. Each study consisted of 16 transaxial slices with a 6.2-mm pixel size. Two separate studies of each patient were displayed together and corresponding images were aligned according to the vertex and temporal poles to obtain consistency between the studies. Among them, five occipitofrontal slices displaying the visual cortex were selected. The corresponding images of two separate studies of each patient were composed in one file, enabling display of two studies in a normalized, standard window adjustment for visual evaluation. The slices displaying the visual cortex were selected by using anatomical structures as landmarks and an anatomical CT atlas (*19*).

Images were also interpreted quantitatively by drawing regions of interest (ROIs) over the left and right occipital cortex of each study. Whole visual cortex activation of the amblyopic eye and normal eye stimulation studies were compared; the ipsilateral and contralateral cerebral cortices of each study were compared as well. For quantitation, the slices were displayed on 128 × 128 matrices to minimize drawing errors and the ROIs were manually positioned over the right and left occipital lobes by using visual inspection and isocount pixels around the cortex. Region selection was based on anatomical structures and activation and they were defined to approximate cerebral structures demonstrated in the anatomical CT atlas. Average counts of ROIs containing at least 100 pixels were obtained from both the right and left occipital cortex and cerebellum of each study.

The primary visual cortex and associative visual cortex could not be delineated separately due to the lower resolution of our tomographic images (18 mm FWHM). Cerebellar counts were obtained by drawing ROIs over the whole cerebellum in a slice displaying both cerebellar hemispheres. The cerebral-to-cerebellar ratios were calculated for each of the five slices of both the normal and amblyopic eye stimulation studies and the average of the five slices was obtained to minimize variances occurring from position changes. The normal eye and amblyopic eye ratio ($C/Cr_{normal} - C/Cr_{amblyop}$) differences, where C/Cr is cerebral-to-cerebellar, for both hemispheres were calculated. The mean ratios of the ipsilateral and contralateral occipital cortex were expressed as a percentage of increase according to the formula (*15*):

$$(C/Cr_{normal} - C/Cr_{amblyop})/(C/Cr_{amblyop}) \times 100\%.$$

The calculated ratios were corrected for flow-dependent back-diffusion as described by Lassen et al. ($\alpha = 1.5$). The highest value of hemispheres were accepted as the maximum increase (*20,21*):

$$\text{corrected } C/Cr = C/Cr/(1 + \alpha - C/Cr).$$

The interpreter and the operator were blinded to the position of stimulated and abnormal eyes. Statistical analysis was performed using a two-tailed, paired, Student's t-test. A value of $p < 0.05$ was considered significant.

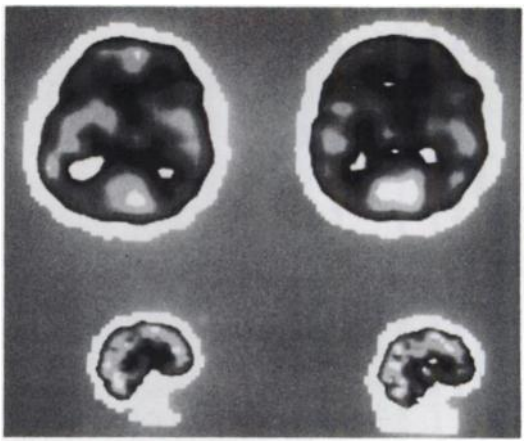

FIGURE 1. Corresponding images of a patient with right-sided amblyopia. Visual cortical activity was prominently higher with stimulation of the normal eye (right) as compared to the amblyopic eye stimulation (left). In each study, the ipsilateral and contralateral hemifields did not show rCBF differences.

RESULTS

Figure 1 demonstrates the SPECT image of a patient with right-sided amblyopia. In all patients, stimulation of the normal eye caused significant increased activity accumulation in the occipital cortex in comparison to amblyopic eye stimulation. Greater hyperactivity of normal eye stimulation was also demonstrated quantitatively (Table 1). The mean cerebral-to-cerebellar ratio was 0.95 ± 0.05 with the amblyopic eye stimulation. With stimulation of the normal eye, this ratio was 1.09 ± 0.07 ($p < 0.0001$). The mean maximum activation difference between cerebral-to-cerebellar ratios of amblyopic and normal eye stimulation was 27.04%. In a comparison of the ipsilateral and contralateral occipital cortex, hemifields did not reveal any significant rCBF difference ($p > 0.05$) (Table 1).

The difference in cerebral-to-cerebellar ratios did not correlate with amblyopia severity (Table 1). Stimulation with the checkerboard pattern reversal produced a lower activity increase than did strobe light stimulation, but the difference was not statistically significant (17.60% and 35.80%, respectively, $p = 0.058$) (Table 1).

DISCUSSION

PET and SPECT imaging can be used to evaluate and quantitate regional physiologic activity in the brain. PET has shown that visual cortex activity is increased during visual hallucinations and decreased in visual cortex ischemia (*11,12*). Decreased glucose uptake has been found bilaterally in the visual cortex in patients with Alzheimer's disease accompanied with visual agnosia (*22*). In conjunction with visual stimulation, PET can delineate those cortical areas involved in complex visual functions (*23*). Recently, color processing areas in the human visual cortex have also been identified (*24*). Demer et al. used PET to

TABLE 1A
Visual Acuity of the Amblyopic Eye, Type of Stimulation and Cerebral-to-Cerebellar Ratios

Patient no.	Amblyopic eye	Acuity	Stimulus	Cerebellum-to-Cerebellar ratios			
				Normal eye		Amblyopic eye	
				Ipsilateral	Contralateral	Ipsilateral	Contralateral
1	R	20/200	Pattern	1.06	1.06	0.99	1.00
2	R	20/200	Strobe	1.18	1.20	0.93	0.93
3	R	20/100	Pattern	1.06	1.08	0.97	1.00
4	R	3 mcf	Pattern	1.01	1.03	0.90	0.91
5	R	20/100	Strobe	1.05	1.04	0.91	0.91
6	R	20/200	Strobe	1.31	1.34	1.08	1.09
7	L	20/200	Strobe	1.03	1.01	0.90	0.89
8	R	20/100	Strobe	0.96	0.99	0.87	0.86
9	L	20/200	Pattern	1.09	1.08	1.00	0.96
10	R	20/200	Pattern	1.04	1.03	0.95	0.97
Mean ± s.e.m.				1.08 ± 0.07	1.09 ± 0.07	0.95 ± 0.05	0.95 ± 0.05

Ipsilateral = ipsilateral hemifield of the visual cortex with the stimulated eye; contralateral = contralateral hemifield of the visual cortex with the stimulated eye.

image amblyopic patients and found a significant reduction in visual cortical blood flow and glucose metabolism during visual stimulation of the amblyopic eye in comparison to periods of normal eye stimulation (*10*). Deprivation, anisometric and strabismic amblyopia were some of the noted conditions. In normal subjects visual cortex is activated to the same extent by visual stimulation of either eye. Because of its much better spatial resolution, PET has definite advantages over other imaging tests of the visual system.

Although the spatial resolution of SPECT is lower than that of PET, it is less expensive, more widely available and offers a more practical approach in routine clinical studies. In addition, the spatial resolution of dedicated multidetector neuro-SPECT cameras are comparable to PET systems (*25*). Moreover, split-dose, same-day SPECT testing may provide additional practical advantages in the clinical use of neuroactivation studies (*26*).

The clinical usefulness of brain SPECT in defining the location, extent and nature of disease in patients with cortical visual loss has been previously documented (*16,17*). In our study, SPECT images demonstrated a lower activity rate in the visual cortex of the stimulated amblyopic eye with respect to normal eye stimulation in every patient. This finding is consistent with PET results of Demer et al. (*10*). Woods et al. used SPECT to demonstrate that visual stimulation causes a significant increase (36.7%) in rCBF of the visual cortex as compared to visual deprivation in normal-sighted subjects (*15*). Crosson et al. recently reported a rCBF increase of 44.39% during visual stimulation in normal controls (*27*). In our study, stimulation of the am-

TABLE 1B
Percent Increases in Cerebral-to-Cerebellar Ratios of the Visual Cortex

Patient no.	Cerebellum-to-Cerebellar ratios				Max increase (%)
	Increase (%)		Increase (%) (Lassen corr.)		
	Ipsilateral	Contralateral	Ipsilateral	Contralateral	
1	7.07	6.00	12.28	10.42	12.28
2	26.88	29.03	50.91	55.83	55.83
3	9.28	8.00	16.11	14.08	16.11
4	12.22	13.19	20.51	22.43	22.43
5	15.38	14.29	26.53	24.46	26.53
6	21.30	22.94	44.74	49.43	49.43
7	14.44	13.48	24.57	22.62	24.57
8	10.34	15.12	16.79	25.03	25.03
9	9.00	12.50	15.96	22.01	22.01
10	9.47	6.19	16.22	10.52	16.22
Mean ± s.e.m.	13.54 ± 4.77	14.07 ± 5.02	24.46 ± 9.78	25.68 ± 10.78	27.04 ± 10.23

Ipsilateral = ipsilateral hemifield of the visual cortex with the stimulated eye; contralateral = contralateral hemifield of the visual cortex with the stimulated eye.

blyopic eye demonstrated a depressed response in the visual cortex, with 27.04% less activity than normal eye stimulation. This finding agrees with the results from animal studies (*8,9*). For example, it is known that the visual cortex of monkeys with one eyelid sutured in infancy contains neurons that respond only to the eye remaining open. Physiologic recordings of cells in lateral geniculate showed completely normal responses in amblyopia, although these cells are reduced in number and size. This indicates that the first cells to show abnormal functional response are situated in the visual cortex.

No difference in rCBF between the ipsilateral and contralateral hemifields of the visual cortex were found in this study. This finding is not surprising since the optic chiasm in humans is symmetrical. This finding also agrees with previously published PET studies (*11,12*). Phelps et al. demonstrated that the left and right visual cortex show symmetrical uptake with one or two eye stimulations as well as with the unstimulated basal states.

The checkerboard pattern reversal we used as a complex visual stimulation has a lower magnitude of visual cortex activity when compared to strobe-light flashing in this study, which contradicts previous reports. Neurophysiologically, cells in the visual cortex respond to more complex stimuli than those exciting cells in the subcortical structures (*28*). In subjects with normal sight, Phelps et al. found visual cortex metabolism to be progressively activated with increasingly complicated visual stimulus (*10*). The increase in metabolic response of the associative visual cortex was higher than the primary visual cortex as the visual scene became more complex. We cannot explain this discrepancy. Studies in larger series and in normal subjects are needed to determine appropriate calculations of this protocol's sensitivity and specificity. In patients with amblyopia, however, spatial resolution, contrast sensitivity and spatial frequency discrimination ability are altered and the healthy eye of these patients cannot be considered as completely normal (*18*). Furthermore, children stimulated with strobe light and pattern reversal have varying electrophysiological responses to each type of stimulation in comparison to adults; the same parameter is true for amblyopic patients in comparison to normals (*29,30*).

Amblyopia can be acquired and treated only during early childhood when there is still plasticity of the visual cortex (*1,2*). The visual system loses its ability to improve with treatment after age 8–9 yr. The early diagnosis of amblyopia and treatment at a young age are the most important determinants of a favorable outcome. This study found promising results in SPECT documentation of amblyopia, an approach that may be used in the early assessment of the disease.

CONCLUSION

SPECT brain perfusion imaging has potential use in the evaluation of the visual cortex of amblyopic patients with amblyopia. SPECT may also be used as an objective method of documenting visual function in the cortex and, perhaps, in predicting whether effective binocular vision can be restored.

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