Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 6830–6834, June 1996
Neurobiology

Neural plasticity in adults with amblyopia

(Vernier acuity/learning/orientation/hyperacuity/practice)

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Communicated by Bela Julesz, Rutgers, The State University of New Jersey, Piscataway, NJ, March 13, 1996 (received for review December 12, 1995)

ABSTRACT **Amblyopia is a neuronal abnormality of vision that is often considered irreversible in adults. We found strong and significant improvement of Vernier acuity in human adults with naturally occurring amblyopia following practice. Learning was strongest at the trained orientation and did not transfer to an untrained task (detection), but it did transfer partially to the untrained eye (primarily at the trained orientation). We conclude that this perceptual learning reflects alterations in early neural processes that are localized beyond the site of convergence of the two eyes. Our results suggest a significant degree of plasticity in the visual system of adults with amblyopia.**

Amblyopia is a developmental disorder that occurs during a period of neural plasticity early in life (1). The consequences of amblyopia include a reduced complement of cortical neurons that can be driven through the amblyopic eye and reduced visual acuity (2, 3). Generally, treatment of amblyopia is only undertaken in infants and young children; however, recent studies suggest that repetitive practice can improve performance on a variety of visual tasks in adult humans with normal visual capacities. The improvement in performance that follows practice may be quite specific to the learned orientation (4–8), retinal location (5, 7–11), spatial frequency (5, 8), and direction of motion (12). Here we report that adult amblyopes also demonstrate substantial and significant perceptual learning of Vernier acuity, and that this learning reflects alterations in early neural processes, perhaps due to sharpening of neural responses (13), that are task- and orientation-specific, but are localized beyond the site of convergence of the two eyes.

To determine the limits of cortical plasticity in humans adults with naturally occurring amblyopia, we studied Vernier acuity. Amblyopes have marked deficits in Vernier acuity that are highly correlated with their loss of Snellen acuity (14), and improvement in Vernier acuity in normal vision has been suggested to be linked to sharpening of neural responses (13) in the visual cortex. Our experiment consisted of three phases: (*i*) *pretraining* measures of Vernier and detection thresholds in each eye for several line orientations, (*ii*) a *training* phase where each observer repetitively trained on the Vernier task at a specific orientation until they had completed 4000–5000 trials, and (*iii*) *posttraining* measures (identical to the pretraining measures). Because we were interested in perceptual learning, as opposed to simply learning the psychophysical technique, or learning a strategy for making psychophysical observations with an amblyopic eye, five of the six observers had previous experience in making Vernier and detection judgments using our signal-detection methods (14). RH, RJ, and BJ had several years of experience (and hundreds of thousands of trials); KW and FG had less previous experience. Only EW had no prior experience. One potential problem with testing highly experienced observers is that they may have already improved to their limit (15) through many trials with feedback. Therefore, we trained our previously experienced observers with oblique lines, since all their previous experiments had been with horizontal or vertical targets. Normal observers, with extensive experience with horizontal and vertical targets, improve with oblique targets (16).

METHODS

The stimuli in our experiments consisted of short, dark line segments presented on a background with a mean luminance of 100 cd/m^2 and are described in detail elsewhere (16). When testing the preferred eyes, each line segment was 4 arc min long and 0.9 arc min wide, at the viewing distance of 4 m. For the amblyopic eyes, the viewing distance was decreased (in proportion to the observer's visual acuity), so the angular dimensions of the stimuli were proportionally larger. The *Vernier* stimulus consisted of two abutting, dark lines, with a Vernier offset between the two lines. The lines had a Weber contrast of 80%. The line *detection* stimulus was one of these Vernier lines, whose contrast was varied in order to measure the line contrast threshold. Stimuli were presented for 1 sec, with an abrupt onset and offset, on a Tektronix model 608 oscilloscope screen with a P31 phosphor, by a Neuroscientific (Farmingdale, NY) Venus stimulus generator, and were viewed through a circular aperture.

In all experiments, viewing was direct and monocular (with the untested eye occluded). Training sessions were generally about 1 hr, and consisted of 5–8 runs (of 125 trials per run).

To obtain criterion-free measures of performance, all thresholds were measured by using a self-paced, signal-detection rating-scale method of constant stimuli (16). On each trial one of five stimulus offsets (Vernier) or four stimulus contrasts (detection) was randomly presented. The magnitude of the steps was chosen based on a small number of preliminary trials, so that the offsets or contrasts bracketed the threshold. Following each Vernier trial, the observer responded by giving integer numbers from -2 to $+2$ and then received feedback as to the both the direction and magnitude of the offset on the previous trial. Each run consisted of 100 (detection) or 125 (Vernier) trials, preceded by about 10 practice trials. We used a maximum-likelihood fit to the rating-scale data to estimate the d' values for each stimulus and interpolated to a d' value of 1 (84% correct).

RESULTS

All six observers showed significant improvement after practicing Vernier acuity at one orientation (Fig. 1). We fit each data set within a daily session with a line so that "local" trends can be easily seen. These local trends are interesting because they highlight the large individual differences in how learning occurs. For example, EW and FG show significant learning

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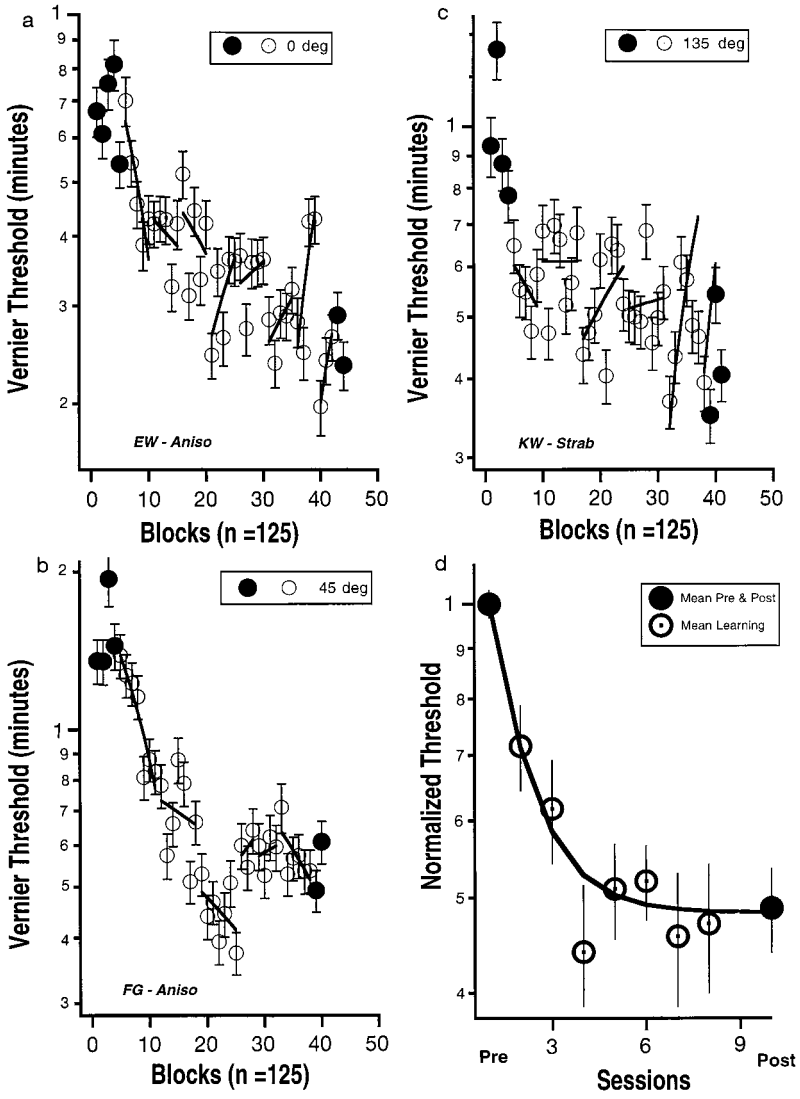

FIG. 1. (*a–c*) Vernier thresholds (in minutes of arc) versus number of 125 trial blocks, for three amblyopic observers [two anisometropes (*a* and *b*) and a strabismic (*c*)]. Error bars represent ±1 SEM. (*d*) Group data. Vernier thresholds for each *session* were normalized by the pretraining threshold and averaged across all six observers. The error bars are ±1 SEM. The line is an exponential fit to the data, which asymptotes at about half of the pretraining value after about five or six sessions (5000–6000 trials).

during the first few sessions; however, most of their subsequent learning takes place between sessions. KW shows little evidence of learning within a session; indeed, in some sessions her thresholds get steadily worse; however, she shows significant learning between sessions. Regression analysis on the overall data showed that each observer's Vernier thresholds improved significantly (five of the six at <0.0001 level) at the trained orientation (Table 1).

We assessed transfer of learning by pre- and posttesting at different orientations in both eyes on both Vernier and detection tasks. Analysis of variance revealed significant effects of orientation, eye and task. Fig. 2 *Top* shows the percent improvement in the trained (amblyopic) eye at each orientation. All six observers showed improvement in the trained orientation (mean improvement and SEM was 46 ± 7%); however, there are substantial individual differences. The two most experienced observers (RH and RJ) showed only about a 23–26% improvement, while the least experienced observers (EW and FG) showed improvements on the order of 60%. Improvement was generally most marked at the trained ori-

Table 1. Regression analysis of training days

Observer	Orientation 1	*P*	Orientation 2	*P*	Orientation 3	*P*	Orientation 4	*P*
BJ	135	<0.0001	45	<0.0001				
FG	45	<0.0001	135	<0.0001				
EW	0	<0.0001	45*	<0.0005				
KW	135	<0.0001						
RJ	135	<0.0001						
RH	45	0.006	135	0.94	90	0.84	0	0.09

Regression analyses were performed on the data across training sessions. The significance of each *F* statistic [*P* (probability) values] is given for each observer and condition.
*Only 2250 learning trials were completed.

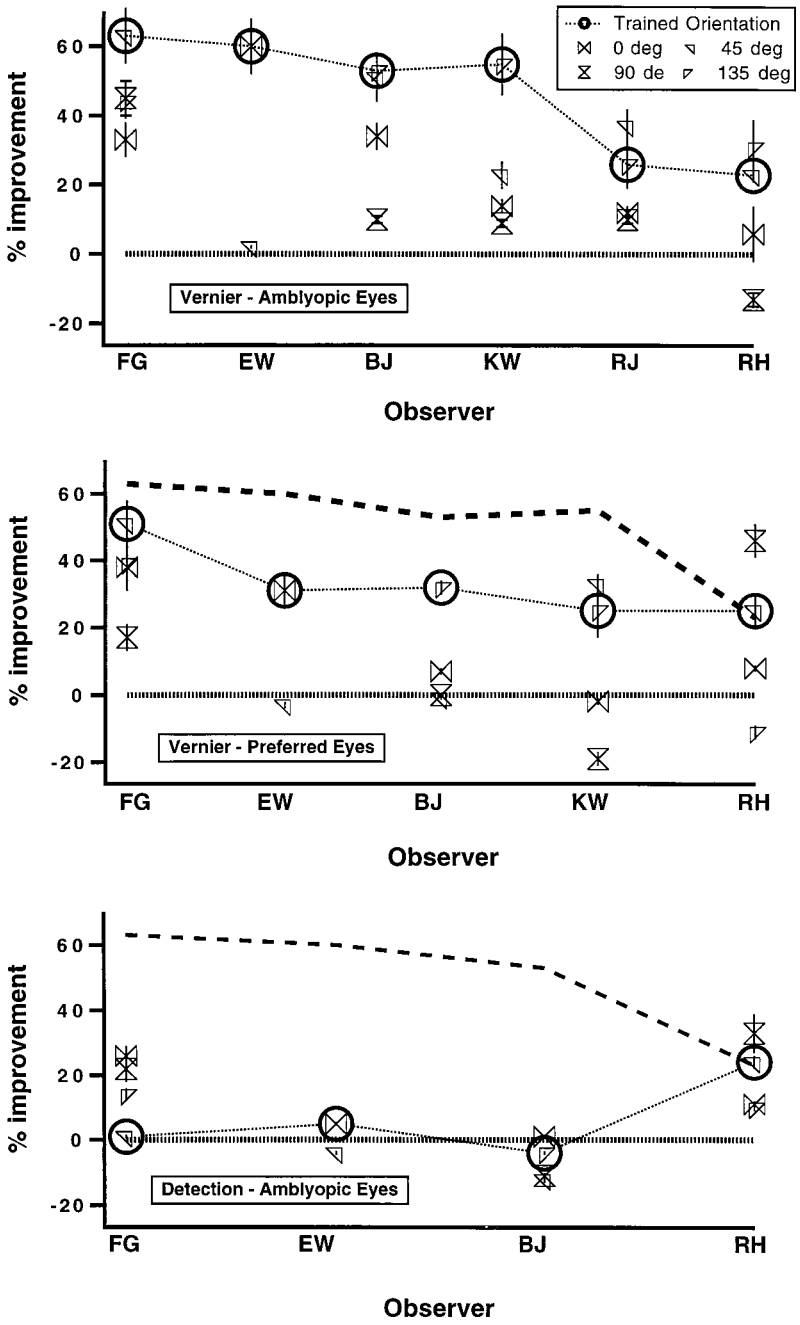

FIG. 2. Percent improvement (pre- to posttraining) for each observer. The horizontal line represents no change. (*Top*) Improvement in the trained (amblyopic) eye at each orientation. In each panel the trained orientation is enclosed in a circle. (*Middle*) Improvement in the untrained eye (the heavy dashed line indicates the improvement in the trained eye at the trained orientation; note that the number of observers in each panel differs). (*Bottom*) Improvement in the untrained (detection task).

entation. At the neighboring orientation (0° for EW, and 90° for the others), improvement was considerably reduced (11 ± 8%); averaged across all of the untrained orientations, it was 21 ± 5%. EW and KW showed substantial improvement at the trained orientation, with little improvement in the untrained conditions. On the other hand, some observers showed considerable transfer to untrained orientations, suggesting some generalized learning too. Our finding of strong improvement at the trained orientation and weak improvement at the other orientations suggests that both cognitive and neural factors can contribute to the improvement.

In contrast to the marked improvement in the (trained) Vernier task, there is very little improvement in the detection task (Fig. 2 *Bottom*, and confirmed by ANOVA). The mean improvement (and SEM) in detection thresholds is 7 ± 6% in the trained orientation and 9 ± 5% in the untrained orientations. Three of the four observers showed no improvement on the untrained task at the trained orientation. Thus, perceptual learning in amblyopia is task specific. It has been postulated that the amblyopic deficit in Vernier acuity reflects noise (or undersampling) at a stage in the visual pathway, beyond the site which limits detection (17, 18). If this view is correct, than it is tempting to speculate that the learning evident in our observers takes place at this later stage.

Fig. 2 *Middle* shows that there is substantial transfer to the untrained eye at the trained orientation. In this condition, the mean improvement is 33 ± 5%. At the neighboring orientation the mean improvement is considerably smaller (8.2 ± 9.9%),

and averaged across all untrained orientations it is 12 ± 6%. Thus, our results show partial transfer of learning to the untrained (nonamblyopic) eye. The transfer averaged ≈62% (± 6.3%) of the direct learning effect in the trained orientation. This partial transfer was significant for the trained orientation, but not for the untrained orientations (23 ± 12% for the untrained orientation of the untrained eye relative to the trained orientation in the trained eye, and 20 ± 28% for the untrained orientation of the untrained eye relative to the untrained orientation of the trained eye). Transfer to the other eye has been reported in previous studies (5, 7, 9) in observers with normal vision. We believe that our results reflect, at least in part, neural learning beyond the site of binocular convergence rather than a general learning. The main argument to support this contention is that the transfer is significant for the trained orientation and not for the untrained orientations. In this context, it is interesting to note that both humans (19) and cats (20) with amblyopia retain neural interactions between the two eyes that are tuned to orientation.

Following the initial practice and posttesting, several observers underwent another round of practice at a new orientation (Fig. 3 and Table 1). Three showed significant improvement at the new orientation, and FG and BJ maintained the level of improvement achieved after the initial training (EW did not complete the study). The most experienced observer (RH) did not show significant improvement at any other orientation.

DISCUSSION

Our results provide evidence for substantial plasticity in the visual cortices of human adults with naturally occurring amblyopia. Our six observers showed substantial perceptual learning of Vernier acuity. The approximately 46% average improvement in Vernier acuity in the trained orientation is identical to the 46% average improvement in *peripheral* orientation discrimination recently reported (7). Since all but one of our observers had substantial previous experience with Vernier acuity, our study may underestimate the degree to which learning can occur in the visual system of adults with amblyopia. Our observers, like normal observers, show substantial improvement in oblique Vernier acuity (15); however, in amblyopes, perceptual learning is not limited to the oblique meridian. EW showed approximately 60% improvement in horizontal Vernier thresholds. Interestingly, following the training, EW's horizontal Vernier thresholds had improved from 0.64 ± 0.05 min to 0.26 ± 0.03 min, comparable to the posttraining thresholds in her preferred eye (0.26 ± 0.02 min), and following completion of these experiments, her Snellen acuity had improved from a minimum angle of resolution of 4 arc min (20/80) to 1.1 arc min (20/22). This improvement in acuity has important ramifications for the treatment of amblyopia. An absence of transfer between tasks would make rehabilitation difficult; on the other hand, the improvement in EW's acuity is rather encouraging and suggests that there may be a close connection (as noted previously) between Vernier and Snellen acuity (14).

The improvement observed is not likely to be a result of learning more accurate fixation or accommodation or other general strategies for viewing with an amblyopic eye. Recall that five of our observers had previous experience (from a few thousand to over a million trials) in making Vernier judgments with their amblyopic eyes. In these observers fixation and accommodation would be expected to be stable, as would their cognitive strategy, yet each showed a significant improvement in performance at the new orientation. Moreover, the absence of transfer of learning to the untrained task makes it difficult to fully explain the training effects in terms of some generalized cognitive change over time or by learning to focus and fixate with an unpracticed eye. Thus, we argue that the improvement in performance reflects the effects of genuine neural plasticity.

We found that improvement was both orientation- and task-dependent. The task and orientation specificity are both strong arguments for learning in orientation tuned neurons, possibly due to fine tuning (or calibration) of the mechanisms mediating the task (13, 15, 21). Interocular transfer of learning provides evidence for the view that learning occurs at or beyond the primary visual cortex where binocular interactions have been reported, perhaps at or beyond V1 (22). Neither the physiological nor the biochemical basis for neural plasticity is fully understood (21, 23); however, there appear to be at least two processes at work. (*i*) A slow process that involves neural modification and requires consolidation (8, 24), so learning occurs between sessions (Fig. 1 *a* and *c*). This process is highly specific and long-lasting. (*ii*) A rapid (5, 25) process (within a session, see Fig. 1 *a* and *b*, first session), which appears to have a different neural basis. Both of these processes may be at work in our observers, and both may contribute to the fine tuning of neural circuitry in the visual cortex (13, 15, 21, 24, 25).

The present results suggest that some adults with amblyopia retain a degree cortical plasticity, which is consistent with

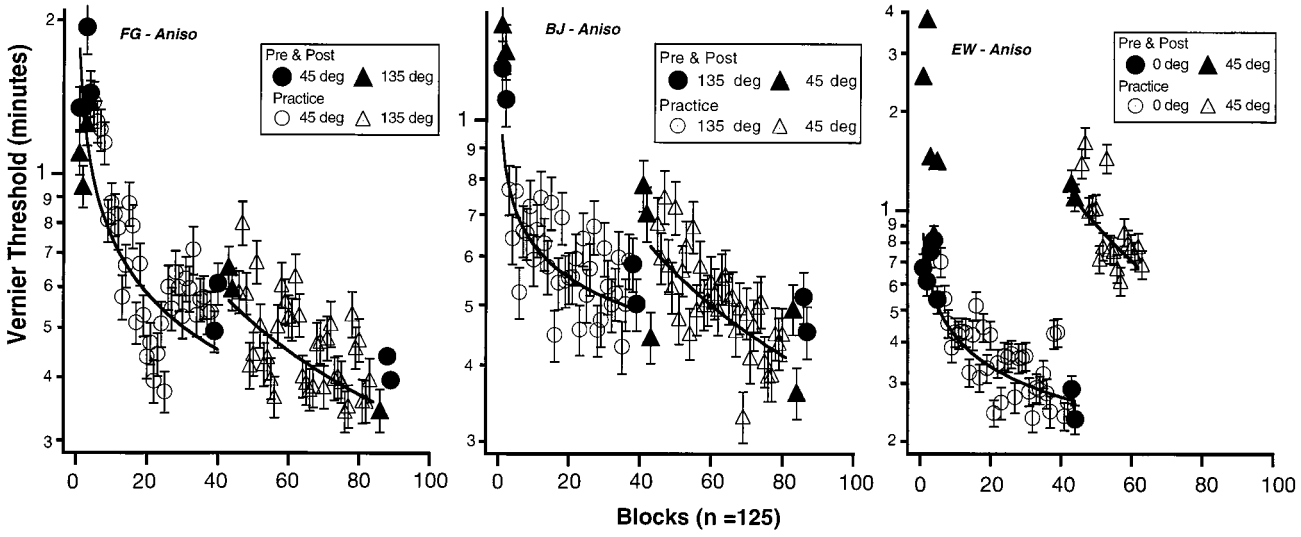

FIG. 3. The results of three observers who underwent a second round of practice at a new orientation. The lines are regression lines fit to the entire training set.

recent evidence for plasticity in the visual cortex of adult cats with experimentally induced retinal lesions (26, 27). They are surprising because the physiological effects of strabismus or lid suture on the cortex are generally thought to be irreversible after a critical period (28). Although it is often stated that amblyopes cannot be treated beyond a certain age, a careful review of the literature suggests otherwise (29–31). Our results raise some interesting questions about the treatment of amblyopia. The "standard" treatment for amblyopia consists of patching the preferred eye (1). While anatomical and physiological studies suggest that early reverse occlusion operates to reverse the physiological dominance of the deprived eye, the mechanisms of improvement in acuity in older children (and adults) are unknown, although it is clear that treatment is frequently quite effective in improving visual acuity. Perhaps the improvements evidenced in clinical treatment of amblyopia represent the effects of the plasticity documented here.

We thank Dr. Hiro Akutsu for help with statistical analysis. We are most grateful to Drs. Tina Beard, Yuzo Chino, and Suzanne McKee and two anonymous reviewers for their insightful comments on an earlier version of this paper. This work was supported by Grant R01EY01728 from the National Eye Institute.

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