Recovery of Contour Integration in Relation to LogMAR Visual Acuity during Treatment of Amblyopia in Children

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PURPOSE. In several studies, researchers have found that integration of orientation information along contours defined by Gabor patches is abnormal in patients with strabismus and in untreated patients with anisometropic amblyopia. In this study, the rate and degree of recovery of contour-integration deficits were compared with the recovery of logMAR (logarithm of the minimum angle of resolution) visual acuity deficits in patients newly diagnosed with amblyopia secondary to anisometropia, strabismus, or both.

METHOD. Contour-detection thresholds and optotype acuity were measured in 17 newly diagnosed anisometropic amblyopes, in 6 patients with strabismic amblyopia, and in 4 patients with combined anisometropic and strabismic amblyopia. Contour-detection thresholds were measured with a card-based procedure. Treatment comprised full refractive correction and full-time total occlusion therapy, when necessary. Visual function was measured at monthly visits during the course of treatment, with an average follow-up period of 16 weeks (12–24 weeks) for the entire group. Complete data were obtained from 25 patients through 8 weeks of follow-up.

RESULTS. Significant interocular differences in contour-detection thresholds were present in 16 of the 23 patients at the first visit after initial refractive correction. Interocular differences in contour-detection thresholds declined to normal levels in most of the patients within 8 weeks of the initiation of treatment. Interocular acuity differences remained significant in many of the patients (19/23) at 8 weeks of follow-up and continued to decline, but did not fully normalize, over the remainder of the follow-up period.

CONCLUSIONS. Refractive correction alone or in combination with occlusion therapy produces a normalization of contour-integration thresholds in amblyopia that is more rapid and complete than that achieved for visual acuity. (Invest Ophtalmol Vis Sci. 2004;45:4016 – 4022) DOI:10.1167/iovs.03-0795

A reduced acuity for reading letters is a defining feature of amblyopia,1 although acuity is also reduced for gratings2,5 and vernier offsets.2,4,7 Contrast sensitivity is also degraded in amblyopia.3,6,7 Letter, vernier, and grating acuities are each limited by the highest spatial frequency that can be resolved by the amblyopic eye. Beyond this, letter and vernier acuities appear to be limited additionally by spatial uncertainty or spatial distortion.8-10 The drawings of suprathreshold gratings made by amblyopic observers show this effect clearly. Although the lines of the gratings are well resolved, their appearance can be highly distorted.8 This simple demonstration indicates that the amblyopic deficit persists well below the resolution limit.

It has been reported recently that many amblyopic observers are unable to detect contours defined by chains of Gabor elements embedded in random Gabor-element backgrounds, even though they can resolve the patches one from the other and register the patches’ orientations.11-15 Similar deficits have also been found in dyslexia.16 Examples of one version of this task are shown in Figure 1. The primary limiting factor in this task is not resolution or contrast sensitivity, but rather the ability to detect collinear sequences of elements.11,15,16 Because natural images show a preponderance of collinear edge co-occurrences,15 selective pressure during evolution may have caused the visual system to become particularly efficient at extracting collinearity as part of the shape-recognition process.

The normal developmental sequences for low-spatial-frequency contrast sensitivity and grating, vernier, and letter acuities differ substantially.17 This is not surprising, given that the detection of gratings is limited by resolution, whereas vernier and letter acuities are also limited by the accuracy of relative position encoding. Visual functions with different developmental sequences may have different critical periods, during which the elaboration of that function is dependent on normal visual experience.18 In several studies, investigators have examined the recovery of contrast sensitivity and letter acuity during treatment for amblyopia.19-24 Whereas both contrast sensitivity and acuity generally improve with therapy, improvements on one function are not highly predictive of improvements on the other. A similar dissociation in recovery rates has been seen with motion-defined letter acuity versus high- and low-contrast letter acuity,25 and with various letter acuity tests and Vernier and displacement thresholds within the same patients.26

The contour-integration task differs from these tasks primarily in its requirement for integrating collinear orientation information over long distances. Contour-detection thresholds (CDTs) continue to mature until middle adolescence,27 well after development of contrast sensitivity and grating acuity is complete.28,29 The very long developmental sequence for contour integration suggests that the critical period for this function may be longer than for other functions that mature earlier and, correspondingly, that this function may be readily modified by treatment.

In the present study, CDTs and logMAR (logarithm of the minimum angle of resolution) acuity were first measured before treatment for amblyopia and then at intervals as amblyopia was being treated with refractive error correction and occlusion therapy. Occlusion therapy was applied if the refractive correction alone did not equalize visual acuity (VA). Both visual

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functions were measured at monthly intervals to quantify the relative rate of change in performance of the two study measures during the course of treatment. In our study, occlusion therapy reversed contour-integration deficits that were initially present in untreated amblyopes, and the reversal was more complete than that obtained for letter acuity.

**METHODS**

**Patients**

Twenty-seven children (age range, 4.40–15.75 years; mean age, 7.02; 13 males, 14 females) presenting with previously untreated amblyopia were recruited to the study. Amblyopia was defined as 0.2 or more log units of interocular acuity difference (IAD). Anisometropia was defined as a >1.00-D power difference between the two eyes in the most anisometropic meridian (see the Appendix). Strabismic amblyopes had a measurable deviation of >4 prism diopters on a prism cover test for distance fixation.

**Protocol**

At recruitment to the study (initial visit), the children underwent a detailed ocular and orthoptic examination, including cycloplegic retinoscopy (cyclopentolate 1% drops) and a dilated fundus examination. Ocular alignment was measured with prism cover–uncover and alternate-cover tests. Ocular movements were assessed in nine positions of gaze and the 4-D base-out prism test (4 DBO) was performed on each patient with no apparent ocular deviation (all anisometropic amblyopes). Each patient was classified on the basis of the examination as anisometropic (A), strabismic (S), or strabismic with anisometropia (SA). Based on the initial examination, full refractive correction (reduction for working distance only) in the form of spectacles was prescribed, and the patient was advised to wear them full time for 2 to 4 weeks before the first baseline visual function assessment visit (0 weeks), which constituted the commencement of the study. Longitudinal follow-up was performed after the baseline at 4-week intervals (±1 week; visits 4, 8, 12, and 16 weeks; the time points are the number of weeks from the initial visit).

Careful verbal questioning of the parent and child was used to assess compliance with treatment. Appropriate encouragement was given at each visit. Compliance was graded good, satisfactory, or poor based on an assessment by experienced examiners. It was graded good when all instructions regarding spectacle wear and occlusion therapy had been followed, satisfactory when reasonable explanations were given for breaks in treatment due to illness or sporting activities such as swimming, and poor when parents gave uncertain answers to carefully questioned or admitting noncompliance due to the child’s behavioral objection to occlusion.

At each visit, monocular logMAR VA thresholds and CDTs were measured, with the order of testing randomized across sessions. The examiner was masked to results obtained in the previous visit until the acuity and contour thresholds had been recorded. The examiner then examined the notes from the previous visit. In addition, the orthoptic examination was repeated. Cycloplegic refraction was repeated at four to six times at monthly intervals, timed from the recruitment date. If acuity in the amblyopic eye did not improve by 0.1 logMAR over two consecutive visits, full-time total occlusion therapy was instituted. For the purposes of initiating occlusion therapy, the VA measured at the initial visit was taken as the first visit value. Occlusion was achieved by means of an appropriately sized adhesive patch with instructions that it was to be applied “first thing in the morning and to be taken off last thing at night.” Occlusion therapy was continued until acuity failed to improve over two consecutive visits, again by 0.1 logMAR. The therapy was discontinued and the best acuity achieved with occlusion therapy was noted. The local ethics committee approved the protocol, and verbal informed consent was obtained from the parents, as well as assent from the participant when appropriate for age. The study protocol was in compliance with the tenets of the Declaration of Helsinki.

**Contour-Detection Test.** Contour stimuli were presented in a card format, and CDTs were measured with a staircase procedure, described later. The contour card set comprised 15 cards. Each card measured 18 × 24.5 cm. Within each card, a nearly circular contour comprising 12 Gabor elements was embedded in a random Gabor background. The contour was located near one of the four corners of the card. The carrier spatial frequency of the Gabor elements was 5 c/deg at a test distance of 50 cm. Inter-element spacing along the contour was fixed at seven wavelengths of the carrier, center to center (1.4°). Contour visibility was varied by varying the average density of the background Gabor elements while holding the contour-element spacing constant. CDTs in adult normal subjects and those with amblyopia are determined primarily by the ratio of background element to contour element spacing. We will refer to this ratio as Δ. The parameter Δ varied between 1.2 and 0.50 in steps of 0.05 across the set of 15 cards used to measure thresholds. At a Δ-value of 1.2, the contour can be detected on the basis of a first-order texture density cue. Contour detection at Δ values of 1 or less can only be accomplished through the detection of the relative orientation of elements along the contour (second-order orientation). Figure 1 presents sections of the cards containing contours for Δ of 1.15, 0.95, 0.80, and 0.65. Normal adult thresholds average 0.65. Monocular thresholds in normal children range from 0.8 in 5- to 6-year-olds to 0.7 in 10- to 14-year-olds.

**Procedure.** Monocular CDTs were measured. Patients were tested with full spectacle correction—that is, that determined by cycloplegic retinoscopy. For the initial visit, all children were naive and were familiarized with the test with practice cards containing highly visible contours. The children were informed that the contour could be in one of the four locations and they were encouraged to scan the four corners of the card to determine the contour shape before providing their responses (four-alternative choice). The practice cards (two) were rotated several times, and the children responded on the basis of the instructions given. The test proceeded when the responses indicated that the child understood the procedure.
Table 1. Patient Characteristics of the 23 Children Who Completed the Required 8-Week Follow-up

| No. | Age | Diagnosis | Sph | Cyl | Axis | Sph | Cyl | Axis | MAM | VA AE | VA NAE | VA DIFF | CT AE | CT NAE | CT DIFF |
|-----|-----|-----------|-----|-----|------|-----|-----|------|-----|------|--------|---------|--------|-------|---------|---------|
| 1   | 4.40| Aniso     | 4.25| 0.50| 90   | 3.25| 0.00| 0    | -1.50| 0.30 | 0.00   | 0.30    | 0.90   | 0.75   | 0.15    |
| 2   | 4.67| Aniso     | 6.25| 1.75| 110  | 1.00| 0.25| 180  | -6.91| 1.00 | 0.20   | 0.80    | 1.20   | 0.85   | 0.35    |
| 3   | 5.27| Aniso     | 0.00| 3.00| 100  | 2.00| 0.25| 90   | 2.08 | 0.90 | -0.10  | 1.00    | 0.95   | 0.95   | 0.00    |
| 4   | 5.60| Aniso     | 4.00| 1.00| 90   | 0.75| 0.00| 0    | -4.25| 1.00 | 0.00   | 1.00    | 1.05   | 0.85   | 0.20    |
| 5   | 7.45| Aniso     | 4.00| 0.50| 75   | 1.25| 0.00| 0    | -3.25| 0.60 | 0.00   | 0.60    | 0.95   | 0.95   | 0.00    |
| 6   | 8.13| Aniso     | 0.00| 4.50| 140  | 0.00| 0.00| 0    | 4.00 | 0.50 | 0.00   | 0.50    | 0.95   | 0.80   | 0.15    |
| 7   | 8.35| Aniso     | 7.00| 2.00| 90   | 1.25| 0.00| 0    | -7.75| 0.90 | -0.10  | 1.00    | 1.20   | 0.95   | 0.25    |
| 8   | 8.40| Aniso     | 6.25| 0.25| 90   | 2.50| 0.25| 180  | -3.97| 0.30 | 0.00   | 0.30    | 0.80   | 0.80   | 0.00    |
| 9   | 8.76| Aniso     | 7.00| 0.50| 30   | 1.25| 0.00| 0    | -6.25| 0.80 | 0.10   | 0.70    | 0.95   | 0.85   | 0.10    |
| 10  | 9.06| Aniso     | 4.00| 1.50| 150  | 2.00| 0.50| 180  | -3.39| 0.20 | 0.00   | 0.20    | 0.95   | 0.85   | 0.10    |
| 11  | 9.24| Aniso     | 2.50| 3.00| 100  | 2.25| 0.00| 0    | -3.00| 0.30 | -0.10  | 0.40    | 0.95   | 0.85   | 0.10    |
| 12  | 9.45| Aniso     | -3.00| 2.75| 10   | -1.00| 1.00| 180  | 2.17 | 0.60 | 0.00   | 0.60    | 0.95   | 0.80   | 0.15    |
| 13  | 10.22| Strab | 7.00| 0.50| 85   | 0.25| 2.50| 155  | 6.79 | 0.90 | -0.10  | 1.00    | 0.90   | 0.80   | 0.10    |
| 14  | 11.82| Aniso/strab | -2.75| 5.00| 105  | 0.00| 0.50| 70   | 2.85 | 0.30 | -0.20  | 0.50    | 0.80   | 0.80   | 0.00    |
| 15  | 15.75| Aniso     | 2.50| 0.75| 90   | 0.25| 0.00| 0    | -3.00| 0.60 | 0.00   | 0.60    | 1.00   | 0.75   | 0.25    |

Mean 8.44  SEM 2.18

Refractive errors for each eye (RE, right eye; LE, left eye) are presented and the power difference at the most anisometropic meridian (MAM) calculated for each child. Optotype acuities are presented as logMAR and contour thresholds are presented in Δ units. Descriptive statistics for continuous variables are presented as the mean ± SEM. Sph, sphere; Cyl, cylinder; NAE, nonamblyopic eye; AE, amblyopic eye; DIFF, difference; VA, visual acuity; CT, contour threshold; Aniso, anisometropia; Strab, strabismus; Aniso/strab, anisometropia and strabismus.

All participants were tested in a staircase paradigm that required a correct response for at least two of three presentations of the same card. The cards were reversed on representation at random to allow progression until incorrect responses led to a step down the staircase (reversal). Three reversals at adjacent cards were needed to define the threshold. The observer was not masked to the contour position. Most subjects indicated the contour by pointing at the contour, or they were encouraged to trace around the contour with the finger (without touching the card), to increase interest and motivation. Verbal indication that the contour was in a particular corner was not sufficient. Children were not given negative feedback when they were incorrect. They received verbal encouragement, even if the contour was identified incorrectly to maintain interest in the test. The child was thus not made aware of incorrect responses and continued to attempt to identify contours on the cards presented by the observer. However, the observer followed the rules of the staircase and kept a tally of correct versus incorrect responses and presented cards accordingly, to determine a reliable threshold.

We have previously established that, when this staircase is used in children, test-retest reliability is such that interocular differences of 0.10 Δ units (two or more cards) are significantly greater than the measurement error and are therefore indicative of a significant interocular difference in the contour-detection threshold.

**Lea Symbols LogMAR Acuity Test**

Monocular acuity thresholds were measured with Lea symbols at the recommended test distance of 3 m. The amblyopic eye was always checked first. The patient was asked to recognize the central symbol of each alternate line. When the patient failed to identify the central symbol correctly, the line above was tested for all symbols. The acuity threshold was the line on which four of five symbols were identified correctly. Acuity was checked twice in each eye, and, if acuity improved by one line on the second test, the measurement was repeated. The best acuity was noted.

**Analysis**

The experimental design had two within-subject factors, time and eye, and one between-subject factor, diagnostic category. Factor effects were assessed using a multivariate analysis of variance (MANOVA; SPSS Science, Chicago, IL) module for repeated measures. Wilks' likelihood ratio was used to derive estimates of F-ratios for significance testing. The dependent variables VA and CDT were tested in separate MANOVA analyses. Of the 27 children who attended the initial visit, 23 attended at appropriate study intervals until the visit at 8 weeks. Therefore, the week-8 visit was taken as the end point for analysis. Five children at the week-12 and additional six children at the week-16 visits did not return at appropriate study intervals and were excluded from further analysis. For the remaining 12 children who attended at appropriate study intervals, descriptive statistics are presented.

**Results**

Table 1 describes the patients’ characteristics and measurements performed on the two visual functions at the initial visit for the 23 of 27 children with complete data through 8 weeks.
be seen by the decline in interocular differences from 0.14 to 0.04 by 8 weeks. Interocular differences were within expected values for normal subjects by 4 weeks after initiation of treatment.

In the 23 children who attended on all three visits (0, 4, and 8 weeks), both VA (F2,19 = 22.95, P < 0.001) and CDT (F2,19 = 13.67, P < 0.001) changed significantly over time after treatment began. The differences between amblyopic and dominant eyes were significant (VA, F1,20 = 60.29, P < 0.001; CDT, F1,20 = 25.47, P < 0.001). Most important, the interaction between eye and time was significant for both variables, showing that interocular differences changed strongly (diminished) over time (VA, F2,19 = 12.73, P < 0.001; CDT, F2,19 = 10.58, P = 0.001). There was no significant interaction between time and amblyopia type for either of these measurements, suggesting that there were no temporal differences in the way the children responded to treatment (VA, F4,38 = 2.09, P = 0.101; CDT, F4,38 = 0.45, P = 0.770). Nor was there any significant interaction between amblyopia type and eye (VA, F2,20 = 2.13, P = 0.145; CDT, F2,20 = 0.12, P = 0.887), indicating that differences between eye did not differ between amblyopia types. Finally, there was a strong three-way interaction between time, eyes, and amblyopia type for VA (F4,38 = 5.64, P = 0.001), clearly supporting the hypothesis that the change in IAD over time differs between amblyopia types. However this interaction was not significant for CDT (F4,38 = 0.74, P = 0.571).

After 8 weeks, CDT thresholds and interocular differences were stable over 12 and 16 weeks in the 12 remaining patients. Significant mean IADs persisted at 12 (0.42 ± 0.07 [SD]) and 16 (0.29 ± 0.05) weeks. There were no significant interocular differences in CDT at these time points.

**DISCUSSION**

Amblyopia, defined on the basis of reduced logMAR acuity, resulted in deficits in CDT in almost all cases. These deficits were usually more pronounced in the amblyopic eye, but mean thresholds were elevated in the dominant eye, as well. In earlier retrospective work involving a group of adults with amblyopia, CDTs were elevated in the dominant eye and in both eyes of nonamblyopic patients with strabismus. Deficits in mean logMAR acuity were not found in the dominant eye, either in the present study, once refractive error had been corrected, or in our previous study. Deficits in the dominant eye have been reported previously on motion-defined forms and contrast sensitivity. The fellow eye deficits in the present study were measured before the initiation of occlusion therapy and thus do not constitute occlusion amblyopia. Rather, the defects in the fellow eye are consistent with a failure of development in the absence of normal binocular interaction.

Both logMAR acuity and contour detectability improved with treatment, with interocular differences in CDT being absent by 8 weeks, despite the persistence of significant IADs. Interocular CDT differences remained within normal levels at 12 and 16 weeks, but IADs persisted. Treatment was thus able to normalize interocular differences for CDT, but not for acuity.

It is possible that the more complete recovery of CDTs occurred because they were less severely disrupted by amblyopia. Comparing the relative severity of losses on the contour and acuity tasks is difficult, because the underlying scales are different. One task is limited by spatial noise and the other by resolution and fine position sensitivity. Alternatively, the differential recovery rates of contour integration and acuity may be due to the retention of a greater degree of residual plasticity in the neural mechanisms responsible for contour detection.
The retention of a greater degree of plasticity may be the result of a longer developmental critical period for contour integration and/or a greater susceptibility to treatment. Different visual functions have different developmental sequences, and presumably this entails differential sensitivity to disruption by abnormal visual experience.17,18 Our results indicate that normalization of interocular differences can be accomplished over a shorter time for CDT than for acuity.

Regarding the inherent plasticity of contour-detection mechanisms, it has been suggested that contour integration relies, at least in part, on the network of long-range horizontal connections in early visual areas.16,33,34 These connections appear to retain plasticity over a much longer period than do vertical connections that connect layers within cortical hypercolumns.35 Adults show strong perceptual learning effects, another form of plasticity, in a related lateral masking task that involves detection of low-contrast patches surrounded by collinear flankers.36

The Role of Practice Effects

The measured improvements in performance represent a combination of the effects of treatment and a potential contribution of practice in performing the tests. The contour-integration task is a novel one, unlike reading a letter chart, for which all participants had considerable experience in the context of reading other materials. Improvements in performance of 0.022 ± 0.051 Δ unit have been reported across four repeated tests taken on the same day,34 0.1 Δ unit across three repeated tests on three successive days in 5- to 6-year-olds, and 0.05 Δ unit in adults.27 These effects are substantially smaller than the measured improvements in the amblyopic eye (0.16 Δ) but are more similar to the effects in the dominant eyes (0.05 Δ). Note, however, that the initial visit scores on contour integration were almost all above the normal monocular mean obtained without practice (Fig. 2). Thus, it is unlikely that the effects over time were solely due to practice effects or that the deficit in the dominant eyes on initial testing was artifactual.

Spectacle Versus Occlusion Effects

Some degree of improvement occurred with spectacle correction alone, although 8 of 15 children with anisometropic amblyopia went on to have occlusion therapy (occlusion group) in comparison to 7 children who improved with spectacles alone. When we analyzed the two subgroups, there was no statistically significant difference (P > 0.05; t-test, two-tailed) in age at presentation, but there was a statistically significant difference between the two groups in amblyopic eye acuity and IAD at presentation (the initial visit). These differences did not remain significant at subsequent visits (4 and 8 weeks), which indicates that occlusion therapy is not necessary in all anisometropic amblyopes, with an indication from our study that children presenting with mean amblyopic eye acuity of 0.79 ± 0.27 (SD) and IAD of 0.79 ± 0.29 are more likely to need occlusion therapy. For comparison, the nonocclusion group’s mean amblyopic eye acuity was 0.41 ± 0.15 logMAR, and their mean IAD was 0.46 ± 0.13 logMAR. Improvement in amblyopic eye acuity with refractive correction alone has been reported,37 with patients with less than 3 D of anisometropia
more likely to improve with refractive correction alone. In our study the spherical equivalent difference for the two groups (nonocclusion group, 2.23 ± 1.24 [SD]; occlusion group, 3.98 ± 1.99) did not achieve statistical significance ($P = 0.07$, one-tailed $t$-test). However, it was true in our study that a mean spherical equivalent difference of more than 3 D was likely to result in the use of occlusion therapy as part of management of amblyopia. Improvements in contrast sensitivity of both eyes with spectacle correction alone have also been reported.38

**Functional Significance of Contour-Integration Deficits**

The contour-detection task relies on ability to detect the global shape of the contour based on the integration of collinear orientation information along the contour. Collinearity is a prominent feature of natural images15 and its extraction is thought to play an important role in detecting the bounding contours and thus the shape of objects. Contour-integration deficits have also been reported in dyslexia,14 suggesting a role for these mechanisms in pattern recognition and discrimination that is independent of spatial resolution.

**Possible Neural Substrates of the Contour-Integration Task**

Successful performance of the contour-integration task appears to rely on a combination of striate and extrastriate areas. Functional magnetic resonance imaging (fMRI) in humans has shown contour-specific activity in areas V1 and V2, but the largest activations were in the lateral occipital complex (LOC), an area of occipitotemporal cortex thought to be involved in object processing.39,40 Functional MRI activation has also been found in V1 and V2 in the macaque for contour in noise targets.39 Single-unit recordings in V1 of the alert macaque have found evidence for a facilitatory interaction between elements along Gabor-defined contours.41 Such facilitatory interactions may rely on the network of horizontal intrinsic connections present in early visual areas or on feedback connections from higher-level visual areas, such as the LOC, onto lower level areas, such as V1 or V2.

**CONCLUSION**

Refractive correction alone, or in combination with occlusion therapy produces a normalization of contour-integration thresholds in amblyopia that is more rapid and complete than that achieved for VA.

**APPENDIX**

Our calculation of anisometropia was derived from Morgan and Peters42 by the Cooperative Amblyopia Classification Study (CACS) steering committee.15

**Definition of Terms**

$A = \text{cylinder amplitude (right eye)}$

$B = \text{cylinder amplitude (left eye)}$

$C = \text{computed anisometric cylinder induced by cylinder}$
Formulae

\[ C^2 = A^2 + B^2 - 2AB \cos(2\text{abs}(AR - AL)) \]

\[ D = \frac{|C - (A - B)|}{2} \]

\[ E = D - (F - G) \text{ if } A > B \]

\[ E = D - (F - G) \text{ if } A < B \]

\[ \text{MAM} = E - C \text{ if } E < C/2 \]

\[ \text{MAM} = E \text{ if } E \geq C/2 \]

\[ \text{LAM} = E - C \text{ if } E > C/2 \]

\[ \text{LAM} = E \text{ if } E \leq C/2 \]

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