



Visual search performance of patients with vision impairment: effect of JPEG image enhancement

Gang Luo, PremNandhini Satgunam and Eli Peli

Schepens Eye Research Institute, Massachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School, Boston, USA

Citation information: Luo G, Satgunam P & Peli E. Visual search performance of patients with vision impairment: effect of JPEG image enhancement. *Ophthalmic Physiol Opt* 2012, **32**, 421–428. doi: 10.1111/j.1475-1313.2012.00908.x

Keywords: central vision loss, image enhancement, low vision rehabilitation, visual search

Correspondence: Gang Luo
E-mail address: gang.luo@schepens.harvard.edu

Received: 6 January 2012; Accepted: 15 March 2012

Abstract

Purpose: To measure natural image search performance in patients with central vision impairment. To evaluate the performance effect for a JPEG based image enhancement technique using the visual search task.

Methods: One hundred and fifty JPEG images were presented on a touch screen monitor in either an enhanced or original version to 19 patients (visual acuity 0.4–1.2 logMAR, 6/15 to 6/90, 20/50 to 20/300) and seven normally sighted controls (visual acuity –0.12 to 0.1 logMAR, 6/4.5 to 6/7.5, 20/15 to 20/25). Each image fell into one of three categories: faces, indoors, and collections. The enhancement was realized by moderately boosting a mid-range spatial frequency band in the discrete cosine transform (DCT) coefficients of the image luminance component. Participants pointed to an object in a picture that matched a given target displayed at the upper-left corner of the monitor. Search performance was quantified by the percentage of correct responses, the median search time of correct responses, and an ‘integrated performance’ measure – the area under the curve of cumulative correct response rate over search time.

Results: Patients were able to perform the search tasks but their performance was substantially worse than the controls. Search performances for the three image categories were significantly different ($p \leq 0.001$) for all the participants, with searching for faces being the most difficult. When search time and correct response were analyzed separately, the effect of enhancement led to increase in one measure but decrease in another for many patients. Using the integrated performance, it was found that search performance declined with decrease in acuity ($p = 0.005$). An improvement with enhancement was found mainly for the patients whose acuity ranged from 0.4 to 0.8 logMAR (6/15 to 6/38, 20/50 to 20/125). Enhancement conferred a small but significant improvement in integrated performance for indoor and collection images ($p = 0.025$) in the patients.

Conclusion: Search performance for natural images can be measured in patients with impaired vision to evaluate the effect of image enhancement. Patients with moderate vision loss might benefit from the moderate level of enhancement used here.

Introduction

The leading cause of vision impairment particularly in the elderly population is age-related macular degeneration.¹ With a projected increase in this population, it is

important to devise and test effective rehabilitation techniques. Image enhancement has been suggested as a viable vision rehabilitation option for patients with vision impairment resulting from loss of visual acuity and or contrast sensitivity.^{2–5} Such techniques can be applied to

activities of daily living such as TV watching and internet use. A recent survey study⁶ has determined that visually impaired people have similar video viewing habits as normally sighted people, and most visually impaired people are interested in image enhancement technologies for TV watching and computer use.^{4,6}

Prior studies have found that visually impaired prefer image enhancement in both static images^{5,7,8} and videos.^{4,9,10} More specifically, it was found that patients preferred moderate level of enhancement, and rejected higher level of enhancement due to the unnatural appearance of the images.¹⁰ A similar preference for only moderate level of enhancement was also found for normally sighted observers.¹¹ While preference is an important criterion for determining the value of image enhancement, it is a subjective outcome. It is also important to objectively measure the functional benefits (i.e. improved performance) of the technology. It is possible that a technology that improves performance may not be preferred by the patients (e.g. bioptic telescopes that would help viewing in a sport arena may be rejected by a patient for cosmetic reasons). An optimal technology should be both preferred by the patients and aid their visual performance.

A few studies have reported the effect of image enhancement on functional visual performance for images.^{3,12,13} Peli *et al.*^{3,14} found improvement with adaptive enhancement, adaptive thresholding, and band enhancement for recognition of celebrities faces. Mei *et al.*¹³ tested enhancement filters preferred by each individual and reported improved recognition of facial expression.

Most of prior studies that examined visual search with impaired vision either used a feature search paradigm, where a square target was asked to be identified amongst distracters¹⁵ or had the subjects locate and identify the orientation of a Landolt's C target.¹⁶ In our study we used natural images (photos) that more closely represent real world tasks to evaluate the visual performance.

The visual search task was used to evaluate a JPEG based image enhancement. The preference for this kind of enhancement has been previously documented for both static image,⁷ and motion videos.^{9,10,17} Since JPEG was adopted for image compression in the 1990s, it has become the most popular static image format. It is well-suited for image storage and transfer because of its high compression and selectable image quality. Similar image compression technology has been adopted in video image coding (for spatial image compression), such as MPEG2 (used by DVD) and H.264 (commonly used in videos on Internet and portable devices). Current digital TV broadcasting also relies on JPEG based video compression technologies to provide many channels

within a limited bandwidth. It is not an overstatement that JPEG image compression is the foundation of modern image information transfer. With increasing dependence on electronic media for information dissemination, it is worthwhile to evaluate image enhancement for compressed images such as JPEG for vision rehabilitation applications. We need to determine if the image compression may interfere and/or restrict the ability to enhance JPEG images.

Methods

Subjects

Nineteen patients (nine males, age: 26–81 years, median 62 years) with binocular visual acuity of 0.4–1.2 logMAR (6/15 to 6/90; 20/50 to 20/300) were enrolled in the study. *Table 1* shows the distribution of these patients along with their ocular diagnosis. Seven normally sighted participants (three males, age: 21–75 years, median 62 years) with binocular visual acuity of 0.1 logMAR (6/7.5, 20/25) or better served as control subjects. All participants signed an informed consent. The study was approved by the institutional review board of Schepens Eye Research Institute and adhered to the tenets of the declaration of Helsinki.

Table 1. Age, sex, visual acuity (VA) distribution along with diagnosis is shown for the patients enrolled in the study

S. no	Age	Sex	VA logMAR (6/YY; 20/XX)	Diagnosis
1	71	Male	0.40 (15; 50)	Diabetic retinopathy
2	81	Female	0.40 (15; 50)	AMD
3	65	Male	0.48 (18; 60)	Angioid streaks
4	68	Female	0.48 (18; 60)	AMD
5	36	Male	0.48 (18; 60)	North Carolina retinal dystrophy
6	81	Female	0.60 (18; 80)	AMD
7	68	Female	0.70 (30; 100)	AMD
8	47	Male	0.70 (30; 100)	Coloboma, nystagmus
9	68	Female	0.80 (38; 125)	AMD
10	79	Female	0.80 (38; 125)	AMD
11	62	Female	0.9 (48; 160)	AMD
12	43	Female	0.90 (48; 160)	JMD
13	46	Male	0.90 (48; 160)	JMD
14	59	Female	0.90 (48; 160)	Myopic degeneration
15	26	Female	1.0 (60; 200)	ROP
16	54	Male	1.1 (75; 250)	Glaucoma, Retinal detachment
17	33	Male	1.1 (75; 250)	JMD
18	52	Male	1.2 (90; 300)	Myopic degeneration
19	62	Male	1.2 (90; 300)	JMD

AMD, age-related macular degeneration; JMD, juvenile macular degeneration; ROP, retinopathy of prematurity.

Stimuli

Static high definition images (1600 x 1200 pixels) in JPEG format were collected from websites such as Flickr and Google images. Images were classified into one of three categories namely faces, indoors and collections (*Figure 1*). The faces category comprised of images with small groups of people, such as sports teams, class pictures etc. Some (not all) images had people wearing uniforms and posing in a similar manner. The indoors category of images contained images of kitchens, living rooms etc. without any people. The collections images contained various objects from the same category such as shells, toys etc. These image categories were selected for specific reasons. Difficulty in face recognition is a common complaint of patients with central vision impairment.^{18,19} Searching for objects in indoor images is closer to real world search tasks, but a top-down knowledge could be used to locate the search targets (e.g. search for a flower vase on a table rather than on the ceiling) Therefore, the third category called collections was added, for which no such top-down knowledge could be applied.

Initially 300 images (100 in each category) were tested in a pilot study with 10 normally sighted individuals (who did not participate in the main study), half of whom wore a contrast-reducing filter to simulate low vision. Based on the average search time of the pilot subjects, 150 images (50 in each category) with shorter search times were selected for the main study. It was determined that the other images were too difficult for some patients, and would extend the experiment time beyond a practical limit.

JPEG image enhancement

Peli *et al.* have proposed an image enhancement method that directly boosts the amplitude (contrast) of mid spatial frequency bands of the quantization table in the JPEG or MPEG decoder.^{7,20} This technique can be performed at the receiver end and requires little

additional computation beyond what is normally done in decoding the transmitted image or video sequence. Using the same technique in this study, the discrete cosine transform (DCT) frequency table of each 8 x 8 pixel block in the JPEG images was multiplied with the filter shown in *Figure 2a*. Each cell in the filter table represents a particular spatial frequency component of the image block, with the upper-left cell being the average luminance, and the lower-right cell being the highest frequency in diagonal direction. The corresponding retinal spatial frequency in our set up for each of the horizontal DCT components is listed above the table (the same values apply for the vertical components). The enhancement filter we used boosts mid-range frequency, while the lower gain at low and high frequencies limits ringing artefacts in the images. Only the luminance component was modified, and the chromatic components were not changed.

Experimental task

Images were presented using a MATLAB program on a touch screen monitor (Multisync LCD 2090UXi, NEC, <http://www.nec.com>; 40.7 cm wide by 30.5 cm high; set at its native resolution 1600 x 1200 pixel; maximum brightness: 190 cd m⁻²). A target object preselected from each of the search images was presented on the upper left corner along with the search image on the screen (*Figure 3*). Subjects were asked to find the targets on the screen as quickly and quickly as possible. A 60-pixel (1.5 cm) wide tolerance zone around the target image was allowed. If the subject was unable to find the target he was encouraged to select the closest matching target or touch anywhere on the screen to begin the next trial. The response time was recorded as the time duration from an image onset to the touch response from the subject.

Subjects were seated at 40 cm, to permit comfortable reach over the entire area of the touch screen. The display was lowered on the stand to permit presbyopes to comfortably view through their reading aids. 150 images



Figure 1. Examples of the search images used in the study. Images were broadly classified into (from left to right) faces, indoors and collections. Given search targets were shown on the left corner in the experiment.

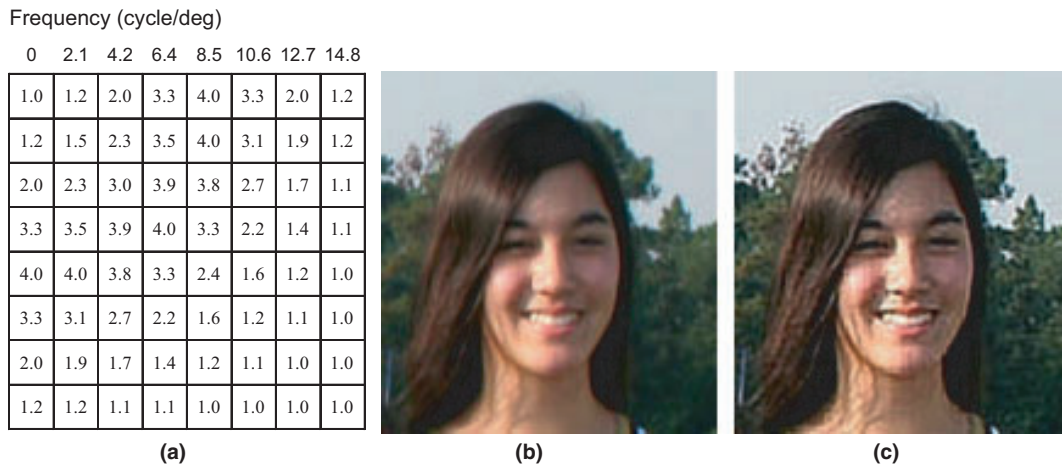


Figure 2. (a) The mid frequency bands in the JPEG quantization table are boosted directly in the JPEG decoder (shown here as scale coefficients larger than one). Retinal spatial frequencies corresponding to the quantization table are listed above the table. Examples (sub-images from the whole pictures) of original and enhanced images are shown in (b) and (c), respectively. The typical JPEG compression artefacts are visible in both images at this high magnification.



Figure 3. Visual search experimental set up. The subject's task is to find the object that matches the target displayed on the upper left corner of the monitor by touching the screen with the stylus.

(50 images per image category) were presented randomly, half of which were enhanced. A break was given after every 30 trials and at any other time if requested by the subject.

Data analysis

Conventional performance measures for visual search include percentage of correct response and median (or average) response time. These two legitimate measures quantify two different aspects of performance and they may change inconsistently from one testing condition to another. The result will be ambiguous when there is an improvement in one measure but a decrement in the

other. The usual practice to deal with this problem is to examine accuracy within a fixed time window, or examine the response time for a fixed accuracy. For instance, Smith *et al.*²¹ measured the search time for 100% correct response on normally sighted glaucoma patients, whereas Mei¹³ tested discrimination performance of facial expression within 0.73 s display duration. The selection of such a time window or accuracy is usually somewhat arbitrary. As the example in *Figure 4* illustrates, where search performances in two conditions are compared, if percentage of correct response is examined at an arbitrary 30 s search time or simply the median search time of each condition is used, performance in condition 1 would be better than condition 2. However, the final percentage of correct response in condition 2 is better than condition 1. In this study we added a novel measure that combines the two conventional measures that we call 'integrated performance'. As shown in *Figure 4*, the integrated performance measure is based on the cumulative percentage of correct response with increase in the search time. The area under the curve generated by the cumulative function is used as the integrated performance measure. Generally, a higher percentage of correct response and a shorter search time will result in a larger area under the curve, which represents better search performance. Having a unitary measure allows us to quantify performance more comprehensively and unambiguously. In the area computation, the search time ranging from the fastest response to the longest response for each individual was normalized to 1, and the percentage of correct response was not normalized. The best performance one can achieve by this computation is 1.

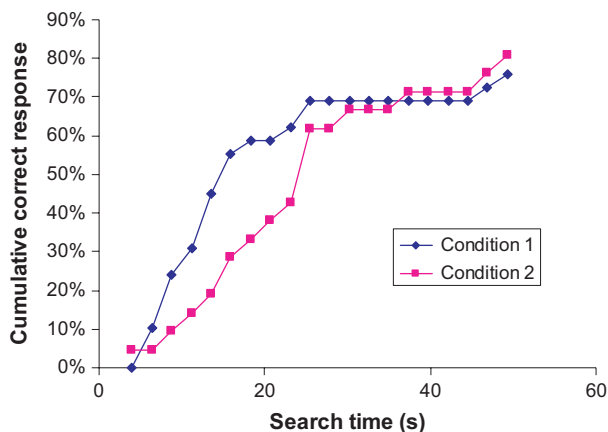


Figure 4. Illustration of cumulative correct response vs search time. These are real data from one subject used only to illustrate the analysis method. Here conditions 1 and 2 are universal, and they do not refer to any specific condition. Search performance can be quantified by the area under the curve, which combines both the percentage of correct response and the search time. A larger area, such as that of condition 1 here, represents a better performance. The area is computed with the longest response time normalized to 1 (not shown here). If measured by final correct response, performance in condition 2 would be better. If measured by median response time, performance in condition 1 would be better.

Repeated Measures of ANOVA was mainly used for statistical analyses of the percentage of correct response (accuracy), median search time and integrated performance measure using SPSS 11.5.0 (SPSS, <http://www.ibm.com>). In addition, a proportion test method was also used.

Results

For all the measures the control group performed substantially and significantly better than the patient group (average of the median search time: 2.3 vs 9.3 s; average accuracy: 99% vs 62%; average integrated performance: 0.81 vs 0.47; $p < 0.001$). Enhancement did not have a significant effect for the control group ($p > 0.12$).

By search time and integrated performance measures, image category was a significant factor ($p = 0.001$) for the control group. By accuracy measure, image category was not significant ($p = 0.7$), as it almost reached 100% for the control group (ceiling effect) with and without enhancement.

All the patients were able to perform the visual search task, but on average they were able to correctly identify about 60% of the targets (Figure 5). Both their search time and accuracy were significantly different across image categories ($F_{2,34} > 10$, $p < 0.001$). Visual search for the face images was the most difficult task, as it took the longest time and yielded the lowest accuracy. Among the three image categories, searching in the collection images was the least difficult task. The effect of enhancement was not statistically significant either for search time ($F_{1,18} = 1.29$, $p = 0.27$), or for accuracy ($F_{1,18} = 0.43$, $p = 0.52$). When individual’s differences in search time and accuracy between searching with and without enhancement were examined (Figure 6), it was found that there were many cases where the patients’ performance improved in one measure but declined in another (data points in the upper right and lower left quadrants). In order to avoid ambiguity, further analyses were conducted using the integrated performance measure.

A repeated measure ANOVA was carried out on the integrated performance with VA and age as covariates. Both the VA ($F_{1,16} = 10.6$, $p = 0.005$) and age ($F_{1,16} = 5.4$, $p = 0.034$) had significant effects on the integrated performance. The effect of enhancement was found to be not significant ($F_{1,16} = 0.95$, $p = 0.34$) when all categories were included. The image category was a significant factor ($F_{2,32} = 11.4$, $p < 0.001$). As Figure 7 shows, enhancement slightly improve search performance for the indoor and collection images, but not for the face images. This suggests that the face image search may be different from the others, as discussed in the discussion section. Excluding the face image category, the effect of enhancement was found to be significant ($F_{1,16} = 6.1$, $p = 0.025$) for the indoor and collection images.

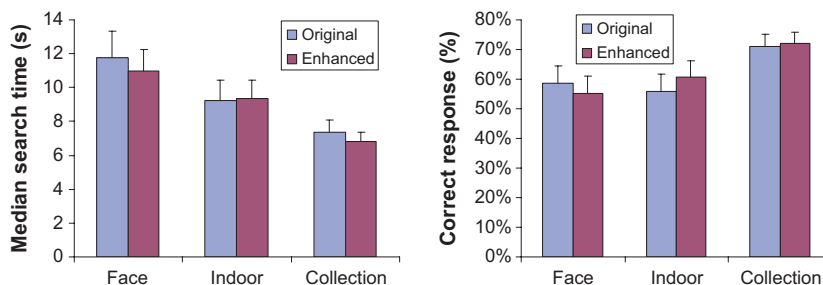


Figure 5. Search time and percentage of correct response (accuracy) performance of the patient group. Searching Face images seemed to be the most difficult task, and searching Collection images seemed to be the least difficult.

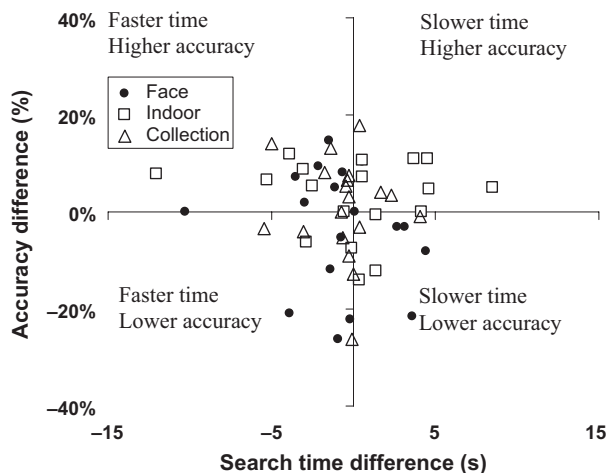


Figure 6. Differences between search with and without enhancement measured by search time and accuracy. Each data point represents performance difference of one patient for one image category. Points in the two upper quadrants represent improved accuracy, and points in the two left quadrants represent shorter search time. Points in the lower right quadrant represent decrement in performance on both measures.

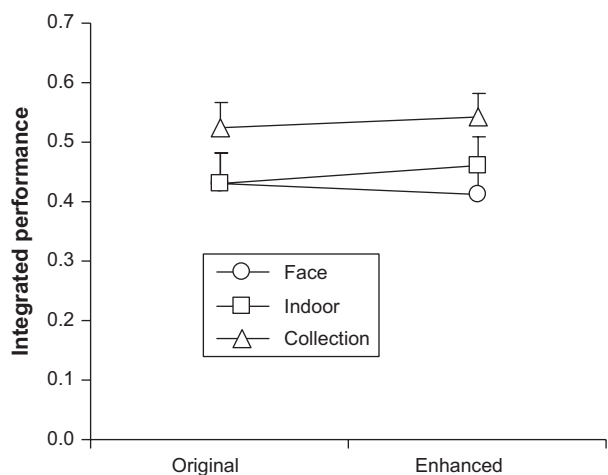


Figure 7. Integrated search performance of the patient group. There is a trend for enhancement to improve search performance for the indoor and collection images but not for the face images.

The effect of VA was further examined. *Figure 8* plots the overall integrated performance (average over all image categories) of each individual patient along with their VA. Patients with better VA had a better search performance; and were more likely to benefit from the enhancement. For patients with VA better than 0.8 LogMAR (6/38, 20/125; subjects S1 to S10), the mean of relative improvement with enhancement was 7%. Linear regression found that VA alone can explain 22%

($R^2 = 0.22, p = 0.04$) of the variability of the integrated performance, and a combination of VA and age can explain 42% ($R^2 = 0.42, p = 0.01$).

The proportion of performance improvement was also examined. It was found that one out of 19 patients (5%) performed better with enhancement for all three categories; eight out of 19 (42%) performed better with enhancement for two image categories; and 10 out of 19 (53%) performed better with enhancement for only one image category. No patient performed worse with enhancement for all three categories. Taken together, all patients had improved performance with enhancement for at least one image category. Assuming the enhancement absolutely had no effect, the arbitrary chance we would observe ‘improved’ performance (not real) for at least one image category would be seven out of eight (87.5%). A proportion Z-test showed that the 100% we observed in our study is significantly different from the arbitrary chance ($p = 0.049$, one-tailed), indicating that the enhancement indeed improved search performance.

Discussion

We have shown that patients with central vision impairment from various diseases and with varying levels of acuity loss were able to perform the natural image search task, although their performance was much worse than that of the normally sighted subjects. Our novel integrated performance measure combines the search time and accuracy measures and provides a comprehensive, unitary measure that allows a greater flexibility of experiment design than using only one single conventional measure (with the other arbitrarily fixed). This and our other on-going studies show that the natural image search task may be used to evaluate the performance of patients with central vision impairment. This paradigm has more face validity than prior search studies conducted with search objects that are graphically produced and with limited features. Using natural images is particularly important when evaluating the effect of image enhancement technologies including the type of spatial filtering used here or any other enhancement technique which may include magnification effects.²²

With a significant difference in search performance for the three different image categories, it is important to consider the nature of the stimuli used when evaluating visual functional performance in visual search. For the indoor and collection images, one may use many clues, such as colour, overall shape, orientation, to find the targets. Searching for faces is more difficult than searching in the indoor and collection images. This finding is not surprising, as face recognition has always been reported as a major difficulty in patients with visual

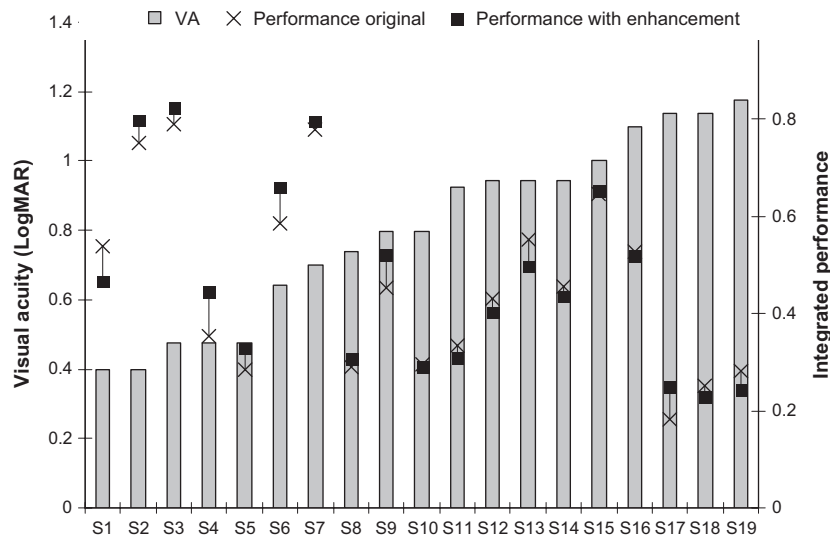


Figure 8. Integrated performance (average over three image categories) of each individual patient along with VA. Bars represent individual VA, and they are plotted in order. Black squares represent performance with enhancement, and crosses represent performance without enhancement. Subjects with better VA had better performance, and they were more likely to benefit from enhancement (square above cross).

impairment^{18,19} and is a frequent clinical complaint. It was more challenging in our study to find a given face target, especially since some of our face images included rather homogeneous groups of people (see *Figure 1*). In order to find the target face correctly when coarse visual information, such as the overall colour and shape, are essentially the same, one needs to be able to distinguish the fine details of facial features between people of the same sex, with similar hair styles and facing directions. However, that is what patients with poor visual acuity are unable to do. It seemed that our image processing parameters did not provide sufficient enhancement for the fine details. The enhancement filter was chosen based on our previous preference studies, where patients preferred moderate enhancement and rejected harsher enhancement that caused the images to look unnatural.^{9,10} Further studies are needed to see if higher enhancement can increase performance of patients with worse visual impairment, even if they may reject the harsh enhancement in the preference evaluation.

Although we did not find a large overall performance improvement with the JPEG image enhancement used here, we did find significant improvement in search performance for some patients and on some image categories. Enhancement significantly improved the integrated performance for indoor and collection images. However, it is unlikely that the small improvement would have any practical value for patients. An interesting finding is that patients with mild to moderate visual impairment (VA between 0.4 to 0.8 logMAR, 6/15

to 6/38, 20/50 to 20/125) are more likely to benefit from the enhancement used here (*Figure 8*). The finding supports our previous speculation⁹ that contrast enhancement may help low vision patients to detect a certain range of frequencies that otherwise they would not be able to see. If these frequencies are critical for object recognition, the enhancement would presumably help with visual search. For higher frequencies, the elevated contrast thresholds in the patients may be so high that they are beyond the improvement that the contrast enhancement can provide. This might also explain why there was a significant improvement for indoor and collection images, but not for face images. Frequencies required for face recognition are higher than that for indoor and collection objects.²³

Based on this understanding, we think that a sound low vision rehabilitation approach may be a combination of magnification and image enhancement. With magnification, the higher spatial retinal frequency range can be shifted to a lower frequency range where the contrast enhancement may become helpful. With enhancement, images may not have to be greatly enlarged, alleviating the problem of loss of field of view inherent in magnification.

Acknowledgements

Supported in part by NIH grants EY05957 and EY016093. We thank Lily Wang for image collection, Matthew Straight for data collection, Akarsha Ramani for processing images.

References

- Congdon N, O'Colmain B, Klaver CC *et al.* Causes and prevalence of visual impairment among adults in the United States. *Arch Ophthalmol* 2004; 122: 477–485.
- Peli E & Peli T. Image enhancement for the visually impaired. *Opt Eng* 1984; 23: 47–51.
- Peli E, Goldstein RB, Young GM, Trempe CL & Buzney SM. Image enhancement for the visually impaired: simulations and experimental results. *Invest Ophthalmol Vis Sci* 1991; 32: 2337–2350.
- Wolffsohn JS, Mukhopadhyay D & Rubinstein M. Image enhancement of real-time television to benefit the visually impaired. *Am J Ophthalmol* 2007; 144: 436–440.
- Leat SJ & Mei M. Custom-devised and generic digital enhancement of images for people with maculopathy. *Ophthalmic Physiol Opt* 2009; 29: 1–19.
- Woods RL & Satgunam P. Television, computer and portable display device use by people with central vision impairment. *Ophthalmic Physiol Opt* 2011; 31: 258–274.
- Tang J, Kim J & Peli E. Image enhancement in the JPEG domain for people with vision impairment. *IEEE Trans Biomed Eng* 2004; 51: 2013–2023.
- Leat SJ, Omoruyi G, Kennedy A & Jernigan E. Generic and customized digital image enhancement filters for the visually impaired. *Vision Res* 2005; 45: 1991–2007.
- Kim J, Vora A & Peli E. MPEG-based image enhancement for the visually impaired. *Opt Eng* 2004; 43: 1318–1328.
- Fullerton M, Woods RL, Vera-Diaz FA & Peli E. Measuring perceived video quality of MPEG enhancement by people with impaired vision. *J Opt Soc Am A Opt Image Sci Vis* 2007; 24: B174–B187.
- Satgunam P, Woods RL, Bronstad PM & Peli E. Factors affecting image quality preferences. The Society for Information Display International Symposium: Society for Information Display; 2010:94–97.
- Peli E, Fine EM & Pisano K. Video enhancement of text and movies for the visually impaired. In: *Low Vision: Research and New Developments in Rehabilitation* (Kooijman AC, Looijestijn PL, Welling JA & van der Wildt GJ, editors), IOS Press: Amsterdam, 1994; pp. 191–198.
- Mei M & Leat SJ. Quantitative assessment of perceived visibility enhancement with image processing for single face images: a preliminary study. *Invest Ophthalmol Vis Sci* 2009; 50: 4502–4508.
- Peli E, Lee E, Trempe CL & Buzney S. Image enhancement for the visually impaired: the effects of enhancement on face recognition. *J Opt Soc Am A*: 1994; 11: 1929–1939.
- Kuyk TK, Liu L & Fuhr PS. Feature search in persons with severe visual impairment. *Vision Res* 2005; 45: 3224–3234.
- MacKeben M & Fletcher DC. Target search and identification performance in low vision patients. *Invest Ophthalmol Vis Sci* 2011; 52: 7603–7609.
- Fullerton M, Woods RL, Vera-Diaz F & Peli E. Image contrast enhancement for the visually impaired: new opportunities in the digital age. Vision 2008-The 9th International Conference on Low Vision. Montreal, QC, Canada: International Society for Low-Vision Research and Rehabilitation (ISLRR), 2008.
- Barnes CS, De L'Aune W & Schuchard RA. A test of face discrimination ability in aging and vision loss. *Optom Vis Sci* 2011; 88: 188–199.
- Bullimore MA, Bailey IL & Wacker RT. Face recognition in age-related maculopathy. *Invest Ophthalmol Vis Sci* 1991; 32: 2020–2029.
- Fullerton M & Peli E. Post-transmission digital video enhancement for people with visual impairments. *J Soc Inf Disp* 2006; 14: 15–24.
- Smith ND, Crabb DP & Garway-Heath DF. An exploratory study of visual search performance in glaucoma. *Ophthalmic Physiol Opt* 2011; 31: 225–232.
- Luo G, Li Z & Peli E. Mobile electronic magnification device for people with central vision loss (abstract). *Invest Ophthalmol Vis Sci* 2011; 52: E-Abstract 386.
- Kwon M & Legge GE. Spatial-frequency cutoff requirements for pattern recognition in central and peripheral vision. *Vision Res* 2011; 51: 1995–2007.