The effect of sildenafil citrate (Viagra®) on visual sensitivity

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The erectile dysfunction medicine sildenafil citrate (Viagra®) inhibits phosphodiesterase type 6 (PDE6), an essential enzyme involved in the activation and modulation of the phototransduction cascade. Although Viagra might thus be expected to impair visual performance, reports of deficits following its ingestion have so far been largely inconclusive or anecdotal. Here, we adopt tests sensitive to the slowing of the visual response likely to result from the inhibition of PDE6. We measured temporal acuity (critical fusion frequency) and modulation sensitivity in four subjects before and after the ingestion of a 100-mg dose of Viagra under conditions chosen to isolate the responses of either their short-wavelength-sensitive (S-) cone photoreceptors or their long- and middle-wavelength-sensitive (L- and M-) cones. When vision was mediated by S-cones, all subjects exhibited some statistically significant losses in sensitivity, which varied from mild to moderate. The two individuals who showed the largest S-cone sensitivity losses also showed comparable losses when their vision was mediated by the L- and M-cones. Some of the losses appear to increase with frequency, which is broadly consistent with Viagra interfering with the ability of PDE6 to shorten the time over which the visual system integrates signals as the light level increases. However, others appear to represent a roughly frequency-independent attenuation of the visual signal, which might also be consistent with Viagra lengthening the integration time (because it has the effect of increasing the effectiveness of steady background lights), but such changes are also open to other interpretations. Even for the more affected observers, however, Viagra is unlikely to impair common visual tasks, except under conditions of reduced visibility when objects are already near visual threshold.

Keywords: Viagra, sildenafil citrate, visual sensitivity, temporal sensitivity, temporal resolution, light adaptation, visual transduction, PDE6

Citation: Stockman, A., Sharpe, L. T., Tufail, A., Kell, P. D., Ripamonti, C., & Jeffery, G. (2007). The effect of sildenafil citrate (Viagra®) on visual sensitivity. *Journal of Vision, 7*(8):4, 1–15, http://journalofvision.org/7/8/4/, doi:10.1167/7.8.4.

Introduction

Since its approval in 1998, over 1 billion doses of sildenafil citrate (Viagra) have been prescribed as a treatment for erectile dysfunction (Pfizer, 2007). It works by inhibiting cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), which is an enzyme expressed in the smooth muscle of the corpus cavernosa (Beavo, 1995; Moreland, Goldstein, & Traish, 1998). As an undesirable secondary effect, it inhibits a closely related phosphodiesterase enzyme PDE6 (e.g., Wallis, Casey, Howe, Leishman, & Napier, 1998). Estimates suggest that Viagra has about 10% of the effect on PDE6 that it has on PDE5 (Food and Drug Administration Joint Clinical Review, 1998a; see Table 1 of Laties & Zrenner, 2002). PDE6 plays an essential role in phototransduction, the process by which photons of light are absorbed and converted into electrical signals for transmission to the visual centers of the brain. Activated PDE6 (PDE6*) catalyzes the hydrolysis of cGMP to GMP. The reduction in cGMP results in the closure of ion

doi: 10.1167/7.8.4 Received September 22, 2006; published June 8, 2007 ISSN 1534-7362

channels in the plasma membrane, which blocks the inward flow of Na^+ and Ca^{2+} ions leading to cell hyperpolarization (for reviews, see Arshavsky, Lamb, & Pugh, 2002; Pugh & Lamb, 2000; Pugh, Nikonov, & Lamb, 1999). PDE6, however, not only activates the transduction cascade but also regulates visual sensitivity. As the concentration of PDE6* increases as the light level rises, the time over which the visual signals are integrated shortens and the visual response speeds up (e.g., Govardovskii, Calvert, & Arshavsky, 2000; Nikonov, Lamb, & Pugh, 2000).

Tests to determine whether Viagra causes visual side effects have so far been largely restricted to standard measures of human visual performance, such as visual acuity and color discrimination. Although such tests can be important for clinical diagnosis, most are not particularly well suited for monitoring the visual effects that are likely to be caused by the inhibition of PDE6. As a result, perhaps, the outcomes of these tests have been inconclusive, providing, at best, evidence that is largely subjective or anecdotal (reviewed in Laties & Fraunfelder, 1999; Laties & Zrenner, 2002; Marmor & Kessler, 1999). Any visual side effects are typically described in subjective reports as a bluish tinge or haze to vision or increased sensitivity to light. These effects are rarely reported (3%) at the lowest clinical doses of 25 and 50 mg, more often reported (11%) at the highest clinical doses of 100 mg, and frequently reported (50%) at doses of 200 mg or higher (Food and Drug Administration Joint Clinical Review, 1998b; Marmor & Kessler, 1999; Morales, Gingell, Collins, Wicker, & Osterloh, 1998). Otherwise, Viagra is claimed to have little or no effect on visual performance. For example, in controlled clinical trials, doses of up to 200 mg of Viagra do not affect visual acuity, visual fields, the Amsler grid, spatial contrast sensitivity, or pupillary responses (Food and Drug Administration Joint Clinical Review, 1998c, 1998d; Laties, Ellis, Koppiker, Patat, & Stuckey, 1998; Laties, Ellis, & Mollon, 1999). Transient, mild impairment of color discrimination has been found with the Farnsworth–Munsell 100 test at the peak plasma levels with doses of 100 mg or more (Food and Drug Administration Joint Clinical Review, 1998c, 1998d; Laties et al., 1998, 1999). However, any effects of Viagra on chromatic discrimination are inconsistent between subjects (see Laties & Fraunfelder, 1999; Laties & Zrenner, 2002; Marmor & Kessler, 1999) and have not been confirmed in recent double-blind studies (Birch, Toler, Swanson, Fish, & Laties, 2002; Jägle et al., 2004).

Such standard visual tests, however, do not address the most likely effect of Viagra, which is to disrupt light adaptation by preventing the visual integration time from shortening enough to offset increases in light level. More appropriate tests for lengthened integration time include those that probe the temporal response, such as measures of temporal acuity or resolution (also known as critical fusion frequency [cff]) and temporal modulation sensitivity (e.g., De Lange, 1958a; Hecht & Verrijp, 1933; Kelly, 1961). In cff measurements, the highest frequency that can be detected is determined as a function of adaptation level. These measurements are complemented by temporal modulation sensitivity measurements, which can be used to determine sensitivity at temporal frequencies below cff and, thus, define the overall temporal frequency response.

If Viagra effectively lengthens the visual integration time, then the way in which it alters temporal sensitivity will depend on the integration times involved. If the integration times are long enough to selectively attenuate visible flicker frequencies (by integrating over more than one cycle at some frequencies), then Viagra should impair the detection of higher rates of flicker relative to low rates, so that the cff is reduced and the falloff in modulation sensitivity with increasing temporal frequency steepens (before the final limiting slope). If, on the other hand, the integration times are very short, Viagra should cause a frequency-independent divisive scaling of sensitivity and, thus, a loss of cff and a vertical shift in the logarithmic modulation sensitivity functions, without a change in shape. Frequency-independent losses might also arise because the lengthening of the integration time makes steady components in the visual stimuli (produced either by the background or by the flickering target, which must be modulated around a mean level) more effective. This greater effectiveness arises simply because the steady (0 Hz) signals are integrated over a longer time. Such effects are particularly likely under S-cone isolation conditions because the intense long-wavelength background typically needed to desensitize the L- and M-cones also chromatically attenuates the S-cone signal (e.g., Pugh & Mollon, 1979). We find both frequency-dependent and frequency-independent changes in our data. Other explanations of these changes are considered in the Discussion section.

Methods

Apparatus

The optical apparatus was a conventional Maxwellian-view optical system with a 2-mm entrance pupil illuminated by a 900-W Xenon arc. Wavelengths were selected by the use of interference filters with full-width at half-maximum bandwidths of between 7 and 11 nm (Ealing or Oriel). The radiance of each beam could be controlled by the insertion of fixed neutral density filters (Oriel) or by the rotation of circular, variable neutral density filters (Rolyn Optics). Sinusoidal modulation was produced by the pulse-width modulation of fast, liquid crystal light shutters (Displaytech) at a carrier frequency of 400 Hz. The position of the observer's head was maintained by a dental wax impression. The experiments were under

computer control. The apparatus is described in more detail elsewhere (Stockman, Plummer, & Montag, 2005).

Stimuli

The experimental conditions were chosen to measure the temporal properties of either the S-cones or the L- (and M-) cones.

S-cone measurements

A flickering target of 4° of visual angle in diameter and 440 nm in wavelength was presented in the center of a 9° diameter background field of 620 nm. Fixation was central. The 620-nm background field, which delivered 11.51 $\log_{10}$ quanta $\cdot$ s^{-1} $\cdot$ deg^{-2} at the cornea (4.95 $\log_{10}$ photopic trolands), selectively desensitized the M- and L-cones but had comparatively little direct effect on the S-cones.

For the cff measurements, the 440-nm target was modulated at 92% contrast and varied in intensity in steps from approximately 6.5 to 11 $\log_{10}$ quanta $\cdot$ s^{-1} $\cdot$ deg^{-2} (c. −1.13 to 3.37 $\log_{10}$ photopic trolands). These conditions isolate the S-cone response up to a 440-nm target radiance of about 10.5 $\log_{10}$ quanta $\cdot$ s^{-1} $\cdot$ deg^{-2} (e.g., Stockman, MacLeod, & DePriest, 1991; Stockman, MacLeod, & Lebrun, 1993; Stockman & Plummer, 1998). The intrusion of the M-cones at the highest levels is clearly marked by a change in the appearance (hue and sharpness) of the target and by an abrupt increase in cff. For the modulation sensitivity measurements, the 440-nm target was fixed at time-averaged radiances of 7.54, 8.82, or 9.75 log quanta $\cdot$ s^{-1} $\cdot$ deg^{-2} (−0.09, 1.19, or 2.12 $\log_{10}$ photopic trolands).

L-cone measurements

A flickering target of 4° of visual angle in diameter and 650 nm in wavelength was presented in the center of a 9° diameter background field of 480 nm. Fixation was again central. The 480-nm background, which delivered 8.26 log quanta $\cdot$ s^{-1} $\cdot$ deg^{-2} at the cornea (1.37 $\log_{10}$ photopic trolands), served primarily to not only saturate the rods but also selectively desensitize the M-cones at lower target radiances.

For the cff measurements, the 650-nm target was varied in intensity from approximately 6.5 to 11.0 $\log_{10}$ quanta $\cdot$ s^{-1} $\cdot$ deg^{-2} (−0.63 to 3.87 $\log_{10}$ photopic trolands) and was modulated at 92%. These conditions isolate the L-cone response over most of the 650-nm intensity range, but at high intensities, the M-cones are also likely to contribute to flicker detection (Stiles, 1978; see Figure 1b of Stockman & Mollon, 1986). We were not concerned about the possibility of a mixed M- and L-cone response at higher levels because there is no reason to suppose that Viagra has a selective effect on either the M- or the L-cones. However, we note that Viagra might have differential effects on the two cone types because the M-cones are at a much lower level of adaptation at high, 650-nm target radiances than are the L-cones. For the modulation sensitivity measurements, the 650-nm target was fixed at time-averaged radiances of 7.56 and 9.52 log quanta $\cdot$ s^{-1} $\cdot$ deg^{-2} (0.43 or 2.39 $\log_{10}$ photopic trolands).

Procedures

Before making any measurements, subjects light adapted to the background and target for 3 min. Subjects interacted with the computer by means of buttons and received feedback and instructions via tones and a computer-controlled voice synthesizer. Two types of temporal measures were made: (a) temporal resolution or cff measurements, in which observers adjusted the flicker frequency (at the maximum fixed stimulus modulation of 92%) to find the frequency at which the flicker just disappeared, and (b) modulation threshold measurements, in which observers adjusted the modulation (at a fixed frequency) to find the modulation at which the flicker just disappeared. Modulation was varied by adjusting the fraction of the light that is flickering, while keeping the time-average intensity of the light constant. Modulation thresholds enable sensitivity to be measured at frequencies below the cff.

Each single measurement of modulation threshold or cff is the average of three settings. The mean data points for the pre- or post-Viagra baseline measurements are the average of at least three measurements, and the error bars are ±1 *SEM*.

A more objective measurement technique, such as two-alternative forced choice, was impractical in the context of these experiments because it is too slow to generate quickly the amount of data required to explore dynamic changes in sensitivity following drug ingestion.

Calibration

The radiant fluxes of test and background fields were measured at the plane of the observer's entrance pupil with a UDT Radiometer that had been calibrated by the manufacturer against a standard traceable to the National Bureau of Standards and cross-calibrated by us. Neutral density filters, fixed and variable, were calibrated in situ for all test and field wavelengths used. Interference filters were calibrated in situ with a spectroradiometer (Gamma Scientific). Quoted radiances are time-averaged values.

Subjects

Four male observers (authors A.S., L.T.S., A.T., and G.J.) participated in these experiments. All observers had

normal color vision according to standard tests. A correction lens of +5D was used for A.T. L.T.S. and A.S. are highly experienced psychophysical subjects. A.T. and G.J. were comparatively naive at the start of the experiments. All four subjects were in good health with no known cardiovascular or other risk factors. These studies conform to the standards set by the Declaration of Helsinki, and the procedures have been approved by local ethics committees at Moorfields Eye Hospital and at University College London. The local ethics committee restricted us to making measurements on ourselves.

Dosage

Subjects orally ingested therapeutic, 100-mg doses of Viagra (sildenafil citrate). Doses were typically taken in the morning with water. No food was eaten from the previous evening until the end of the measurements to minimize interference with its absorption. Successive doses were separated by at least 1 week. Only 100-mg doses were taken. The dose numbers given in each figure refer to separate trials, before which a single 100-mg dose was ingested. Frequently, different types of measures were interleaved during a single trial.

Different dosages vary slightly in their effects on visual performance, which is presumably related to variations in the Viagra plasma concentration (see Jägle, Jägle, Sèrey, & Sharpe, 2005; Jägle et al., 2004). An example of different dose effectiveness can be seen in the cff data for L.T.S. in Figure 1. Although the effects of Viagra are consistent across doses, Dose 3 (circles) is clearly less effective than the other doses. In addition, the time course of the effect varies across subjects. For example, subjects L.T.S. and G.J. show measurable visual losses after taking Viagra at shorter postingestion intervals than does A.T. Although the thresholds did not always recover to their baseline values during the course of our measurements, which were usually limited to 3 hr after drug ingestion, their recovery was always complete by the time of the post-Viagra measurements, which were usually made 1–3 days following a dose.

For a particular set of measurements, the pre-Viagra measurements were made on separate days before the Viagra measurements, whereas the post-Viagra measurements (if carried out) were made at least 3 days after them.

Statistical tests

To test for an effect of Viagra on each subject, we adopted the conservative test of collapsing the drug data from 20 to 300 min following drug ingestion into a single group and then compared this group with the control, nondrug groups. Because the influence of Viagra on vision varies between 20 and 300 min as well as between different dose trials (see below), collapsing the data in this way introduces extra variability into the drug group. Given that this extra variability works against rejection of the null hypothesis (that Viagra has no effect on visual performance), the tests may be deemed very conservative.

Specifically, the data were analyzed with a two-way ANOVA, with radiance or frequency as one factor and drug condition as a second factor. Drug condition was considered as a two- or three-level factor: predrug, drug, and postdrug (if available). A p value $<.05$ was assumed to be significant.

Results

S-cone cff versus intensity functions

Our initial measurements of temporal resolution were made under experimental conditions chosen to isolate the S-cone response, partly because of the subjective evidence for a blue tinge to vision following Viagra ingestion (e.g., Laties & Zrenner, 2002). S-cone-mediated cff, plotted as a function of the radiance of a 440-nm target, is shown in Figure 1 for G.J. (top left panels), L.T.S. (bottom left), A.S. (top right), and A.T. (bottom right). The symbols in Figure 1 and the other figures (except Figure 2) refer to the dose trial number given to each subject: Dose 1 (squares), Dose 2 (triangles), Dose 3 (circles), Dose 4 (inverted triangles), and Dose 5 (hexagons, only in Figure 5). In each case, the dose was 100 mg. The time after dose ingestion is color coded according to the spectral key (the time given is the midpoint of each run, which typically lasted 12 min), which runs from violet for short times after drug ingestion to red for long. The larger panel for each subject shows the subject's cff or modulation sensitivity functions. The smaller panel shows the losses in cff or the losses in modulation sensitivity relative to the mean pre- and post-Viagra control data. The mean losses, averaged across drug data obtained between 20 and 300 min following Viagra ingestion, are shown by the red lines. The same window of 20 to 300 min was used for the two-way ANOVA.

With increasing target radiance, the baseline (pre- and post-Viagra) S-cone cff functions for each subject (dotted open and gray circles) are typical for S-cone-mediated detection (Marks & Bornstein, 1973; Stockman et al., 1991; Stockman & Plummer, 1998). The fastest rate of flicker that can just be seen increases steadily with increasing radiance over the first 2.5 log units but then reaches a plateau at between 19 and 25 Hz. The functions thereafter remain constant or fall slightly before rising again at the highest levels. The slight fall is caused by a saturation of the S-cone response that occurs at high S-cone adaptation levels on the intense orange field required to isolate the S-cones (Mollon & Polden, 1977; Stockman & Plummer, 1998; Stromeyer, Kronauer, &

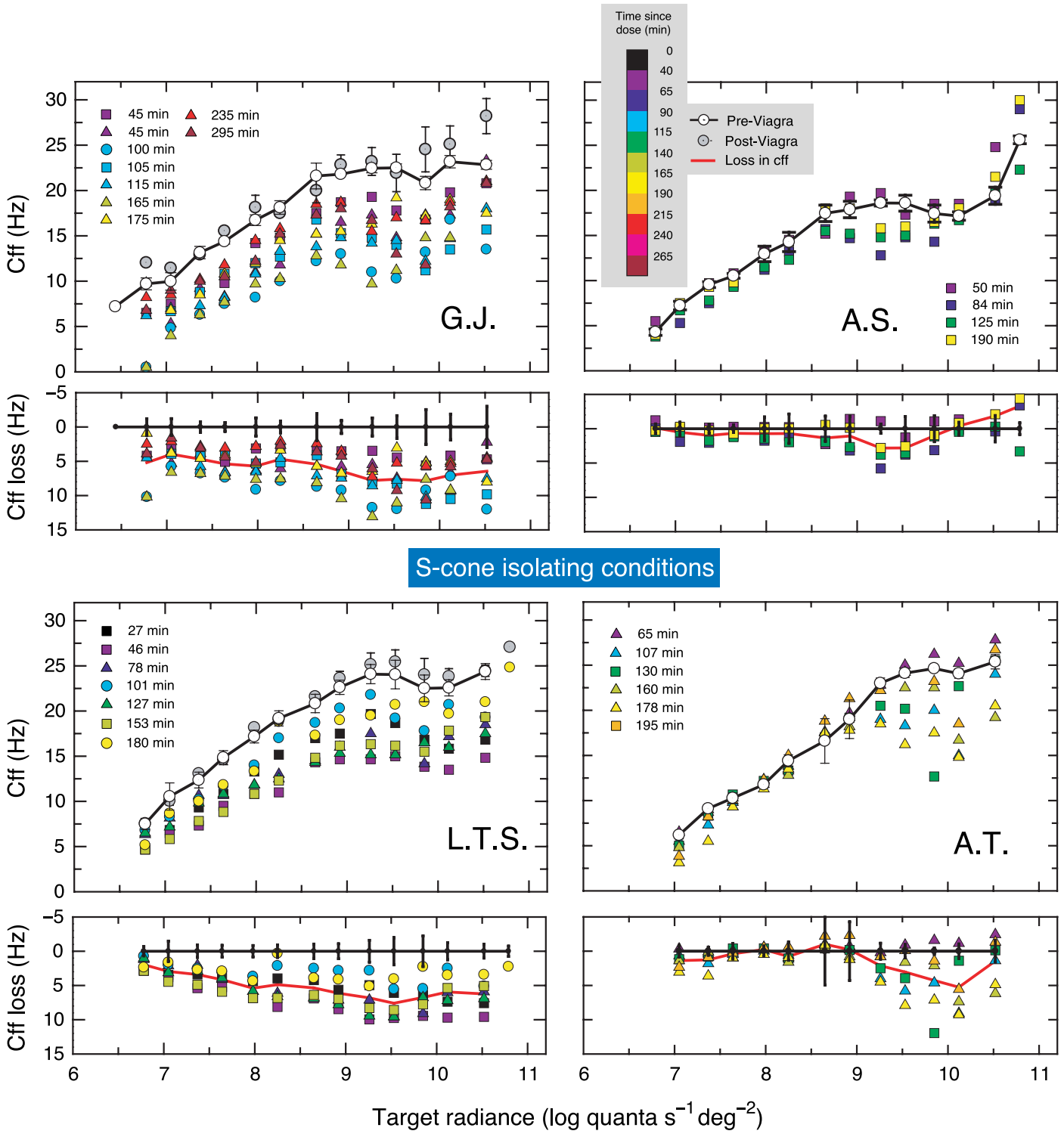


Figure 1. S-cone cff control and drug data for G.J. (upper left panels), L.T.S. (lower left), A.S. (upper right), and A.T. (lower right). The pre-Viagra cff data (dotted open circles) are the average of three or more separate measurements made on days before ingestion of a 100-mg dose of Viagra, whereas the post-Viagra cff data (dotted gray circles), measured for only L.T.S. and G.J., are the average of three or more separate measurements made at least 3 days after drug ingestion (the error bars are ±1 *SE*). The shapes of the colored symbols in this figure and in Figures 3 and 4 denote the dose number, which correspond to separate trials: Dose 1 (squares), Dose 2 (triangles), Dose 3 (circles), and Dose 4 (inverted triangles). The time after dose ingestion is coded by the color of the symbols (see key) and indicated in the legend for each subject. The smaller panels highlight the losses in cff for each subject relative to the subject's mean pre- and post-Viagra data (black line). The red line indicates the mean loss averaged over time from 20 to 300 min after Viagra ingestion. The black error bars are ±2 *SE* for the combined pre- and post-Viagra data.

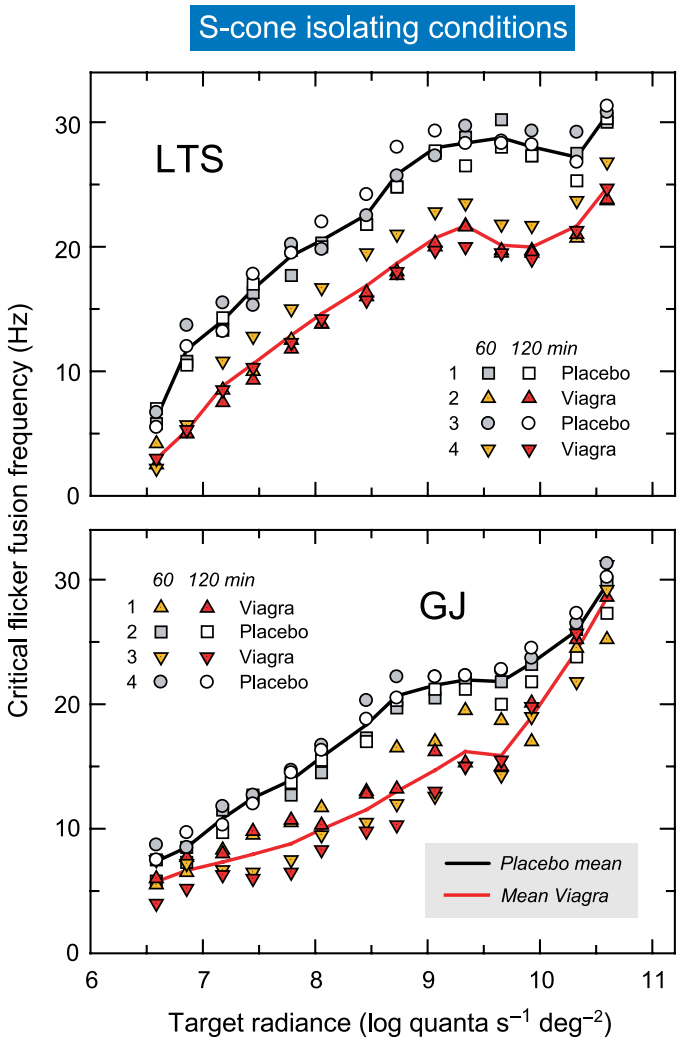


Figure 2. S-cone cff data from four (1–4) trials for L.T.S. (top panel) and G.J. (bottom panel), measured 60 or 120 min after the ingestion of either a placebo or a 100-mg dose of Viagra (see key). The mean placebo cff values are indicated by the continuous black lines, and the mean Viagra values, which include both the 60- and the 120-min post-Viagra measurements, are indicated by the continuous red lines.

Madsen, 1979), whereas the final rise is due to the M-cones taking over detection (see Figure 4 of Stockman & Plummer, 1998). The S-cone cff functions for all four subjects show some losses in cff following ingestion of a standard 100-mg dose of Viagra. For G.J. and L.T.S., the losses are found across all target radiances, increasing slightly as the target radiance increases and reaching 11 Hz for L.T.S. and 12 Hz for G.J. In contrast, for A.T. and A.S., minimal losses are found at low target radiances. For subject A.T., the losses increase with radiance, reaching approximately 10 Hz at the S-cone saturating levels, whereas for A.S., they reach only approximately 5 Hz.

Statistical analyses using a two-way ANOVA reveal that the main drug effect of Viagra on S-cone cff was significant for G.J., $F(2, 166) = 183.4$, $p < .001$, L.T.S., $F(2, 159) = 154.8$, $p < .001$, and A.T., $F(1, 84) = 5.1$, $p = .027$, but insignificant for A.S., $F(1, 84) = 2.3$, $p = .133$.

Given the large variability between observers, we decided to run a double-blind placebo control experiment on the two more affected subjects, L.T.S. and G.J., to rule out the possibility that extraneous factors, such as the subject's expectations, had affected the Viagra measurements. However, we should point out that the ultimate reliability of placebo controls is questionable with drugs such as Viagra, which, in our subjects, frequently had noticeable side effects (e.g., dry mouth, headache, and indigestion). G.J., in particular, was sometimes aware of Viagra-induced visual haloes and color changes.

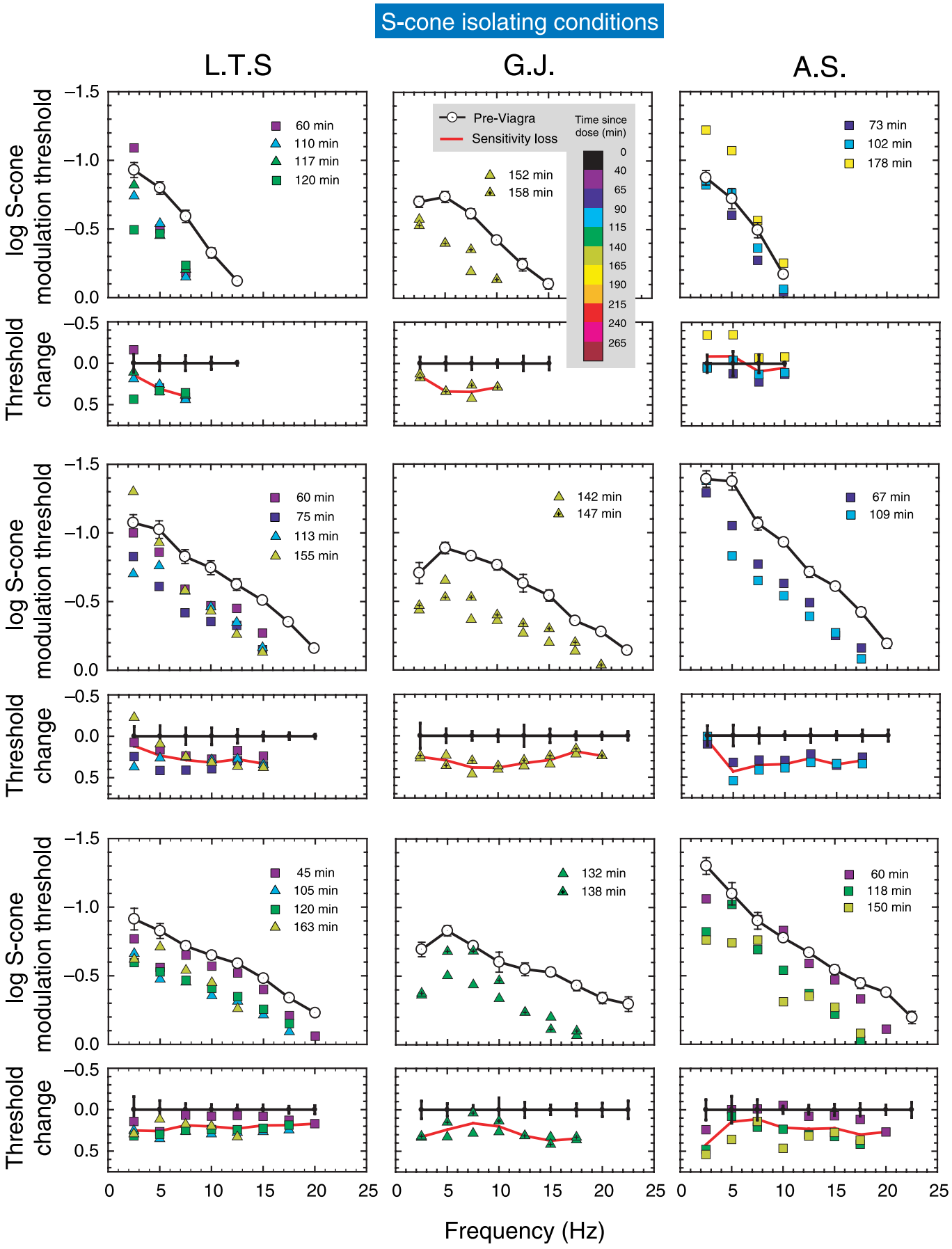
Figure 2 shows the results of the placebo control experiment. Four trials were carried out: Two of which were preceded by a 100-mg dose of Viagra (corresponding to Doses 6 and 7 for these subjects), and two of which were preceded by a placebo dose. Drug and placebo trials were chosen randomly in the order listed in the figure key, and neither the experimenter nor the subject was informed which had been taken until after the conclusion of the entire control experiment. Measurements were made either 60 or 120 min following drug ingestion.

Both subjects show substantial losses of S-cone cff during the drug trials but not during the placebo trials. The losses clearly mirror those found for each subject in Figure 1.

We note that the absolute cff measurements in Figures 1 and 2, particularly those for L.T.S., differ by a few hertz. In general, we found that S-cone cff measurements are stable over short periods of a week or so, as shown by the stability of the pre- and post-Viagra measurements, but that they can vary by several hertz over longer periods of a month or more. The measurements in Figures 1 and 2 were separated by more than 2 years. Clearly, for both G.J. and L.T.S., the Viagra-induced losses are substantially larger than any long-term variability.

S-cone modulation sensitivity functions

Figure 3 shows temporal modulation sensitivities for three of the observers: L.T.S. (left panels), G.J. (center panels), and A.S. (right panels), measured at low (440-nm target radiance of 7.54 log quanta $\cdot$ s^{-1} $\cdot$ deg^{-2}, top panels), medium (8.82 log quanta $\cdot$ s^{-1} $\cdot$ deg^{-2}, middle panels), and high (9.75 log quanta $\cdot$ s^{-1} $\cdot$ deg^{-2}, bottom panels) S-cone adaptation levels. The symbols and symbol colors are as described in Figure 1. In all three observers, as the S-cone adaptation level rises (as it does in successive panels downward for each subject), the baseline (pre-Viagra) sensitivities exhibit a relative improvement in sensitivity at higher frequencies. Such changes are consistent with a speeding up of the S-cone visual response with adaptation and a shortening of the integration time (e.g., De Lange, 1958a; Kelly, 1961; Matin, 1968; Stockman et al., 1991).


S-cone isolating conditions
L.T.S
G.J.
A.S.
log S-cone modulation threshold
Threshold change
Pre-Viagra
Sensitivity loss
Time since dose (min)
0
40
65
90
115
140
165
190
215
240
265
60 min
110 min
117 min
120 min
152 min
158 min
73 min
102 min
178 min
60 min
75 min
113 min
155 min
142 min
147 min
67 min
109 min
45 min
105 min
120 min
163 min
132 min
138 min
60 min
118 min
150 min
−1.5
−1.0
−0.5
0.0
0.5
0
5
10
15
20
25
Frequency (Hz)

The general form of the baseline functions show a good deal of variability, across observers, but they are consistent with previous measurements (e.g., Stockman et al., 1991; Wisowaty & Boynton, 1980).

The effect of Viagra on S-cone modulation sensitivity was significant at the low level for G.J., $F(1, 21) = 71.4$, $p < .001$, and L.T.S., $F(1, 44) = 42.0$, $p < .001$, but insignificant for A.S., $F(1, 20) = 0.0$, $p = .882$. Its effect at the medium level was significant for all three subjects: G.J., $F(1, 44) = 118.4$, $p < .001$, L.T.S., $F(1, 77) = 69.5$, $p < .001$, and A.S., $F(1, 33) = 122.9$, $p < .001$; and, likewise, at the high level: G.J., $F(1, 43) = 76.4$, $p < .001$, L.T.S., $F(1, 78) = 52.3$, $p < .001$, and A.S., $F(1, 33) = 97.7$, $p < .001$. Thus, following ingestion of Viagra, the three observers show losses of modulation sensitivity consistent with the changes in their cff settings. L.T.S. and G.J. lose sensitivity at all three adaptation levels, whereas A.S. loses sensitivity only at the two highest levels (cf. Figure 1; there is little change in his cff at adaptation levels below 9.00 log quanta $\cdot s^{-1} \cdot deg^{-2}$).

The S-cone sensitivity losses are not confined to the highest frequencies at each level, which correspond to the cff settings; they also occur at lower frequencies. The nature of the losses, which are highlighted by the red lines in the smaller panels of Figure 3, varies across subjects and levels. In most cases, the logarithmic losses tend to increase slightly with frequency, whereas in others, they are roughly constant with frequency or slightly decrease. These differences may reflect the complexity of the effects that Viagra is likely to have on S-cone sensitivity under these conditions, which can be either direct or indirect. The Viagra-induced steepening of the modulation sensitivity functions is consistent with the lengthening of the integration time of the S-cone signal, while the frequency-independent losses across frequency are consistent with an increase in the effectiveness of the steady components of the target and the background. In the latter case, the increased effectiveness of the 610-nm background on S-cone sensitivity may be mostly indirect—by way of a postreceptoral, chromatically opponent nonlinear attenuation (e.g., Pugh, 1976; Pugh & Mollon, 1979; Stiles, 1953). Other possibilities are considered in the Discussion section.

One way to disambiguate these factors is to look at L-cone modulation sensitivities, which extend to much higher frequencies and are likely to be less subject to opponent attenuation, thus making any frequency-dependent sensitivity losses much more obvious.

L-cone cff versus intensity functions

A visual loss restricted to S-cone-mediated vision might not have particularly serious behavioral consequences, given that the S-cone signals predominantly feed into sluggish chromatic channels rather than the brisk luminance channel responsible for flicker and motion perception (e.g., Boynton, 1979; De Lange, 1958b; Eisner & MacLeod, 1980; Guth, Alexander, Chumbly, Gillman, & Patterson, 1968; Luther, 1927; Schrödinger, 1925; Smith & Pokorny, 1975; Walls, 1955). If, however, the M- or L-cone cff functions are also compromised by Viagra, the behavioral consequences could be of more concern.

L-cone-mediated cff was measured in all four subjects as a function of the 650-nm target radiance on a moderate-intensity 480-nm background. The results are shown in Figure 4 for G.J. (upper left panels), L.T.S. (lower left panels), A.S. (upper right panels), and A.T. (lower right panels).

With increasing target radiance, the baseline L-cone cff functions for each subject (dotted open and gray circles) rise steadily until reaching a plateau between 38 and 52 Hz, in accord with previous L- and M-cone measurements (Hecht & Verrijp, 1933). As compared with the S-cone functions shown in Figure 1, the L-cone cff functions rise more steeply and reach a much higher plateau. These differences are due mainly to postreceptoral rather than to receptoral differences between the cone systems (e.g., see Schnapf, Nunn, Meister, & Baylor, 1990; Stockman et al., 1993; Stockman & Plummer, 1998), partly because the S-cone signals are mainly confined to more sluggish chromatic pathways.

The effect of Viagra on L-cone cff was significant for G.J., $F(1, 53) = 85.97$, $p < .001$, L.T.S., $F(2, 99) = 257.0$, $p < .001$, and A.T., $F(2, 134) = 9.5$, $p < .001$, but insignificant for A.S., $F(2, 127) = 1.0$, $p = .377$. Finding a significant effect for A.T. was unexpected. However, a post hoc pairwise comparison (Scheffé) of his data reveals that the significant difference is only between the postdrug and the drug trials ($p = .015$), not between the predrug and drug trials ($p = .948$).

Importantly, the severity of the adverse effects of Viagra on S-cone-mediated vision for each of the four observers is mirrored in its effect on their L-cone-mediated vision. For subjects L.T.S. and G.J., for whom Viagra caused a sensitivity loss over the entire S-cone cff, Viagra causes a comparable loss over the entire L-cone range. Like the S-cone cff data, the losses increase slightly as the target radiance increases, reaching approximately 10 Hz for L.T.S. and 5 Hz for G.J. For A.T. and A.S., for whom Viagra affected mainly the plateau of their S-cone cff functions (see Figure 1), Viagra had little effect on L-cone cff.

Figure 3. S-cone modulation threshold control and drug data for L.T.S. (left panels), G.J. (central panels), and A.S. (right panels), measured at 440-nm target radiances of 7.54 (upper panels), 8.82 (middle panels), and 9.75 (lower panels) log quanta $\cdot s^{-1} \cdot deg^{-2}$. The larger panels show the S-cone modulation thresholds. The smaller panels highlight the changes in threshold for each subject relative to the subject's mean pre-Viagra data (black continuous lines). The red lines indicate the mean losses averaged over time from 20 to 300 min after Viagra ingestion. The error bars are ±1 *SE* in the larger panels and ±2 *SE* in the smaller panels. Other details are as described in Figure 1.

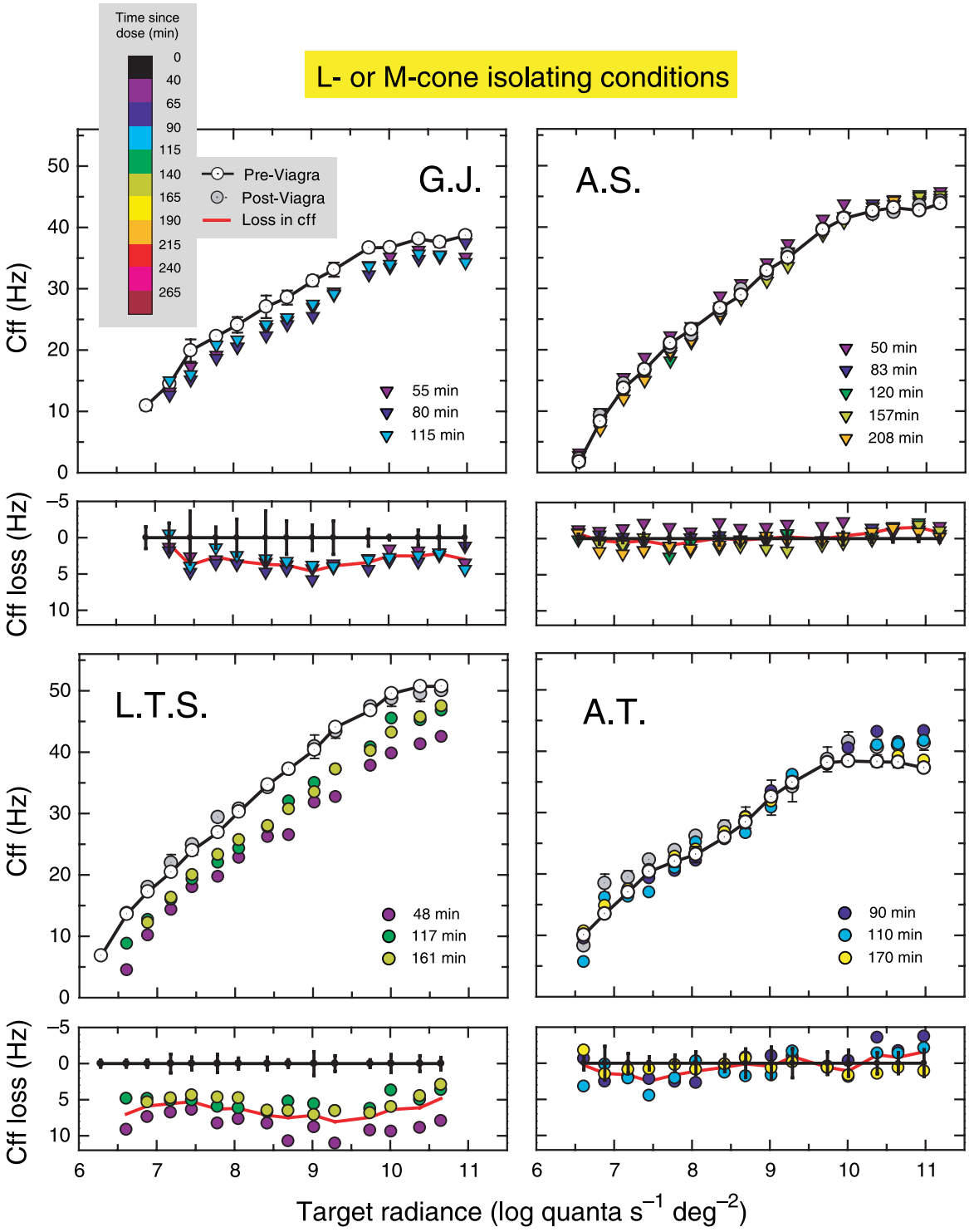


Figure 4. L-cone cff control and drug data for G.J. (upper left panels), L.T.S. (lower left), A.S. (upper right), and A.T. (lower right). The larger panels show the L-cone cff data. The smaller panels highlight the losses in cff for each subject relative to their mean pre- and post-Viagra data (black continuous line). The error bars are ±1 *SE* in the larger panels and ±2 *SE* in the smaller panels. Other details are as described in Figure 1. G.J. did not make the post-Viagra measurements.

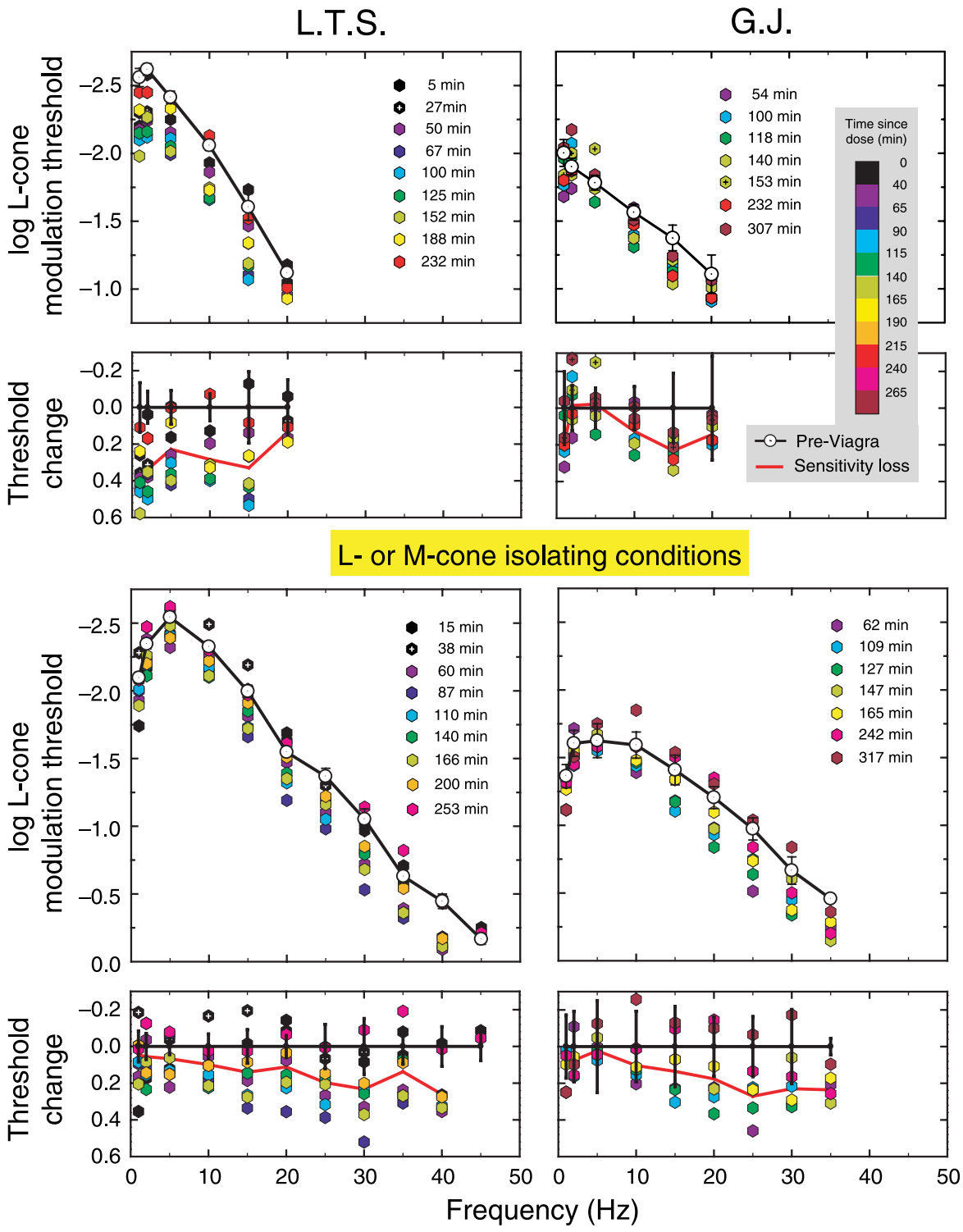


Figure 5. L-cone modulation threshold control and drug data for L.T.S. (left panels) and G.J. (right panels), measured at 650-nm target radiances of 7.56 (upper panels) and 9.52 (lower panels) log quanta · s^{-1} · deg^{-2}. The larger panels show the L-cone modulation thresholds. The hexagons indicate the measurements that were made following ingestion of Dose 5 of Viagra. Dotted symbols have been included where necessary to distinguish between two runs made during the same color-coded time window. The smaller panels highlight the changes in threshold for each subject relative to the subject's mean pre-Viagra data (black continuous lines). The red lines indicate the mean loss between 20 and 300 min after drug ingestion. The error bars are ±1 *SE* in the larger panels and ±2 *SE* in the smaller panels. Other details are as described in Figure 1.

L-cone modulation sensitivity functions

Figure 5 shows temporal modulation sensitivities for L.T.S. (left panels) and G.J. (right panels), measured at low (650-nm target radiance of 7.56 log quanta $\cdot$ s^{-1} $\cdot$ deg^{-2}, top panels) and high (9.52 log quanta $\cdot$ s^{-1} $\cdot$ deg^{-2}, bottom panels) L-cone adaptation levels. Details of the colored symbols are as described in Figure 1. The hexagons indicate that this was Dose 5 for both observers. The baseline L-cone modulation sensitivities for both L.T.S. and G.J. (dotted circles) show a marked relative improvement in modulation sensitivity to higher frequencies between the two levels but little change at low frequencies, as expected (e.g., De Lange, 1958a; Kelly, 1961; Matin, 1968). Such improvements with adaptation accord, like the S-cone improvements in Figure 3, with a speeding up of the visual response and a shortening of the integration time with increasing light level.

The effect of Viagra on L-cone modulation sensitivity was significant for G.J., $F(1, 70) = 16.6$, $p < .001$, and L.T.S., $F(1, 102) = 6.4$, $p = .013$, at the high level, as well as for G.J., $F(1, 51) = 816.1$, $p < .001$, and L.T.S., $F(1, 59) = 219.9$, $p < .001$, at the low level.

In agreement with the Viagra-induced changes to their L-cone cff data, both L.T.S. and G.J. show a loss of L-cone modulation sensitivity after ingesting Viagra at both the low and the high L-cone adaptation levels. The sensitivity losses at the high level, which extend to 40 or 45 Hz, are consistent with a slight steepening of the high-frequency slope (see the threshold losses as highlighted in the smaller panels), a characteristic signature of a lengthening of the integration time of the visual response (see above). In Stockman, Sharpe, Tufail, Kell, and Jeffery (2006), these losses were modeled by assuming that the change in time constant occurred at a single integrating stage with an exponential decay (which was assumed to reflect the activity of some biochemical process, such as the hydrolysis of cGMP catalyzed by PDE6*). Viagra was found to lengthen the integration time *roughly* from approximately 6.9 to 12.6 ms, and, in addition, overall sensitivity was reduced by 0.34 $\log_{10}$ unit. The overall reduction in sensitivity was attributed to the increased effectiveness of the steady components of the target and background acting on an adaptational nonlinearity (see, for details, Stockman et al., 2006).

Discussion

Viagra caused some degradation of visual performance in all four subjects tested. In two of the four subjects (L.T.S. and G.J.), the losses for cone-detected flicker were ubiquitous, occurring across cone types, flicker frequencies, and adaptation levels. For such individuals, Viagra may impair some behavioral tasks performed outside the laboratory for several hours postingestion but probably only under conditions of reduced visibility when objects are already near contrast threshold (e.g., under foggy conditions or under conditions of reduced illumination). In the two remaining subjects (A.S. and A.T.), losses were restricted to more extreme conditions of S-cone isolation and strong chromatic adaptation, which are unlikely to be encountered outside the laboratory.

Viagra and PDE6

The ingestion of Viagra provides a unique opportunity for pharmacologically modifying the human visual transduction cascade and determining the consequences of the inhibition of PDE6* on the transmission and regulation of the human light response. Our findings, which show both frequency-dependent and frequency-independent Viagra-induced losses, are consistent with Viagra interfering with the ability of PDE6* to shorten the time over which the visual system integrates signals as the light level increases (Stockman et al., 2006). The S-cone modulation sensitivity losses shown in Figure 3 are more complex.

Changes in the time constant of the visual response, which affect sensitivity, should also affect the delay of the visual response. There is one psychophysical study—available only in abstract form—in which the effects of Viagra upon temporal persistence have been investigated (Mollon, Regan, Foo, & Morris, 2003). Performance on a perceptual grouping task that depended on visual persistence for its successful execution, modestly improved following ingestion of 100 mg of Viagra. This *increase* in visual persistence is consistent with the *detriments* in temporal acuity and sensitivity that we report here. Having an integration time that is ill matched to the environmental light level will, in general, *degrade* visual performance, unless a special task that takes advantage of the added visual delay is devised.

Human electroretinogram (ERG) recordings are another potential source of evidence about the effects of Viagra on the delay of the visual response. Unfortunately, the effects of Viagra on the ERG are somewhat inconsistent, and any effects that have been found have typically been analyzed in terms of changes in implicit time and in amplitude of the a- and b-wave components. Although transient reductions in the rod (Vobig et al., 1999) and cone (Luu, Chappelow, McCulley, & Marmor, 2001) ERG amplitudes have been reported, they have not been confirmed by more recent studies (Jägle et al., 2005, 2004), which found only small, insignificant changes. On the other hand, several studies have reported small but significant prolongations in the implicit times of the cone ERG responses (Jägle et al., 2005, 2004; Luu et al., 2001) and prolongations in some but not all measures of rod ERG (Jägle et al., 2004). These results are important in the context of this work for two reasons. First, they suggest

that the visual side effects caused by Viagra are indeed retinal in origin (and, in the case of the a-wave data, mainly receptoral) rather than being attributable to some nonspecific attentional deficit, which is central in origin. Second, they suggest that the Viagra-induced lengthening of the time constant of temporal integration implied by our results also causes, as expected, increases in the delay of the visual response.

Other considerations

S- and L-cones

The S-cone sensitivity measured on an intense long-wavelength background field will depend upon the direct effects of the target and background lights on the S-cones and, because of chromatically opponent attenuation, upon the indirect effects of those lights on the L- and M-cones. Our failure to find an effect of Viagra at lower S-cone adaptation levels for A.S. and A.T. might be due to Viagra having no effect on their L-cones, the signals from which, because of the intense 620-nm background, are much larger than those from the S-cones at lower 440-nm radiances, rather than to Viagra having no effect on their S-cones. Consequently, both the S-cone and the L-cone data might be consistent in showing that in A.S. and A.T. Viagra affects only the S-cones, whereas in G.J. and L.T.S., it affects both the L- and S-cones. Why such a difference should occur, however, is not easily explained.

Cardiovascular changes and flicker

Flicker sensitivity has been related to some systemic cardiovascular measures, but the results are complex. Eisner and Samples (2000) reported that the ratio of mean arterial blood pressure to heart rate was inversely related to flicker sensitivity on some adapting backgrounds, whereas Gutherie and Hammond (2004) reported that resting systolic blood pressure was positively related to cff measured without a background. Other work has shown that luminance or chromatic flicker itself can increase retinal vessel diameter and retinal blood flow (e.g., Falsini, Riva, & Logean, 2002; Formaz, Riva, & Geiser, 1997; Kotliar, Vilser, Nagel, & Lanzl, 2004; Nagel & Vilser, 2004; Riva, Falsini, & Logean, 2001; Riva, Harino, Shonat, & Petrig, 1991). Such changes, it should be noted, are in response to flickering lights that are strongly suprathreshold, in contrast to the near-threshold flickering lights used in modulation sensitivity and cff measurements. Nonetheless, these results suggest that the Viagra-induced increases in retinal venous diameters and retinal blood flow found in healthy subjects (Polak, Wimpissinger, Berisha, Georgopoulos, & Schmetterer, 2003) could indirectly influence flicker sensitivity.

Although the systemic cardiovascular results are complex, it seems likely that increases in blood flow produced by Viagra will, if anything, generally increase flicker sensitivity, which is opposite to what we find, and presumably may actually mitigate losses caused by the inhibition of PDE6.

Higher level effects

We cannot exclude the possibility that some of the Viagra-induced losses may be due to high-level drug effects, such as attentional deficits or general feelings of malaise. However, the finding by Mollon et al. (2003) that Viagra can improve performance in a perceptual grouping task argues against the prevalence of a general, overall nonspecific loss in performance.

Nonarteritic anterior ischemic optic neuropathy

Viagra has been implicated as a possible cause of blindness—diagnosed as nonarteritic anterior ischemic optic neuropathy—in 14 cases of men who had preexisting hypertension, diabetes-elevated cholesterol, or heart disease (e.g., Cunningham & Smith, 2001; Pomeranz & Bhavsar, 2005; Pomeranz, Smith, Hart, & Egan, 2002). These cases are presently under investigation by the Food and Drug Administration. Although any link to the visual side effects generated by Viagra, or indeed to Viagra itself, is weak, a better understanding of the nature and extent of the visual side effects has become more pressing.

Acknowledgments

This work was supported by the Wellcome Trust and Fight for Sight. We thank Bruce Henning and Rhea Eskew for helpful advice.

Commercial relationships: none.
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