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Effect of Psilocybin, LSD, and Mescaline on Small, Involuntary Eye Movements

FREDERICK W. HEBBARD and ROLAND FISCHER

School of Optometry and Department of Psychiatry,
The Ohio State University, Columbus, Ohio 43210, U.S.A.

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Small, involuntary movements of the eyes occur even during the steadiest fixation of a small spot. These movements, first accurately recorded by DOHLMAN (1925), are known as physiological nystagmus and have three principal components: 1. tremor or micronystagmus, having a mean amplitude of 10—14 sec of arc and a mean frequency of 85 cycles per second (cps); 2. saccades, rapid flick-like movements with a mean frequency of 1.08 per second within a range of 0.16—2.75 and having an amplitude of 5—10 min of arc; and 3. irregular drifts and waves (HEBBARD, 1957). Research by RIGGS et al. (1953) and by DITCHBURN and FENDER (1955) showed that rather than being a useless or even undesirable by-product of the ocular motility apparatus, the physiological nystagmus is, in fact, essential for vision, since immobilization of the retinal image by optical means produces a fading away of detailed vision. This phenomenon may be accounted for by HARTLINE's (1938) findings, which showed that the optic nerve impulses resulting from illumination of the retina occur largely from *changes* in illumination and that most of the impulses are either "on" impulses or "off" impulses, with comparatively few resulting from steady illumination. Consequently, when the retinal image is immobilized there are no "on" or "off" impulses. However, when the eye is normally fixating, owing to the physiological nystagmus there are frequent changes in illumination of the retinal elements near contours of the retinal image, with a resultant peaking of neural activity at such sites.

Working with the cat, HEBBARD and MARG (1960) have shown that systemic administration of Nembutal or curare reduces and, in sufficient doses, eliminates the physiological nystagmus while neostigmine increases its amplitude markedly. It may be, therefore, that recordings of the physiological nystagmus provide an additional quantitative method for determining drug effects and their duration in man.

In this study we have investigated the influence of the psychotomimetic drug, Psilocybin (HOFMANN et al., 1959), on the physio-

logical nystagmus in healthy young men. Control experiments, without the drug, and a few comparative experiments with D-lysergic acid diethylamide (LSD), mescaline, and alcohol were also conducted.

Method

Eye movements of four healthy men were recorded using the optical-lever method described by HEBBARD (1962). A tightly fitting scleral contact lens was placed in the subject's left eye. The subjects were experienced in wearing such a contact lens and could usually keep it in the eye for 6 consecutive hours or longer without noticing significant discomfort or a reduction in visual acuity. A small plane mirror mounted on the lens reflected a beam of light to an oscillographic camera. During the photographic sessions, the subject attempted steadily to fixate the center of a small ring of light 10 min in diameter located 3 m directly in front of his left eye, while his right eye was occluded. The ring target was selected because previous work (HEBBARD, 1957) had shown that it was the most effective type of target for minimizing the physiological nystagmus. When crosshairs, for instance, were fixated, it was found that they disappeared temporarily, producing larger changes in fixation position.

The effect of Psilocybin on physiological nystagmus was studied for each of the four subjects. Two of them were also studied after they received LSD; one was studied after the administration of mescaline, and one with alcohol.

In a typical experiment, 20 recording sessions each of 45 sec duration were scheduled. The first sessions were recorded in the half-hour before the oral administration of the drug. The remaining sessions followed at intervals of a few minutes to several hours. At least 1 week elapsed between experiments. Control experiments, without a drug, were also performed on each subject. All records were made on Kodak Linagraph paper 9.2 cm wide, traveling past the camera aperture 3.3 cm per second. The records showed all components of the eye movements, except unusually large fixation movements causing the eye trace to fall off the recording paper.

Subject 1, age 24, weight 84 kg, was a participant in other research on Psilocybin, and for his first two experiments, with doses of 10 mg (119 μg/kg) and 13.5 mg (161 μg/kg), he was not available for eye-movement recording during the first 90 min after taking the drug. However, during his third experiment, with a dose of 15 mg (179 μg/kg), he was continuously available.

Subject 2, age 22, weight 59 kg, took 10 mg of Psilocybin (170 μg/kg) during his first experiment and 12.5 mg (212 μg/kg) during his second experiment. During his third experiment he was given a placebo that

looked like a Psilocybin tablet. During his fourth experiment he was given 12.5 mg of Psilocybin (212 μg/kg).

Subject 3, age 23, weight 79.5 kg, participated in two experiments with Psilocybin, the first with 12.5 mg (157 μg/kg) and the second with 15 mg (189 μg/kg). Following these, he participated in an experiment during which he was given 123 μg of LSD (1.55 μg/kg), and another during which he was given 450 mg of mescaline hydrochloride(5.65mg/kg).

Subject 4, age 22, weight 91 kg, participated in three experiments with Psilocybin, with doses of 10 mg (110 μg/kg), 12.5 mg (137 μg/kg), and 15 mg (165 μg/kg), respectively. His next experiment, with LSD, was with a dose of 120 μg (1.32 μg/kg).

Results

Inspection of the records revealed that probably the most conspicuous effect of Psilocybin, LSD, or mescaline on the physiological nystagmus was the increase in frequency of the saccades. We obtained 1,020 eye-movement records made over a year's time on subject 1 without any drugs, each record having a duration of 45 sec. His mean frequency of

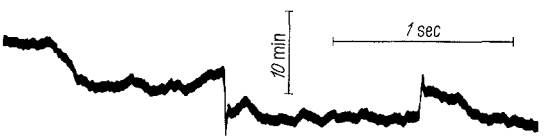

Fig. 1. Representative control record of eye movements of subject 1. The two larger, rapid displacements are saccades. The drift and micronystagmus are also evident. The length of the vertical arrow corresponds to 10 min of arc eye rotation. The length of the horizontal arrow corresponds to 1 sec of time

saccades was 0.35 cps, with a range of 0.05 cps to 0.80 cps. On some other occasions, for no obvious reason, the contact lens produced definite irritation, but even so, the highest saccadic frequency did not exceed 0.97 cps.

A section of a record obtained for subject 1, prior to the ingestion of 15 mg of Psilocybin, is shown in Fig. 1. Three 45-sec records were obtained, with mean saccadic frequencies of 0.43, 0.41, and 0.65 cps. Fig. 2 shows a section of a record taken 141 min after giving the Psilocybin. The increased *frequency* of saccades is evident, its mean being 2.95 cps during this session. The saccadic *amplitude* also increased markedly when the frequency was considerably elevated (Fig. 2), but for lesser increases in saccadic frequency, saccadic amplitudes were close to normal. In Fig. 2, the eye-movement pattern shows more or less the form of square waves; i.e., saccades were followed by saccades in the opposite direction. During this session, the subject reported some difficulty in fixating the spot, although he claimed to see it clearly.

Prior to taking Psilocybin, almost 52% of this subject's saccades could be said to form square waves. Under Psilocybin this increased to a maximum of 89% simultaneously with the saccadic frequency peak. However, the decline in square waves was slower than that in frequency of saccades, with 80% of the saccades still forming square waves 3.5 hours after ingestion of the drug.

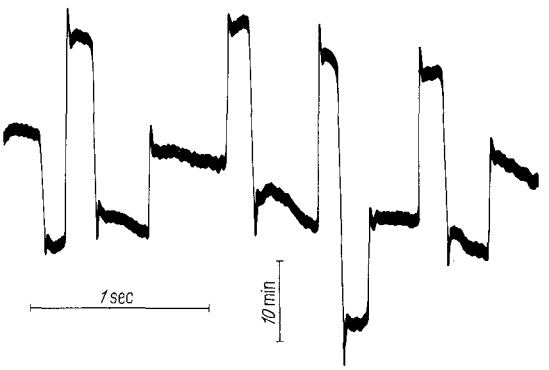

Fig. 2. Eye-movement record of subject 1, 141 min after taking 15 mg of Psilocybin. The saccades are larger and more frequent than for the control record. The square-wave pattern of the trace was typical of all records showing the effects of Psilocybin, LSD, and mescaline

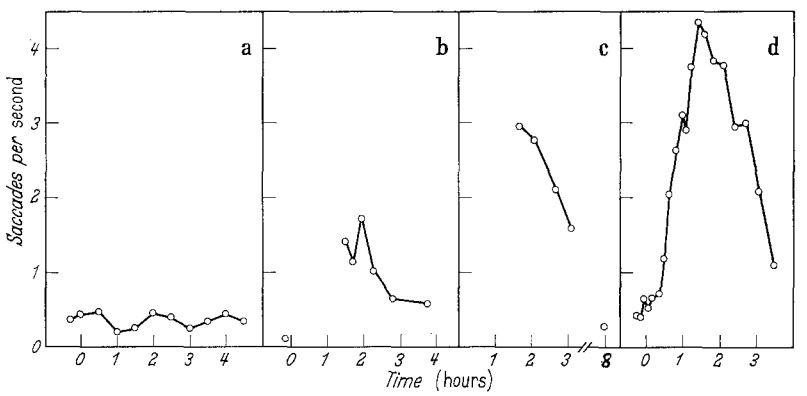

Fig. 3 a—d. Frequency of saccades during the course of experiments with subject 1. a Control experiment, without drug. b and c After 10 mg and 13.5 mg of Psilocybin at zero hour. The subject was not available for eye-movement recording for the first 90 min after taking the drug. d After 15 mg of Psilocybin at zero hour

The relationship between frequency of saccades and time after taking Psilocybin for subject 1 is shown in Fig. 3 b—d. Within the dosage range studied, the effect of Psilocybin on saccadic frequency followed a dose-response relationship. The time course of saccadic frequency for the 15 mg dose of Psilocybin (Fig. 3 d) follows a slightly-skewed, bell-shaped curve with a peak frequency at 75 min. This peak agrees reasonably well with

the time of maximum effect of Psilocybin on pupillary size and intensity of drug experience (ISBELL, 1959). The increase in frequency of saccades near the 1—2-hour time segment is not likely a result of irritation from wearing the contact lens since, after the peak, the frequency of saccades decreased, returning in less than 3 hours to what can be considered a normal level (Fig. 3b). For the larger dose, the frequencies were still somewhat elevated after 3.5 hours, but after 8 hours a normal level had been reached (Fig. 3c). Moreover, typical control records, such as that for subject 1 (Fig. 3a), do not show a significant increase in saccadic frequency.

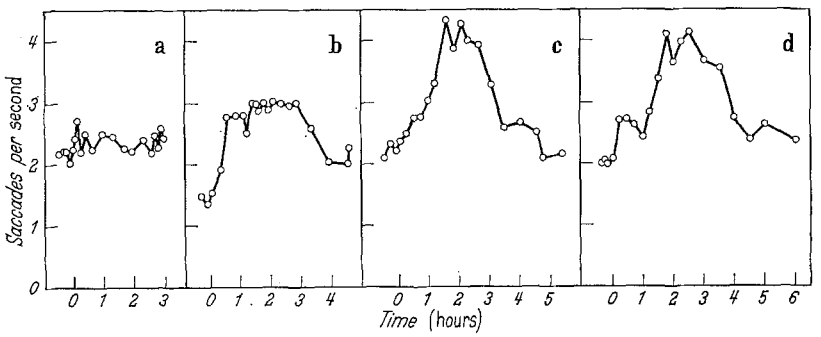

Fig. 4 a—d. Frequency of saccades during the course of experiments with subject 2. a After placebo at zero hour. b—d After 10 mg, 12.5 mg, and 12.5 mg of Psilocybin at zero hour

The time course of saccadic frequency for subject 2 after the administration of a placebo (Fig. 4a) is not noticeably different from that obtained during an ordinary control recording. It should be noted that subject 2, with a mean frequency of 2.33 saccades per second, always had a higher base line of saccadic frequency than subject 1, but it was well within the normal limit of saccadic frequency of the twelve subjects of HEBBARD (1957). About 40 min after the placebo administration, subject 2, who had twice previously taken Psilocybin, was questioning the efficacy of the "drug" and wondered whether he had been given a "tranquilizer."

Fig. 4b and c show the dose-effect relationship, in the 10—12.5 mg Psilocybin dose range, with an increase in maximum saccadic frequency from 3.0—4.5 cps. A comparison of Fig. 4c and d illustrates the reasonably good reproducibility of the experimental results. Fig. 4d shows the results obtained 2.5 months later, when 12.5 mg of Psilocybin was administered again.

Fig. 5a shows the time course of saccadic frequency for a control experiment of subject 3, who, with a higher variability in response to Psilocybin (Fig. 5b and c), nonetheless displayed the dose-effect relation-

ship shown for subjects 1 and 2. Fig. 5b and c are response curves showing the influence of 12.5 mg (157 μg/kg) and 15 mg (189 μg/kg) of Psilocybin, respectively.

Fig. 5d and e illustrate saccadic frequency responses of the same subject, but during experiments with 123 μg of LSD, i.e., 1.55 μg/kg (Fig. 5d), and, at another time, after ingestion of 450 mg of mescaline, i.e.,

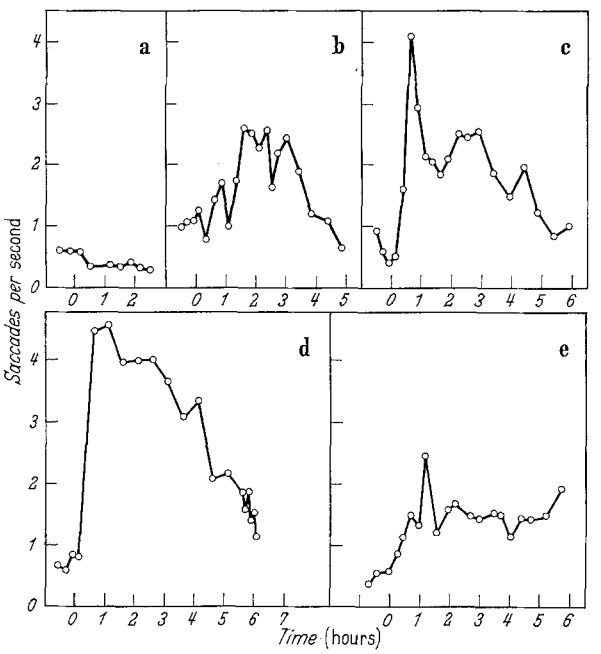

Fig. 5 a—e. Frequency of saccades during the course of experiments with subject 3. a Control experiment, without drug. b—e After 12.5 mg and 15 mg of Psilocybin, 123 μg of LSD, and 450 mg of mescaline, at zero hour

5.65 mg/kg (Fig. 5e). The peak in saccadic frequency, reached after 40 min, occurred sooner than with the dose of 12.5 mg of Psilocybin and was comparable to the response obtained with 15 mg of Psilocybin. With LSD, the decrease in frequency after the peak was delayed as compared to Psilocybin.

The main features of the mescaline response (Fig. 5e) are a less pronounced peak frequency compared to Psilocybin or LSD, and a longer duration of response, with the frequency still well above normal after 6 hours.

Fig. 6 shows the saccadic frequency response curves of subject 4, Fig. 6a during a control experiment, and Fig. 6b—d during experiments with 10, 12.5, and 15 mg of Psilocybin, respectively. The last three curves provide another illustration of a clear-cut dose-effect relationship in this

range. Fig. 6e depicts the response of the same subject under the influence of 120 μg of LSD (1.32 μg/kg). The patterns of the LSD responses in this subject and subject 3 are similar, displaying a delayed decline in saccadic frequency after the peak.

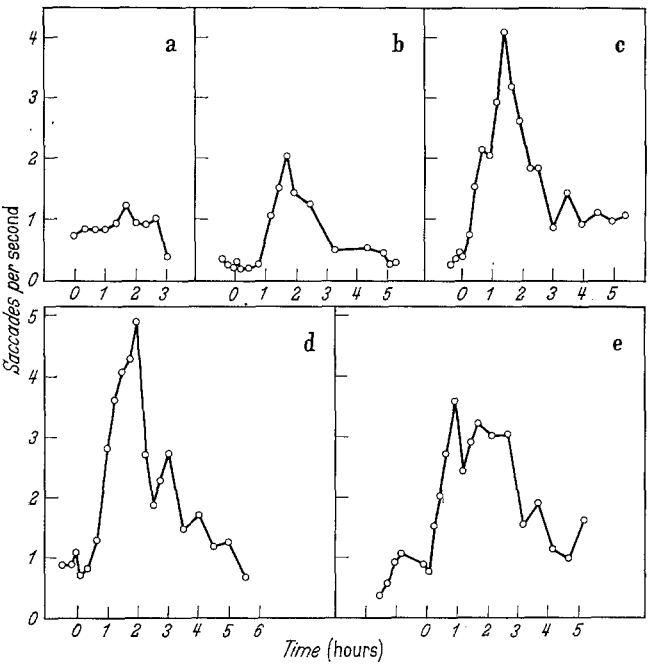

Fig. 6 a—e. Frequency of saccades during the course of experiments with subject 4. a Control experiment, without drug. b—d After 10 mg, 12.5 mg, and 15 mg of Psilocybin at zero hour. e After 120 μg of LSD at zero hour

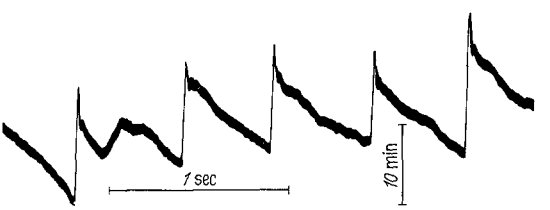

Fig. 7. Eye-movement record of subject 1 after alcohol. The saccadic amplitude and frequency are higher than for the control record, and the eye-movement trace forms a saw-tooth pattern, distinctively different from the square-wave pattern found with Psilocybin, LSD, and mescaline. For the meaning of arrows, see legend of Fig. 1

A fairly large amount of alcohol (corresponding to 125 cm^3 of ethyl alcohol) was also administered to subject 1, in the form of vodka in five portions over at 2-hour period. Fig. 7 is a record obtained 195 min after the subject took his first dose of alcohol. In addition to the higher saccadic

amplitude and frequency as compared to the control (Fig. 1), the eye-movement trace forms a saw-tooth pattern; i.e., saccades were compensated by slow movements and followed by saccades in the same direction. This pattern is different from the square-wave pattern consistently observed in this and other subjects after the administration of the psychotomimetic drugs Psilocybin, LSD, or mescaline. This finding is consistent with that of RAUSCHKE (1958), who reported a fixation nystagmus and a position nystagmus of characteristic saw-tooth pattern after ethanol administration.

Following the administration of alcohol to subject 1, the proportion of square waves declined to a low of 15%, which preceded the frequency peak by half an hour. At the frequency peak only 37% of the saccades formed square waves. After the saccadic frequency returned to normal, the proportion of square waves had risen to a normal level of 60%.

ASCHAN et al. (1956) had previously recorded positional nystagmus produced by alcohol intoxication in man and found it to be of saw-tooth form; i.e., the rapid movements, or saccades, were in one direction, and the slow movements were in the opposite direction. The direction of the rapid phase depended on the lateral position of the head, whether to the right or left. In other positions, such as the supine, they seldom observed nystagmus. They recorded eye movements behind the closed eyelids using electro-oculography, a procedure by which eye movements of about one degree or larger may be objectively studied. Their published records indicate that the positional nystagmus was generally larger than 10 degrees, as compared to amplitudes no larger than 15 min of arc for the alcohol-induced fixation nystagmus of our subject. Movements smaller than 30 min are almost impossible to detect with the unaided observing eye, whereas 10-degree movements are readily seen.

Discussion

The temporal pattern of saccadic frequency in our Psilocybin or LSD studies closely parallels the temporal pattern of pupillary diameter, as noted by ISBELL (1959). HIDALGO (1960), confirming the work of ISBELL, showed that the most reliable autonomic response was, indeed, pupillary dilation (mydriasis), which occurred in 100% of his subjects not only after Psilocybin, but also after LSD and mescaline, if these drugs were administered in the doses of 110 μg/kg, 1.5 μg/kg, and 300—400 mg/total body weight, respectively. The consistent significant increase in saccadic frequency of all our subjects under Psilocybin, LSD, and mescaline, and the repeatedly demonstrated dose-effect relationship, suggest that saccadic frequency is another quantitative parameter of psychotomimetic drug effect, along with the size of the Weber ratio in gustatory chemoreception (FISCHER, GRIFFIN et al., 1965), mean computed finger-tapping rate

(FISCHER, ENGLAND et al., 1966), and changes in handwriting size and pressure (FISCHER and MEAD, in press; FISCHER, in press). These findings, when added to those of HEBBARD and MARG (1960), imply that the recording of physiological nystagmus may also have value in characterizing compounds sharing common biological activity and action mechanisms. Such reasoning is substantiated by the contrast between the saw-tooth pattern found with alcohol and the square-wave pattern of saccades recorded under Psilocybin, LSD, or mescaline, suggesting that these drugs have a common mode of action. ISBELL (1959), in observing the markedly similar effects of Psilocybin and LSD on autonomic activity and mental performance, has already hypothesized that common biochemical or biophysical mechanisms may account for the drug effects.

However, the most direct evidence for the concept of biological identity in the ultimate mechanism of action of these drugs has come from the demonstration of cross tolerance between Psilocybin, LSD, and mescaline. ROSENBERG et al. (1963) have found that on chronic administration, cross tolerance develops between LSD and Psilocybin, as has previously been shown by ISBELL et al. (1961). Similar cross tolerance has also been shown to develop between LSD and mescaline (WOLBACH et al., 1962).

The two distinctive patterns of saccadic movement, one for alcohol, the other for Psilocybin, LSD, and mescaline, suggest that certain species of drugs may produce a characteristic pattern of eye movements, and these patterns may aid in the classification of types of excitatory and depressant drugs. However, the drugs may also produce these effects by acting on the fixation feedback mechanism. Indeed, RASHBASS (1961) has previously shown that barbiturates interfere with smooth tracking movements and tend to produce step-like movements.

We infer that the increased frequency of saccades is a corollary of the excitation produced by pyretogenic, psychotomimetic compounds, such as LSD, Psilocybin, and mescaline. The changed pattern of saccadic response could be a result of direct drug action on the neuromuscular or fixation feedback systems of the eye, or it could result from some common substance produced under the effect of either LSD, Psilocybin, or mescaline. It might even be a direct expression of the excitation syndrome that is characterized by hyperthermia, hyperglycemia, mydriasis, etc. (HOFMANN, 1963). If the latter assumption is correct, excitation without drugs could also be expected to increase the saccadic frequency.

Although the contact lens method used in this study provides a means for recording all components of the physiological nystagmus, it has limited applicability. In view of our results, indicative of possible wider applicability, another, somewhat less sensitive method not requiring a contact lens, such as one described by YOUNG (1963), could be recommended.

This method makes use of a pair of photocells to detect the position of the limbus, or boundary between the white sclera and dark iris seen behind the clear cornea. This procedure does not involve any discomfort for the subject, does not interfere with eye movements, and is not complicated. It therefore provides a practical means for studying saccadic frequency.

Summary

The influence of Psilocybin, LSD, mescaline, or alcohol on physiological nystagmus was investigated. Eleven hundred eye-movement records served as control data. In 242 sessions, a significant, dose dependent increase in frequency and, to some extent, amplitude of saccades was found after the oral administration of 10—15 mg of Psilocybin, 120 μg of LSD, or 450 mg of mescaline. These three drugs produced a characteristic square-wave pattern of saccades distinctively dissimilar from the saw-tooth pattern produced by alcohol. There was no difference between the control and placebo patterns. The recording of physiological nystagmus may provide a valuable biological parameter for studying the effects of various drugs.

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Professor F. W. HEBBARD
Eye Movement Laboratory
School of Optometry
The Ohio State University
Columbus, Ohio 43210, U.S.A.

Professor ROLAND FISCHER
Division of Behavioral Sciences
Department of Psychiatry
The Ohio State University
Columbus, Ohio 43210, U.S.A.