INDIVIDUAL PUPILLARY REACTIONS TO CERTAIN CENTRALLY ACTING DRUGS IN MAN

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Individual variations in response are a common but little explored aspect of the action of many drugs, and those drugs which have important behavioral and emotional effects are especially likely to produce differing reactions from one person to another. This study is concerned primarily with evaluating the reliability and consistency of individual differences in pupillary response to four such drugs: lysergic acid diethylamide (LSD), chlorpromazine hydrochloride, secobarbital sodium and meperidine hydrochloride.

LSD characteristically produces dilatation of the pupil, whereas chlorpromazine produces constriction. Some individuals show these effects markedly; others, only slightly. The first question is whether individual deviations from the average effect are reliable, representing stable individual characteristics of response, or due to errors of measurement, unpredictable fluctuations in physiological state, or other chance factors. If individual variations in pupillary reaction are reliable for LSD and chlorpromazine separately, then we are particularly concerned with determining whether these individual variations show some consistency from the one drug to the other. Interest in meperidine and secobarbital here lies principally in exploring the possibility that reliable individual pupillary reactions might be obtained with two centrally acting drugs exhibiting little or no average pupillary effect.

METHODS. *Procedures.* The pupillary measurement for this study was incorporated as one test given 10 normal subjects in a comparative drug study (Kornetsky *et al.*, 1957). The subjects were 6 males and 4 females, 18 to 23 years of age. Each subject was tested under 10 conditions: a high dose and a low dose for each of the 4 drugs and 2 placebos. The dosages were 50 and 100 microgm. for LSD, 100 and 200 mgm. for secobarbital, 50 and 100 mgm. for meperidine, and 100, 200 and 400 mgm. for chlorpromazine, all administered orally. Doses of 200 and 400 mgm. of chlorpromazine were used with the first 4 subjects but had to be lowered to 100 and 200 mgm. for the other 6. Each subject still received a higher dose and a lower dose, and all subjects received 200 mgm. for one of the two doses. These drug conditions were randomly scheduled on different days with neither the subject nor the experimenter knowing which condition was being administered on a particular day. At least one day intervened between successive conditions. The pupillary measurements always occurred 2 to 3 hours after drug administration, following a series of relatively non-stressful and non-fatiguing psychological performance tests.

Pupil photographs were obtained under dark infrared illumination according to the following schedule: Five minutes was allowed for dark adaptation and 5 photographs were taken just before the end of the dark period. Then the stimulus light came on and photographs were taken for a period of 5 seconds. After 2 minutes' exposure to light, the stimulus

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light went off and photographs were taken over the first 10 seconds and at 5 minutes in the dark. The complete series was then repeated.

Apparatus. The subject was seated in an ophthalmic chair, his head held in a headrest with the right eye positioned in front of the camera lens. The stimulus light was a microscope illuminator producing an illuminance of 23 foot-candles on a test plate placed in the location of the eye. The light beam was directed on the eye through a lens, neutral density filter, and prism system from a location equivalent to a distance of 35 cm. and 15 deg. to the left of the optic axis. The light stimulus appeared subjectively to the eye as a bright, homogeneously illuminated disc, 2.8 cm. in diameter. It was controlled by an automatic timing system which interrupted the electrical circuit to the lamp. With eyes directed straight ahead a low luminance spot was visible through the prism to the left eye at a distance of approximately 1 m. The subject was instructed to fixate this point as an aid in keeping the orientation of the pupil of the right eye constant with respect to the camera lens and in minimizing accommodative changes. The camera took successive pictures on 35 mm. film at a fixed rate of 2.25 pictures per second. Pupil image diameters were measured directly from the film to the nearest 0.1 mm. and corrected by reference to a scale photographed at the same distance as the eye.

Measures. The 5 pupil diameters obtained at the end of 5 minutes in the dark were averaged together for a dilated pupil size score. The last 3 diameters at the end of 5 seconds' light exposure and the single diameter after 2 minutes' light exposure were averaged together for a constricted pupil size score. The slope of the best fitting straight line was computed by the least-squares method for the differences between drug and placebo diameters along the contraction curve, yielding a score for effect on average contraction speed. A similar slope measure for the points along the dilation curve was computed for effect on average dilation speed. The points beyond which each curve leveled off were not used. These various measures refer to the light and dark conditions of the experiment, and two of each measure were obtained at the same testing session for each subject under each drug condition.

Analysis. The primary method of analysis was correlational, and all correlations referred to in this paper are product-moment coefficients. A zero-order coefficient of 0.63 and a first-order partial coefficient of 0.67 are required here at the 5 per cent level of confidence (Fisher, 1950). All partial correlations referred to are based on statistically significant zero-order relationships between the two main variables involved. Wherever correlation coefficients were averaged, the averaging was done by means of Fisher's z-transformation.

RESULTS. *Average effects.* The overall effects of LSD and chlorpromazine were in the expected directions (table 1), and the higher doses produced greater effects than the lower doses (table 2). In addition LSD had a significantly greater effect on the constricted pupil than on the dilated pupil ($p < 0.01$). The difference between the 100-mgm. dose of meperidine and placebo is of the same order of magnitude as that reported by Fraser *et al.* (1954). This difference is of doubtful significance here, probably because the measurements occurred well into the period of declining effect for this drug. The averaged values for secobarbital were very nearly the same as the placebo values. Individual effects varied appreciably, however. The average difference from placebo for the subject showing the greatest effect of LSD was 2.04 mm., while this difference for the subject showing the least effect was 0.38 mm. The corresponding values for chlorpromazine are 1.89 mm. and 0.15 mm., respectively. Individual variations were nearly as great for meperidine and secobarbital, and differences in direction as well as magnitude occurred.

In fig. 1 a line parallel to the zero level would indicate no average effect on

TABLE 1

Average pupil diameters in mm.

Light condition		Placebo	LSD		Chlorpromazine		Meperidine	
			Measure					
			100 microgm.	50 microgm.	200, 400 mgm.	100, 200 mgm.	100 mgm.	50 mgm.
Pupil, dilated	Mean	6.83	7.57	7.27	5.56	6.63	6.36	7.01
	σ	1.16	0.51	0.73	1.53	0.97	1.31	0.85
	p*	—	<0.05	<0.10	<0.001	<0.10	>0.10	>0.10
Pupil, constricted	Mean	2.91	4.48	3.83	2.22	2.66	2.74	3.16
	σ	0.60	0.88	0.91	0.36	0.47	0.37	0.62
	p	—	<0.001	<0.001	<0.001	<0.05	>0.10	>0.10

* Probability associated with the t-value for the difference between correlated drug and placebo means, df = 9.

TABLE 2

Average high-dose pupil diameter minus low-dose pupil diameter in mm.

Light condition		LSD	Chlorpromazine	Meperidine
		Measure		
		100 microgm. vs. 50 microgm.	200, 400. mgm. vs. 100, 200 mgm.	100 mgm. vs. 50 mgm.
Pupil, dilated	Mean	0.30	−1.07	−0.65
	σ	0.32	0.70	0.83
	p*	0.02	<0.01	<0.05
Pupil, constricted	Mean	0.65	−0.43	−0.42
	σ	0.24	0.19	0.41
	p	<0.001	<0.001	<0.02

* Probability associated with the t-value for the difference between correlated higher and lower drug dose means, df = 9.

contraction and dilation speeds. Positive slope reflects a decrease in contraction speed, while negative slope reflects a decrease in dilation speed. The departures of the curves from zero slope were evaluated by means of a trend test (Alexander, 1946), leading to the conclusion that the speeds of pupillary contraction and dilation are significantly slower on the average for LSD, meperidine (100 mgm.), and chlorpromazine ($p \leqq 0.01$). In the case of LSD this effect on speed would appear to be a secondary consequence of the fact that the drug effect is relatively much greater on the constricted pupil than on the dilated pupil. For chlorpromazine the lack of a differential effect on constricted and dilated pupil sizes suggests that the effects on stable size and on speed may not be interdependent. The statistical analysis also provided a test for the significance of individual subject differences in the speed measures, and for all four drugs individual differences contributed highly significant proportions of the variance ($p < 0.001$).

Reliability of individual effects. The reliability of the pupillary measurement itself and the stability of individual pupil size may be shown by the correlations

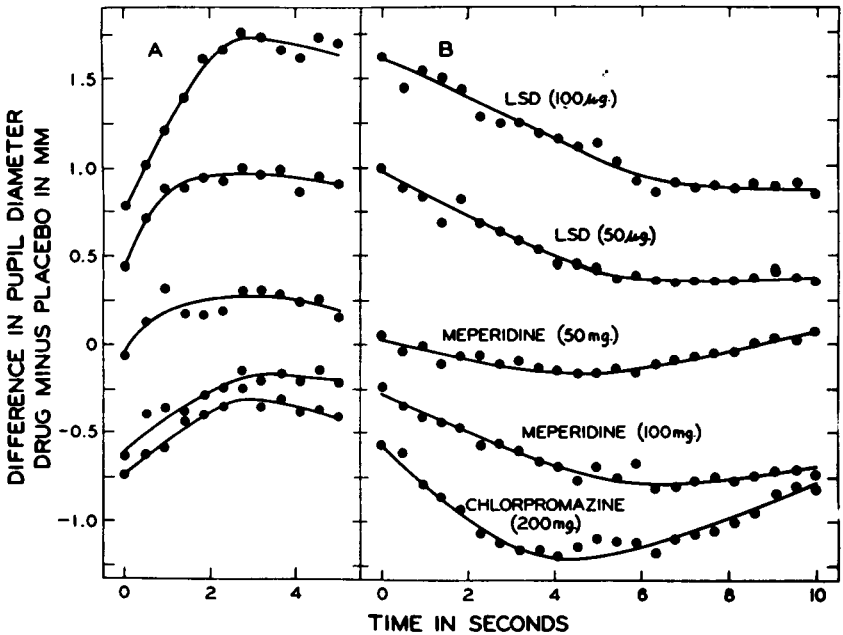

FIG. 1. Average differences between drug and placebo pupil diameters, (A) during contraction in response to the light stimulus and (B) during dilation in response to cessation of the light stimulus.

between the individual subject measures for placebo. The values for measures obtained on the same day are 0.96 and 0.89 for dilated and constricted pupil sizes, respectively. The values for measures obtained on different days are 0.80 and 0.90, respectively. Since pupil size in the various drug conditions is generally correlated with placebo pupil size, however, it is necessary to correct for variation in the placebo values in order to evaluate the reliability of the pupillary scores as measures of drug effect. This correction was accomplished by computing first-order partial correlation coefficients with the placebo values partialed out.

The partial correlations between the first and second measurements taken on the same drug day were uniformly high for all drug conditions except one. The average value for dilated pupil size is 0.89, for constricted size, 0.81. The only coefficient not reaching significance was that for the constricted pupil measure for the 100-mgm. dose of meperidine. This generally substantial within-day reliability means that the individual variations were not momentary chance fluctuations. Day-to-day reliability for LSD and chlorpromazine is evident from the significant correlations between the higher and lower dose conditions for both of these drugs (table 3). Those subjects tending to show a relatively greater pupillary effect with a low dose tended also to show a relatively greater effect on a different occasion with a larger dose. This is a more stringent test of relia-

TABLE 3

Correlations between higher and lower drug dose pupil diameters

Light condition	Measure	LSD	Chlorpromazine	Meperidine	Secobarbital
Pupil, dilated	r_{HL}	0.93	0.94	0.79	0.56
	$r_{HL \cdot P}$*	0.82	0.68	0.54	0.05
Pupil, constricted	r_{HL}	0.97	0.94	0.77	0.68
	$r_{HL \cdot P}$	0.86	0.72	0.46	0.19

* Placebo values partialed out.

bility than an ordinary reliability coefficient, and the correlations for meperidine might reach significance if the same dosages were used on the two different occasions. The extremely low correlations for secobarbital, however, indicate no consistency at all between the two occasions.

The results for the reliabilities of the individual pupillary speed measures were substantially the same as those presented for the size measures, except that drug effect on dilation speed tended consistently to be more reliable than drug effect on contraction speed. The speed measures were significantly related to the size measures for LSD, individually greater effect on stable size correlating with greater effect on pupillary speed. This was not true for chlorpromazine, bearing out the possibility of independence noted above between the average effects of chlorpromazine on stable pupil size and on pupillary speed.

Between-drug correlations. The partial correlations between LSD and chlorpromazine were computed separately for higher and lower doses, constricted and dilated pupil sizes, and contraction and dilation speeds. The correlations for effects on stable pupil size were in general not significant, although they consistently showed an inverse relationship. The correlations for effects on pupillary speed were significant separately, however, and the average correlation was -0.74. Referring to fig. 1, this means that the individual subject showing a steeper curve (greater slowing down) with LSD tended to show a less steep curve (less slowing down) with chlorpromazine, and vice-versa, for both contraction and dilation speeds.

DISCUSSION. For the drugs tested the degree of reliability of individual variations in pupillary response agreed exactly with the order of average pupillary potency, from most to least: LSD, chlorpromazine, meperidine and secobarbital. This would be a very useful principle in organizing data on the difficult problem of individual differences, if it should prove to possess sufficiently wide generality. It is not true of necessity, for one individual may react reliably in one direction and another in a different direction, resulting in what appears to be no effect in averaged data.

From the average effects for LSD and chlorpromazine it is clear that these two drugs have different rather than simply opposite effects on pupillary behavior. This is in agreement with the view that LSD may exert a primarily central sympathicotonic influence on the pupil (Rothlin, 1957), while chlorpromazine may affect the pupil through a predominantly peripheral adrenolytic action (Holzbauer and Vogt, 1954). There would appear to be meaningfully

related aspects of action, however, for if both drugs are administered together chlorpromazine reduces both the psychological and the autonomic manifestations of LSD (Hoch, 1955), including a reduction in the pupillary effect of LSD (Isbell and Logan, 1957). Although it is an over-simplification to reduce the emotional effects of these two drugs to a single dimension, we may think of LSD as having, generally, an agitating, anxiety-producing effect and chlorpromazine, a calming effect. The pupillary effects appear to be compatible with the emotional effects for both drugs in that fear, anxiety and emotion-provoking stimuli produce pupillary dilatation (Bender, 1933; Gang, 1945) whereas sleep and other quiescent conditions tend to produce pupillary constriction (Kleitman, 1923; Byrne, 1942). In terms of the consistency of individual pupillary reactions obtained here, a subject showing relatively greater effect with LSD tends to show relatively less effect with chlorpromazine. Psychologically, it would also be entirely reasonable for the individual who is most "agitated" by LSD to be the least "calmed" by chlorpromazine. This is a matter for further test, of course, since subjective effects do not necessarily correspond closely to what one might predict from physiological effects.

SUMMARY

Ten normal subjects received higher and lower oral doses of LSD, chlorpromazine, meperidine, secobarbital and placebo. Pupil photographs were obtained under light and dark stimulus conditions for each of the drug conditions, yielding measures of effect on pupil size and on speeds of contraction and dilation. The data were analyzed primarily in terms of the reliability and consistency of individual pupillary reactions to these drugs.

LSD and chlorpromazine produced significant average pupillary effects, meperidine produced little effect and secobarbital, none. The degree of reliability of individual variations in response corresponded to the degree of average pupillary potency among these four drugs. A relationship was found between the effects of LSD and chlorpromazine on the speed of pupillary contraction and dilation, subjects showing relatively greater effect with LSD tending to show relatively less effect with chlorpromazine.

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