ETHOLOGICAL AND STATISTICAL ANALYSIS OF DRUG EFFECTS ON THE SOCIAL BEHAVIOUR OF LABORATORY RATS

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Ethology provides a way of observing animal behaviour with increasing precision, and allows quantitative descriptions to be made of animal behaviour in the wild as well as in the laboratory. The limit is what the observer can see, rather than what the animal is allowed the opportunity to do.

Work on the social behaviour of laboratory rats, chiefly by E. C. Grant in this laboratory, shows the results of this approach in a species convenient for pharmacological and other experimental treatment (see also Chance & Silverman, 1964). This paper describes ^a method for such a pharmacological study. The results of one experiment will be described as a detailed illustration, but the specific results, with different dosages and different drugs, will be discussed elsewhere.

Social behaviour of the laboratory rat

An observational study of behaviour has to be demonstrably objective, and it will therefore be useful to outline not only the behaviour itself, but also the method Grant used to analyse it.

The first stage in such a method is to watch animals in the same cage, to recognize the responses that the animals are making and to identify the units of which these responses are composed. Over forty such elements (acts or postures) are described and illustrated by Grant & Mackintosh (1963), and are listed, with brief descriptions, in Table 1. The elements are morphological units, but are given descriptive names which are easier for an observer to learn than purely morphological ones or mere syllables.

If these elements are then counted in the sequence in which they occur, the probability with which each leads to each can be calculated. It then becomes clear (Grant, 1963) that the elements occur in fairly discrete groups; some sequences occur at very considerably above the chance level, and many possible ones do not occur at all. Whatever the factors are which bind elements together (such factors being termed tendencies), it becomes helpful to give each one some name. The terminology adopted should be understood as follows. Consecutive actions of an animal are not at random; they must presumably have related but not identical functions. Actions with related functions are likely to have related causes (that is, motivation) and, although they must be distinguished, it is heuristically helpful to name the motivation in terms of its presumed function (compare Miller, 1964).

The most reliable way of doing this is to take one element, for example RETREAT, and use it as a *definition*. Thus the elements which are described as having a Flight component are those with a high probability of leading to or from RETREAT. Similarly, Mating elements lead to or from MOUNT, and Aggressive elements are associated with BITE.

These three tendencies account for nearly the whole of the behaviour oriented to another adult rat. However, in fact, BITE occurs very rarely, the elements leading to it lead more commonly to AGGRESSIVE POSTURE. This is an end-point of ^a sequence, and is associated with the corresponding end-point of another sequence in another rat, SUBMIT. Two subgroups can be distinguished in the Flight tendency of rats, one leading to SUBMIT and allowing the animals to remain in close proximity, the other termed Escape and typically resulting in their spatial separation.

Other types of behaviour are also seen, of course, even in a social situation, notably Exploration of the physical environment and of the other rat (exploration of the latter being labelled Investigation), Eating and Self-grooming. Sometimes these elements occur in a form and context which suggest they are being used as Displacement Activities (see Bastock, Morris & Moynihan, 1953); these occasions imply motivational conflict.

The elements appear to function as signals of the performer's probable next actions. Thus a hypothetical threat posture, if the other animal did not go away, would most likely be followed by a bite, but less likely by the actor's own retreat. Since rats do react differently to different elements, they must be able to discriminate them, and if a rat can, so can a man.

Elements are morphological units, but many (like the above " threat ") represent more than one tendency, tendencies being at levels and in proportions characteristic for each element. The elements listed in Table ¹ are classified into categories by the tendency predominating in the motivation for each one (information on this is taken mainly from Grant, 1963, and unpublished). The categories seem to be valid, but are not homogeneous: there would presumably be no selective advantage in evolving two elements to signal precisely the same thing. Note that Investigation, Mating, Aggression and Submission represent approach to the other rat, while Escape and Submission represent withdrawal from him. The Exploration and Maintenance categories are not oriented to the other rat; the Residual category is for elements of uncertain motivation or rare occurrence.

The elements with subsidiary motivation most marked are as follows: FOLLOW, SNIFF and LICK PENIS are associated with MOUNT (Mating). TO-FRO, WALK ROUND, STRETCHED ATTENTION and TAIL RATTLE represent approach-avoidance ambivalence from any cause (the last two being at high intensity). Both UPRIGHTs and both SIDEWAYS postures (the latter at high intensity) are ambivalent between Aggression and Submission, but can be subdivided according to which predominates. ELEVATED CROUCH may have an Aggressive component. ATTEND is strictly introductory to all other social behaviour but, being often superimposed on CROUCH, etc., an increase in it usually indicates Escape.

TABLE ¹

BRIEF DESCRIPTION OF TERMS USED IN THE TEXT

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METHODS

Rats were isolated one per cage for ^a few days, then one was introduced into the home cage of another, This concentrated their normal social behaviour into ^a short period of the experimenter's choice. One rat of each pair had been injected with saline or one of two drugs, and was observed on one occasion only. The other (the "partner ") had not been injected, but was introduced on three occasions on successive days, meeting one rat from each experimental set in a suitably counter-balanced order.

The animals used were male rats (Rattus norvegicus) of an agouti strain bred in the laboratory. As far as possible they were not inbred. They were used at ¹⁰ to ¹² weeks of age, that is as young adults, and after weaning had been kept in monosexual groups of six; in subsequent tests, groups were of four, allowing ^a rank order to be set up (Grant & Chance, 1958) which is felt to be helpful.

Cages were of wire, $42 \times 30 \times 24$ cm, with a food hopper suspended in one corner, the space underneath which was commonly used as a refuge. They rested on ^a tray covered with sawdust, changed weekly, and food and water were freely available at all times. Temperature was about 18^o C. At least 2 weeks before testing, animals were moved into the experimental room, where the light cycle was "reversed "-a 150-W white light overnight, a dim red light replacing it at the time of day when observations started; observations were thus made when rats are normally most active.

One week before testing, the animals were isolated, and during that week were handled individually on three occasions (to habituate them to the experimenter and to being held for intraperitoneal injection). On the last of these occasions they were weighed, and the partners were marked for identification by clipping a little fur with scissors. Subsequent experiments suggested that a greater variety of drug effects could be revealed by isolating for a shorter period (say ³ days), especially if there were a repeat test ⁷ days later (with individual rats reassigned to equate experience).

There were twenty-four rats per test, six partners and six in each experimental set. In assigning individuals, care was taken that litter- and cage-mates were distributed evenly across treatments (this includes the order in which cage-mates came to hand); that treatments were in equal numbers on each day and each time of day; and that partners met individuals from each experimental set in different orders. The experimental rats were in their home cages, and none had met the individual partner previously.

Injections were intraperitoneal, in a volume of 1 ml./kg, and were made about 30 sec before starting the introduction. Other periods of delay have been tried (15 min or¹ hr), with no difference to the results. In the example to be described, experimental rats were given chlorpromazine in a dose of 1 or 4 mg/kg, or saline.

Introductions lasted ¹⁰ min each, and six (two of each set) were made within 1.5 hr or so on each of three successive mornings. One observer watched all experimental rats, and another observed the partners. Every time an animal performed ^a recognized element, his observer spoke the element's code name on to ^a stereophonic tape-recorder. The observer also caused ^a mark on ^a paper-strip pen-recorder, to make ^a permanent record in which the ticks on two lines on the paper represent the actions of two rats, with ^a 1-sec time marker between. The average number of all elements of all kinds shown by one rat in a 10-min introduction was about 280 to 300, about one every ² sec. The maximum was 500, with up to four elements recorded in ¹ sec.

RESULTS

If ^a drug has had an effect on motivation, it would be expected to alter the sequences of elements, the frequency with which each element is followed by each other element in the same animal, or the cross-correlation sequences between animals. For example, if an ambivalent element in an experimental rat (or partner) is most commonly followed by ^a purely Aggressive element in the saline controls, but by a purely Flight element in the drugged animals, then it could be inferred that the drug had relatively increased the Flight tendency.

Routine analysis of sequences is difficult and unnecessary. A simple indirect method is to count the total occurrence of each element. If in sequences an UPRIGHT leads mainly

to ATTACK in the controls but to CROUCH in the drugged animals, then the total numbers of these two elements in a set period will alter accordingly, and similar inferences can be made.

It is true that some elements, notably CROUCH and EXPLORE, tend to last for ^a longer time than others, so that total occurrence, without measurement of total duration, may not reflect the relative importance of the competing tendencies adequately. In practice it works quite well, however, since, if some elements are of relatively long duration, then the total numbers are fewer, and the slow elements form a larger proportion of the whole.

The statistical test used is the x^2 , since it is quick, makes few assumptions about the populations sampled and, above all, since it will distinguish differences in pattern. Drug effects on total activity, the total of all kinds of elements, are of interest, but are less important than differences in the distribution of the forty or so elements in the two sets of animals (this assumes, by the way, what has been true so far, that there is a significant overall difference between the three experimental sets).

The numbers of each element shown by all six drugged and all six saline-injected rats are cast in a table of 2×30 cells or so; in any one test, some elements occur only rarely and have to be combined with other elements of related motivation, or as a " residual " element at the end. Table 2 gives the results of the test with chlorpromazine, 1 mg/kg , as an example, and shows each element's contribution to the total χ^2 . [Expected for each cell=(Row total × Column total)/(Grand total). Each element's contribution to x^2 is then found by the formula $\chi^2 = k(O-E)^2/E$, where O and E refer as usual to the Observed and Expected occurrence of the element in one set of rats (one column), and $k=$ (Grand total)/(Other column total).]

It can be seen that chlorpromazine depressed overall activity, reducing the total number of elements recorded from 2,170 to 1,898 (for which χ^2 ₁=18.2, P<0.001). More interesting is that there is a highly significant difference (χ^2_{30} =163.1) in the distribution of the elements, that is to say, a difference in the behaviour as such.

What is the effect on behaviour ? It can be seen that different elements did not contribute equally to the overall x^2 . APPROACH, AGGRESSIVE GROOM and others had a contribution of zero, and it is inferred that the drug had no action on them. On the other hand, there are obvious differences in the numbers of ATTEND, OFFENSIVE SIDE-WAYS, etc., observed in the two sets of animals. Comparing each element with all other elements in the two sets of rats, a χ^2 at one degree of freedom will be found to be numerically virtually identical with that element's contribution as shown in Table 2. Although some caution is of course necessary, since one element in twenty would be expected to appear significantly different at the 5% level, an element's contribution to the total χ^2 can therefore be used to measure the extent to which it has been individually affected by the drug.

The elements which were significantly affected in this test are marked in Table 2. Comparison of observed with expected shows whether the element has been increased or reduced by the drug. Thus, the elements which have been individually significantly increased by ^I mg/kg of chlorpromazine are: ATTEND, CROUCH, UNDER HOPPER and WASH; those reduced are: FOLLOW, ATTEMPT MOUNT/MOUNT, TO-FRO/WALK-ROUND, AGGRESSIVE POSTURE, THREAT, OFFENSIVE UPRIGHT and OFFEN-SIVE SIDEWAYS. It can be seen that these elements fall into a pattern. Three of the

*, ** and *** refer to probabilities of $\langle 0.05, \langle 0.01 \rangle$ and $\langle 0.001 \rangle$ respectively

four increased are in the Escape category, while nearly all the Mating and Aggression elements were reduced. Some approach motivation remained, however, since Submission and the unmixed Investigation elements were not reduced, and the increase in WASH (the rat's commonest displacement activity) implies some conflict.

Discrimination of motivational from other drug effects is most reliably made by consideration of which elements have been individually altered. This will be discussed below. Meanwhile, since all the elements in each category have their principal motivation in common, any drug effects on motivation should be reflected on the category as a whole. Each category total is therefore compared separately in 2×2 tables of x^2 at one degree of freedom. However, a significant effect in this Category χ^2 could appear in two ways. First, by a uniform change of all its constituent elements, which would be a genuine change in motivation, and secondly by a large change in a single element, perhaps by some drug effect quite unconnected with the other elements of the category. This can be checked by a third set of χ^2 s, to measure the variability within each category: the smaller is this χ^2 , the more likely is any Category effect to be a genuine motivational one.

Calculation of the Category and Variability χ^2 s is illustrated in Table 3 for the same example as Table 2, and the results are displayed in a histogram (Fig. 1), together with the results of the parallel test for 4 mg/kg of chlorpromazine. In the histograms, the rectangles represent the Category χ^2 , above or below the centre line respectively when the drug set's Observed is more or less than Expected. The thin lines represent the Variability χ^2 , taking the Category x^2 as the baseline and summing the contributions of the elements with observed occurrences more or less than expected respectively. It is clear from this histo-

Fig. 1. The behaviour of rats injected with ¹ or 4 mg/kg of chlorpromazine compared with that of saline controls (six rats per set) meeting the same partners. The rectangles of the histogram represent the value of x^2 for the total occurrence of all elements in each category (at one degree of freedom). the lines the χ^2 for the variability of the two to eight elements within the category. The histograms are above and below the centre line when the drug set's observed is more or less than expected, respectively. Significance levels are indicated on the ordinate for $P<0.05$, <0.01 and <0.001 at one degree of freedom. EXPL=EXPLORATION; INV+M=INVESTIGATION and MATING; AGGR= AGGRESSION; SUBM=SUBMISSION; ESC=ESCAPE; MAINT=MAINTENANCE; and RES=RESIDUAL.

TABLE 3 x²s BETWEEN CATEGORIES AND FOR VARIABILITY WITHIN THEM, FOR THE EFFECT OF CHLORPROMAZINE (1 mg/kg)

*, ** and *** refer to probabilities of $\lt 0.05$, $\lt 0.01$ and $\lt 0.001$ respectively

gram that chlorpromazine has reduced Investigation and Mating (this category not uniformly, at ¹ mg/kg, as we know also from Table 2) and Aggression, and has increased Escape. Those tendencies involving neither approach nor avoidance of the other rat were not systematically affected, nor was Submission which involves both. A dose of ⁴ mg/kg of chlorpromazine has effects similar in kind, but greater, on a comparison with the same controls. It will be shown in a future paper that this effect and its dose-sensitivity are consistent in repeated tests.

Finally, if a drug has affected motivation, then such an effect should be reflected in the behaviour of the partners. The partners did behave very significantly differently (χ^2_{28} =98.7) towards rats given ¹ mg/kg of chlorpromazine compared with saline controls. They showed less Flight (for WALK-ROUND, OFFENSIVE- and DEFENSIVE-UPRIGHTs, FLAG/ CROUCH, and ATTEND were all reduced) while ATTACK was increased; but ^a crouching rat does not present the correct releasing stimuli for Aggression, and Maintenance elements (WASH, SELF-GROOM, DIG) with EXPLORE and RESIDUAL were increased, perhaps as displacement acts. Thus, the drug had an effect on the animals not receiving it, an effect of the kind, moreover, to be expected from the direct effects. This shows, however, that the partners cannot themselves be used as saline controls.

Fig. 2. The behaviour of twelve rats observed by one observer (C.A.S., who was "experimentally naive") at the time of Experiment 2) compared with that of twelve rats watched by another (A. P. S.). Symbols and abbreviations as in Fig. 1. Note that in Experiment 17, a year later, the difference is very small (a Spearman rank-order correlation at forty degrees of freedom has a coefficient $r_a = 0.9217$, for which $t = 15.03$).

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The same methods of analysis can, of course, be applied to factors other than drugs. In this way it has been shown, for example, that it does make a little difference to a laboratory rat to be in a stranger's cage, but this effect is small, not very consistent from one test to another, and not systematic in terms of these categories. The same is true for such factors as delaying introductions for 15 min after injection of saline, or as experience of a previous introduction.

Observers can also show differences as big as drug effects, though the experimental design prevents them masking the latter. Two comparisons are shown in Fig. 2, in the first of which one observer was " experimentally naive." In contrast to drugs, observer-differences depend on relatively big effects on a few scattered elements; they are not systematic in terms of categories. (This shows also that significant Category χ^2 s are not a function of the number of elements composing the category.) Moreover, a Spearman rank-order correlation test has a more conventional null hypothesis for comparing observers, and in Test 17 it shows a remarkably high correlation: $r_s=0.922$, d.f. $=40$, $t=15.03$, $P \le 0.001$.

DISCUSSION

Any reliable measure of behaviour in a laboratory must necessarily limit the animal's flexibility of response to some extent, but it seems from reviews (Miller & Barry, 1960; Dews & Morse, 1961; Hunt, 1961; Cook & Kelleher, 1963) that there is room for additional reliable psychopharmacological methods which would do so as little as possible (Irwin, 1964). For the published observational techniques, such as that of Norton (1957), rarely give evidence for the validity of the measures they take, and are also liable to be imprecise. Yet it seems a fair generalization that those methods which succeed in being objective and quantitative do so by training the animal to canalize all its responses into at most two channels, albeit simple and easily counted ones. The single- and multi-response approaches should not be incompatible, but complementary.

This comment is illustrated by most of the few papers published on drug effects on social behaviour. For example, Tedeschi, Tedeschi, Mucha, Cook, Mattis & Fellows (1959) studied shock-induced fighting in mice, and Janssen, Jageneau & Niemegeers (1960) induced it, as in the present paper, by pre-experimental isolation, though they could only use a proportion of their animals. In both papers, " fighting " was taken as a single, simple unit without internal structure, and this limited the information obtainable. They looked for drugs selectively reducing fighting, and would not have detected one which increased it, besides needing separate tests to discriminate drug effects on analgesia, activity, motor co-ordination, etc.

There is, nevertheless, an internal structure to social behaviour whose parts can be separately influenced by drugs (Norton, 1957). Evans & Abramson (1958) and Evans, Abramson & Fremont Smith (1958) showed for the newt Triturus viridescens and the Siamese fighting fish Betta splendens, respectively, that lysergic acid diethylamide lowered the threshold for aggression, on criteria of threats and displays, as well as the more obvious chases and bites; so that the drug enabled low-ranking individuals to rise in the normal dominance hierarchy.

Motivational effects of drugs, of course, are not the only possible ones. Observation does not replace more specialized techniques for evaluating these, but it can detect them. For instance, in this social situation, ataxia due to amylobarbitone sodium can be observed at 15 mg/kg, but not at 10 mg/kg; this agrees with the threshold measured by Rushton & Steinberg (1963).

The more measures are taken of a motivational effect, the more information is available to discriminate it from others. Fig. ¹ shows that chlorpromazine can be described as reducing Aggression and Mating and increasing Escape. If the separate elements are considered (Table 2), they give internal evidence on other possible effects.

Thus, it might be argued that the drug causes ataxia or some comparable motor depression, so that (in anthropomorphic terms, for clarity) the animal might want to attack or mount, but be unable to do so. However, elements posturally similar, thus making similar demands on the motor system, were not affected in the same way: OFFENSIVE UPRIGHT was reduced, but, of the other postures where the rat stands on hindlegs and tail with forelegs in the air, DEFENSIVE UPRIGHT and SCAN were unchanged and WASH was increased.

Secondly, locomotion might be reduced, in the sense that all movements might be slowed down, or the faster elements might not occur. There is some evidence for this occurring, for some of the elements reduced are quicker than the average, while CROUCH and ATTEND (increased by chlorpromazine) often lasted ^a relatively long time. This correlates with the overall reduction in the number of elements recorded. Such an effect probably does play a part in the observed results, but does not account for all of them, since OFFEN-SIVE UPRIGHT (a fairly slow-moving element) was reduced, while RETREAT and ON BARS (which are fast ones) were unchanged. A reduction in locomotion could cause the observed re-distribution of elements, or could be its consequence, or could be unrelated to it.

Thirdly, the drug could have interfered with the exteroceptive senses. If this had occurred in any simple way, some alteration would be expected in exploration, either of the cage or the partner. Yet, of EXPLORE, SCAN, APPROACH and NOSE (unlike the elements with a Mating component), none was significantly either increased or reduced.

The real change seems, therefore, to be in the tendencies released by essentially the same sensory stimuli, the same partner rats. It may be necessary to regard a Tendency (an empirical entity) as having two more hypothetical aspects, Drive (the purely internal " causes " of a particular behaviour) and responsiveness to particular types of stimuli. Chlorpromazine may well act predominantly on the latter.

It is hoped to discuss this more fully elsewhere, since the present paper is intended merely to illustrate the implications of attempting to observe everything the animal does in a comparatively open situation. This does demand care and practice, but is not nearly as difficult as it sounds. It depends, however, on a prior detailed analysis of the relationships of the behaviour's component elements and, further, on a statistical method which, though crude, allows the simultaneous analysis of several variables. It is also noteworthy that, unless a drug's effects are of dramatic extent, they are generally apparent only after the statistical analysis. Hence the method may be claimed to be more sensitive than " simple observation," as well as free from subjective bias. Finally, without an attempt at including everything, either the behaviour itself would again become unnecessarily restricted or one's knowledge of it would, and the method would be no useful addition to present psychopharmacological techniques.

SUMMARY

1. Reference is made to an analysis of the social behaviour of the male laboratory rat. Over forty elements have been recognized in rats' social behaviour, and they can be classified into categories of Exploration, Investigation and Mating, Aggression, Flight (in the two forms, Submission and Escape), Maintenance and a Residual category.

2. A method is described for investigating the pharmacology of this system. One rat (the "partner ") is introduced into the home cage of another which has been injected with saline or a drug, and two observers record the 300 or so elements displayed by each rat in 10 min.

3. Numbers of each element in sets of control and drugged rats are compared by a series of x^2 tests. The first $(2 \times N)$, measures the overall drug effect and which of the N elements have been individually altered. For each motivational category another (2×2) χ^2 measures alteration of its occurrence as a whole, and a third $(2 \times n)$ the variability of effect on the n elements composing it. Non-injected partners show corresponding differences.

4. An example shows that chlorpromazine reduces Aggression and Mating and increases Escape in rats in this situation, whereas other variables have less systematic effect.

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