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Rapid visual learning in the rat: Effects at the 5-HT_{1a} receptor subtype

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The 5-hydroxytryptamine$_{1a}$ (5-HT_{1a}) receptor agonist 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT; 0.15 mg/kg) impaired rats' rapid visual learning on a computerized maze. This treatment also increased decision time (DT) but the learning impairment was not necessarily a side-effect of slower responding because, in this task, responses made at long DT are more accurate than those at short DT. The selective 5-HT_{1a} receptor antagonist WAY–100635 (0.3 mg/kg) was itself without effect on accuracy, but was effective in reversing effects of 8-OH-DPAT (on both accuracy and DT). Within problems (i.e., over the 40–60 trials of a single discrimination), performance was reduced by treatment with 8-OH-DPAT at all stages of learning. We conclude that this effect is mediated through the 5-HT_{1a} receptor site (rather than through some other serotonergic receptor site or non-specific mechanism) as it was reversible by treatment with WAY–100635. Although it could still arise from behaviourally non-specific effects, the performance deficit finds its best account in terms of the psychological processes necessary to visual learning. Its reversal with WAY–100635 offers support to the hypothesis that 5-HT_{1a} receptor antagonists could improve cognitive function, under conditions of pre-existing impairment due to overactive serotonergic inhibition, as is thought to occur in Alzheimer's disease.

The serotonergic (5-hydroxytryptamine, 5-HT) system is implicated in normal learning and in impairments of learning due to ageing and dementia (Altman & Normile, 1988; McEntee & Crook, 1991). Thus antagonists at the 5-HT_{1a} receptor site could provide a mechanism to increase the function of cortical pyramidal cells in Alzheimer's disease (e.g., Bowen, Francis, Pangalos, Stephens, & Proctor, 1992; Francis, Sims, Procter, & Bowen, 1993). Such antagonists might work by blocking the tonic hyperpolarizing effects of endogenous 5-HT and thus enhance glutamatergic excitation in functioning cells (Dijk,

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Francis, Stratmann, & Bowen, 1995). Further, in normal animals, 5-HT_{1a} receptor agonists like 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) might similarly "switch off" cortical pyramidal neurones and result in cognitive deficits (Francis et al., 1993).

We previously found that 8-OH-DPAT impaired visual learning as measured by discriminative accuracy, independent of its effects on response time, which was used as a measure of non-specific effects (Cassaday & Gaffan, 1996). However, 8-OH-DPAT is now known to bind 5-HT_7 receptor sites (Shen et al., 1993). To define further the relevant receptor subtypes, in the present study we tested whether 8-OH-DPAT's effects in this task are reversible by treatment with a 5-HT_{1a} receptor antagonist. WAY–100635 is 100-fold selective for the 5-HT_{1a} receptor site relative to its binding at other sites (Forster et al., 1995).

Although 5-HT_{1a} receptor antagonists have been shown to block a number of 8-OH-DPAT effects (Fletcher et al., 1996), there have been relatively few clear demonstrations that 8-OH-DPAT has cognitive effects (but see Carli & Samanin, 1992), and a number of studies have highlighted the difficulty in dissociating cognitive effects from non-specific effects on performance when 8-OH-DPAT is given systemically (e.g., Stanhope, McLenachan, & Dourish, 1995; Warburton, Harrison, Robbins, & Everitt, 1997). Given this difficulty, there is scant evidence that cognitive effects of 8-OH-DPAT are blocked by pre-treatment with selective 5-HT_{1a} receptor antagonists. Carli and Samanin (1992) found that 8-OH-DPAT impaired spatial learning in the water maze and went on to demonstrate that spatial impairment could be demonstrated by (intrahippocampal) 8-OH-DPAT treatment that was without effect on visual learning in the same water maze task (Carli, Luschi, Garofalo, & Samanin, 1995). This dissociation suggests that the spatial impairment was not simply a consequence of non-specific deleterious effects of the 8-OH-DPAT treatment.

In the present study, we assessed the effect of systemic 8-OH-DPAT and WAY–100635 using exactly the same paradigm and apparatus as previously (constant-negative discrimination training in a computer-controlled Y-maze, Cassaday & Gaffan, 1996), to allow direct comparison. In this procedure, rats learn a series of discrimination problems in which the stimuli are complex, wide-angle visual displays ("scenes") drawn from a large population. Each problem consists of a series of trials in which the rat chooses between two scenes: the constant, which is the same on every trial, and the variable, which is different on every trial. Food reward is given for choosing the variable not the constant.

We tested pigmented rats of two strains, Dark Agouti (DA) and Hooded Lister (HL). HLs are less proficient than DAs at visual learning (Aggleton, 1996; Gaffan & Eacott, 1995) so it was necessary to give them a slightly less demanding version of the task in order to maintain constant discrimination and to keep the baseline performance comparable to that of the DAs. Thus the DAs learned two new problems per session for 40 trials each (a similar procedure to that of Cassaday & Gaffan, 1996), whereas the HLs had only one new problem per session for 60 trials. We analysed to check that drug effects were consistent across the groups.

It is important to dissociate the motor side-effects of a drug such as 8-OH-DPAT from its effects on learning per se. In our apparatus, accuracy of discrimination varies with decision latency, faster responses being less accurate than slower responses (Cassaday &

Gaffan, 1996; Gaffan & Eacott, 1997). 8-OH-DPAT can affect response time, lengthening or shortening it at different doses, and such effects must be compensated for when assessing whether a particular dose of the drug changes choice accuracy during discrimination learning. Cassaday and Gaffan (1996) developed a method of partialling out the effects of a drug on speed of responding from its effect on discrimination.

Method

Subjects

Subjects were 10 male rats (Harlan-UK, Bicester, Oxfordshire, England); 6 were of the HL strain, and 4 were DA rats. The HL rats had previously taken part in an experiment on food choice, but were otherwise naïve at the start of training in the maze, when they were aged 27 weeks. They commenced drug testing at 44 weeks of age. The male DA rats were aged approximately 90 weeks at the start of drug testing; they had extensive previous experience in the constant-negative paradigm with a variety of stimuli (Simpson & Gaffan, 1999), including scenes of the type used in this study. All the rats were drug-naïve. They were housed in pairs, with free access to water, and were maintained at or above 85% of ad libitum weight by feeding after experimental sessions. They were kept on a 12: 12-hr light cycle and were tested during the light phase.

Apparatus and stimuli

Two computer-controlled Y-mazes were used. The two mazes were similar in overall dimensions and equipment but differed in some details (for a floor plan see Gaffan & Eacott, 1995; Simpson & Gaffan, 1999). The second maze had the same layout as that of the first maze, but the entrances to the arms were 200 mm wide at their narrowest point, about 40 mm wider than those in the first maze.

In other respects the mazes were the same: Each of the three arms was equipped with two monochrome VGA monitors (Philips or Hyundai) placed side-by-side at a shallow angle, 430 mm from the maze centre. This dimension is the equivalent of arm length in a conventional maze. The monitors provided a total image area 470 mm wide by 185 mm high, subtending about 94° horizontally at the maze centre. In each arm, in the space between the two screens, was a food magazine, into which 45-mg diet pellets (Bioserv, Campden Instruments, Loughborough, Leics., or Noyes, Sandown Scientific, Esher, Surrey) were dropped from a dispenser (first maze: Campden Instruments, Loughborough, Leics.; second maze: Cambridge Cognition, Ely, Cambs.) located above the maze. The magazine could be internally illuminated. Each arm was crossed by two infrared photodetector beams, 230 and 300 mm from the maze centre, to monitor the rat's presence in the arms. The transparent flap in front of the food tray was fitted with a microswitch to monitor tray entries. The maze was painted matt black and roofed with Perspex. The room was dimly lit by a 40-W bulb reflecting off a white wall 2 m from the nearest maze edge, and overhead video cameras allowed the experimenter to monitor events from an adjacent room. All inputs and outputs, including stimulus presentation, were handled by a 486DX IBM-compatible computer (one for each maze) fitted with three Dual VGA Plus or Warp 2 video cards (Colorgraphics Communications, Atlanta, Georgia, U.S.A.), each capable of independently controlling two VGA monitors. Control programs were written in Turbo Pascal 6.0.

Stimuli. These were 120 different complex scenes. Each scene could be displayed across the whole area of the two monitor screens in a maze arm and was left–right symmetrical. A scene

comprised a background, which could be plain or include some large ellipse segments, and between 4 and 10 foreground figures of various sizes and shapes (e.g., rectangles, irregular polygons) scattered randomly across it. Half the scenes had a light-grey background and foreground figures in darker greys, the remainder had a dark-grey background and lighter grey foreground figures. Luminance of the greys fell between 0 and 15 cd/m^2 (Gaffan & Eacott, 1995; Gaffan & Woolmore, 1996).

Procedure

Pretraining. The DA rats required no special training as they were already trained in this procedure; they simply received a few sessions of the variant to be used for drug testing (see later) preceded by saline injections.

The HL rats were habituated to the maze and trained to collect food pellets from the illuminated food tray and to approach any maze arm in which a pattern appeared (for details, see Gaffan & Eacott, 1995; Gaffan & Woolmore, 1996). They were then given a series of constant-negative discrimination problems. Each problem had a different constant scene, drawn randomly from the pool of 120 scenes (see Stimuli), and different rats had different sequences of constant scenes. Within any one session, every trial had a different variable scene, again sampled randomly from the remainder of the pool. The number of trials per problem was gradually reduced, as described later.

The events within a trial were as follows (see Cassaday & Gaffan, 1996; Gaffan & Woolmore, 1996). One of the three maze arms was defined as the start arm, and the choice scenes were drawn (invisibly, at first) in the remaining two arms, the constant being randomly positioned to the right or left of the start arm. In the first trial of a session, the start arm could be any of the three at random, and a white bar was displayed in that arm to show the rat where to go; in all later trials, the start arm was the arm that the rat had chosen on the preceding trial. When the rat entered the start arm, the two choice stimuli were made visible in the remaining two arms. The choice was between the constant and a variable scene, which, as previously stated, was different on every trial (for illustration of procedure see Simpson & Gaffan, 1999).

A correct response (i.e., choice of the variable) was rewarded with two food pellets. As soon as the rat had collected the pellets, the stimuli were turned off, and the next trial's choice stimuli were made visible in the other two arms. An error (i.e., choice of the constant) caused both stimuli to be turned off immediately. Following a minimum interval of 8 s, the next time the rat entered the new start arm (the arm it had chosen on the preceding trial) the choice stimuli for the next trial were presented. There was no correction procedure following errors. The rat's response latency, from onset of the choice stimuli to entering the chosen arm, was recorded in 0.01-s units (centiseconds, cs) on every choice trial whether correct or wrong.

During the first four problems, each problem continued across more than one session if necessary, for a maximum of 80 trials per session, until the rat reached a criterion of discrimination, 80% correct within 50 successive trials. The next four problems were each given for a maximum of two sessions of 80 trials, without requiring criterion to be reached, and the next four problems were given for one session each. Ten sessions followed in which two new problems were given in each session, for 40 trials each, separated by a 12-s inter-problem interval. However, the HL rats did not discriminate well enough under these conditions (compared with the original acquisition of the DAs), and their poor performance did not provide a good basis for drug testing. We therefore reinstated the earlier procedure for the HLs where each problem was given for one session with an increased number of trials (up to 80). Between ten and twenty more sessions of this kind were given until choice accuracy stabilized. Saline injections preceded some of the later sessions.

A block of drug-testing sessions followed pretraining, as described in the following section.

Treatments. 8-OH-DPAT (hydrobromide, Sigma, U.K.) and WAY–100635 (Wyeth-Ayerst, U.S.A.) were dissolved in saline vehicle (the 8-OH-DPAT suspension first needed gentle warming) for administration by subcutaneous injection. Injection volume was in each case 1 ml/kg. The following four treatments were compared: 0.15 mg/kg 8-OH-DPAT; 0.3 mg/kg WAY–100635; the two treatments combined; and saline alone. In each case two injections were administered, 2 to 3 min apart. For the combined treatment WAY–100635 was injected first and 8-OH-DPAT second. For the single-drug conditions, rats also received two injections: one containing the drug and the other containing just the equivalent volume of saline. In saline control sessions, two saline injections were given. Testing in the maze commenced 30 min after the second injection, and session duration was typically between 15 and 20 min.

Drug testing. The DA group was given two problems per session for 40 trials each; the HL group was given one problem per session for 60 trials. As before, each new problem had a different constant scene, and different rats received different random assignments of constant scenes across the different treatments. DAs underwent three replications of each of the above four treatments (completing a total of six problems per drug condition as there were two problems per session), and HLs had four replications of each treatment condition (a total of four problems per condition). Each block of four sessions included one replication of each of the treatments. The order of treatments varied between blocks and was counterbalanced across rats within each strain. Five sessions took place per week, of which four or five were preceded by drug and/or saline injections. There were occasional interspersed sessions without injection, used for "retraining" after apparatus problems and/or gaps in the testing sequence and not intended for analysis.

Data analysis

Differences between the four treatment conditions were tested by mixed-design analyses of variance (ANOVAs) and by planned comparisons between the active treatments and saline, and between 8-OH-DPAT alone and its combination with the antagonist. Planned comparisons employed separate error terms (Hays, 1988). Where repeated measures ANOVA factors had more than two levels, significance tests were corrected for deviations from sphericity (Huynh & Feldt, 1976). Accuracy was expressed as percentage data, so for these analyses, the p-values cited must be considered as approximations of the true p-values.

As the two groups of rats (DA vs. HL) were different in a number of aspects (strain and details of acquisition), all analyses include group as a factor to determine the generality of effects.

Data handling. The primary measure of interest is discrimination accuracy, and it must be asked whether the slowing of responding produced by 8-OH-DPAT might itself affect accuracy. We previously analysed the relationship between latency and accuracy in DA rats' performance in the constant-negative task (Cassaday & Gaffan, 1996; Gaffan & Eacott, 1997). We found that fast responses (latencies less than 200 cs) were relatively inaccurate, whatever the drug condition. Where accuracy of responding differs depending on response latency and these response latencies are affected by the drug treatments in use, these treatments might seem to affect accuracy as a "side-effect" of their effects on response latency.

To anticipate, data from this experiment showed a similar pattern, and we therefore considered how the drug treatments affected accuracy with responses categorized by latency. To identify the bands we used the same criteria as before (Cassaday & Gaffan, 1996; Gaffan & Eacott, 1997) so that every rat made some choices within each band in every drug condition, all latency bands were

TABLE 1
Experiment 1: Mean response latency (M) and standard error of mean[a] (SE)

	Drug condition							
	Saline		*8-OH-DPAT*		*WAY-100635*		*DPAT+WAY*	
Group	*M*	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*
Dark Agouti[b]	398	24	522	27	446	27	383	35
Hooded Lister[c]	324	11	547	48	347	33	308	17

[a] In cs.
[b] $n = 4$.
[c] $n = 6$.

well-represented under all drug conditions, and accuracy was relatively low in the shortest of the three bands.[1]

Results

Table 1 shows the mean response latency, averaged across all rats' choices and all sessions under each of the four treatment conditions. The DA group was a little slower than the HL group overall, and both groups responded more slowly under 8-OH-DPAT than under saline. There was also some indication of slowing by the antagonist WAY–100635 on its own, but the combination of 8-OH-DPAT and its antagonist (DPAT+WAY) produced behaviour similar to that under saline. A mixed-design 2 × 4 ANOVA (Group × Drug) showed that although the overall difference between the groups was marginal, $F(1, 8) = 3.66$, $p = .09$, the Group × Drug interaction was not significant, $F(3, 24) = 1.99$, so the major effects of the drugs were similar, irrespective of strain and training history. The drug effect was significant, $F(3, 24) = 19.21$, $p < .001$. Planned comparisons showed that 8-OH-DPAT slowed responding relative to saline, $F(1, 8) = 29.71$, $p < .001$, whereas the apparent slowing by WAY–100635 was nonsignificant, $F(1, 8) = 3.39$, $p > .10$. The DPAT+WAY combination did not differ from saline, $F(1, 8) = 1.43$, but did differ from 8-OH-DPAT alone, $F(1, 8) = 42.57$, $p < .001$; so the antagonist completely reversed the effect of 8-OH-DPAT on speed of responding.

As shown in Table 1, the HL rats generally responded faster than the DAs, so the cut-off for short-latency responses was set at 175 cs for the HLs and 200 cs for the DAs. As the DAs responded more slowly on average than the HLs, and their profile of accuracy against response latency was different, we could not use identical bands for the two

[1] The determination of bands is done with the control (zero dose) data. The procedure followed is first to estimate a limit for the lower band that will in principle provide an accuracy score for every combination of band and dose, then to divide the remainder of the distribution into roughly equal halves and to compute accuracy for each band. This process is then repeated, raising the limit for the lowest band by small increments until it reaches a point where accuracy increases. The lowest band is set just below this point. Thus the first cut-off is determined empirically, and so its particular value varies from one group of rats to the next. In both groups of the present study, the range of latencies above which accuracy started to increase contained only about 20% of responses; the remaining two bands contained about 40% each.

strains. For the DAs, the ranges were up to 200 cs, 200–450 cs, and over 450 cs; for the HLs, the ranges were up to 175 cs, 175–300 cs, and over 300 cs. Figure 1 shows the mean percentage of choices made by each strain that fell within each latency band, separately for each of the treatment conditions; Figure 2 shows the accuracy—that is, the percentage of choices in each latency band that were correct, again classified by strain and by treatment condition.

In Figure 1, the slowing of response latency by 8-OH-DPAT and WAY–100635 is evident in the shift of the distributions toward the two longer latency bands. Analysis of these data was by a mixed-design 2 × 4 × 2 ANOVA, Group × Drug × Band (only the two longer latency bands were included because percentage of choices in the third band was redundant, given the other two percentages). The Group, Group × Band, and Group × Drug effects were not significant, largest $F(1, 8) = 1.7$. The effect of interest is the Drug × Band interaction, $F(3, 24) = 10.21$, $p < .001$, indicating that the distribution of responses in the two longer latency bands differed between treatment conditions. Interaction contrasts showed that both 8-OH-DPAT and WAY–100635 differed from saline in that respect, Fs$(1, 8) \geq 8.38$, ps $\leq .02$. Both drugs increased the number of responses in the longest latency band and reduced the number in the medium band, relative to saline. The DPAT+WAY combination did not differ from saline, $F < 1$, but did differ from DPAT alone, $F(1, 8) = 12.49$, $p < .01$. As none of these effects differed significantly between the groups, they were true irrespective of strain and past training history.

This analysis shows that the two single-drug conditions did change the distributions of responses among the latency bands. Figure 2 shows that, as before, overall accuracy was poorer for responses made within the shortest latency band than for the other two; but there was no systematic difference between the two longer bands—that is, longer latencies

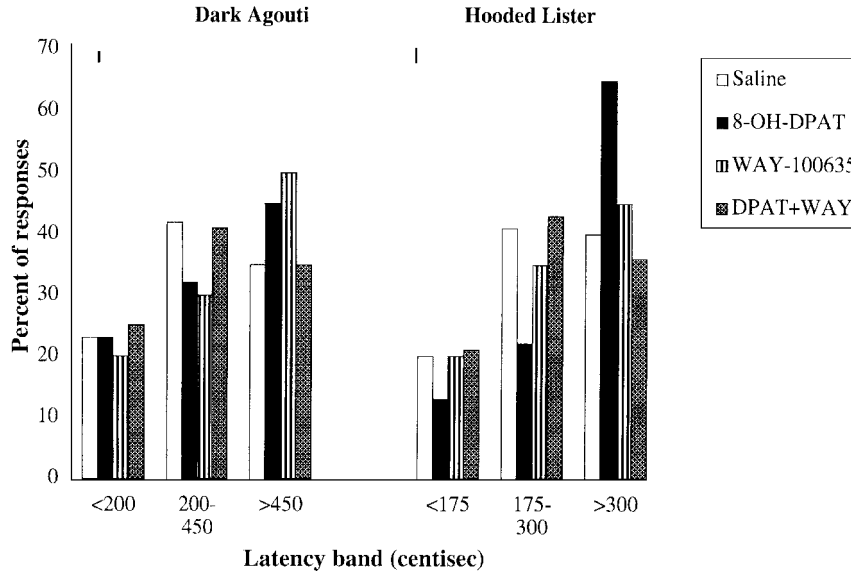

Figure 1. Distribution of the proportion of choices across three DT bands, for (left) Dark Agouti and (right) Hooded Lister rat groups. The error bar shows the standard error of the difference (*SED*), based on the pooled error term for the main effect of drug.

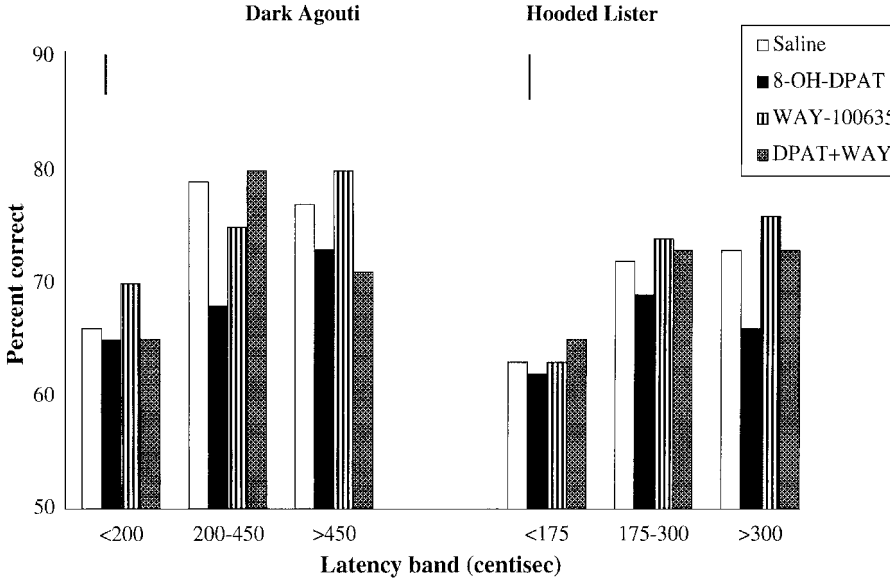

Figure 2. Distribution of the accuracy of choices across three DT bands, for (left) Dark Agouti and (right) Hooded Lister rat groups. The error bar shows the standard error of the difference (*SED*), based on the pooled error term for the main effect of drug.

(over 175 or 200 cs for HL and DA groups, respectively) were associated with similar levels of accuracy. Measuring performance in the bands separately, rather than averaging across all choices, allows us to partial out the effect of responding being differentially distributed across the bands between treatment conditions (given that we know short-latency responses are typically inaccurate). In all latency bands, particularly the longer two, discrimination accuracy was slightly but consistently poorer under 8-OH-DPAT than under any other drug treatment.

For accuracy statistical analysis was by a $2 \times 4 \times 3$ ANOVA, Group $\times$ Drug $\times$ Band. The overall group difference, reflecting slightly better discrimination by the DAs, was nonsignificant, $F(1, 8) = 2.95$, showing that our adjustment of training parameters had succeeded in equalizing the overall performance levels of the two groups. However, choice accuracy differed between the three bands, $F(2, 16) = 20.4$, $p < .001$, each of the two longer bands yielding higher scores than the shortest, Fs$(1, 8) \geq 21.9$, ps $< .001$.

The omnibus test on the drug effect was marginal, $F(3, 24) = 2.72$, $p = .07$, but the planned comparisons confirmed the foregoing description. Under 8-OH-DPAT, accuracy was worse than under saline, $F(1, 8) = 6.66$, $p < .05$. Neither WAY–100635 nor DPAT+WAY differed from saline, Fs < 1, but DPAT+WAY produced higher accuracy than 8-OH-DPAT alone, $F(1, 8) = 5.99$, $p < .05$. In other words, the 5-HT_{1a} antagonist had no effect on accuracy when given alone, but completely reversed the impairment caused by 8-OH-DPAT. However, the apparent Drug $\times$ Band interaction, whereby the effect of 8-OH-DPAT was less clear on short-latency than on long-latency choices (see Figure 2), was not statistically reliable, $F < 1$. Finally, there were no significant interactions

involving group, largest $F(1, 8) = 1.32$, so the drug effects on accuracy did not depend on strain or training history.

The preceding analyses combined data from all 40 trials or 60 trials of all problems. We also examined learning rate within problems. Figure 3 shows performance in successive blocks of 10 trials under the four treatments. To compensate for effects of the drugs on response latency, data were taken only from choices whose latency fell into the two longer bands because, as shown in Figure 2, accuracy effects were stable at these longer latencies—that is, for latencies above the shortest band, there is no evidence that accuracy changes with DT. From Figure 1, it can be seen that this entailed omitting about 20% of the DAs' trials and about 18% of the HLs' trials.

Figure 3 shows that the learning functions under WAY–100635 and the DPAT+WAY combination were little different to those under saline, but that 8-OH-DPAT slightly impaired choice accuracy. Statistical analysis was applied to the first four blocks of trials (because, to match baseline performance, the DAs had only received four blocks of trials) by a 2 × 4 × 4 ANOVA, Group × Drug × Blocks. As well as the obvious improvement across blocks, $F(3, 24) = 15.21$, $p < .001$, there was a significant group difference, $F(1, 8) = 17.30$, $p < .01$, and a Group × Block interaction, $F(3, 24) = 3.98$, $p < .05$, reflecting the fact that the DAs learned faster than the HLs within the first 40 trials of a problem. The main variable of interest, drug, gave rise to a nonsignificant omnibus, $F(3, 24) = 1.86$. However, the planned comparisons confirmed that choice accuracy under 8-OH-DPAT was significantly worse than that under saline, $F(1, 8) = 9.60$, $p < .05$, and marginally worse than under DPAT+WAY, $F(1, 8) = 4.93$, $p = .057$. Choice accuracy in the WAY–100635 condition did not differ from that under saline, $F < 1$. These drug

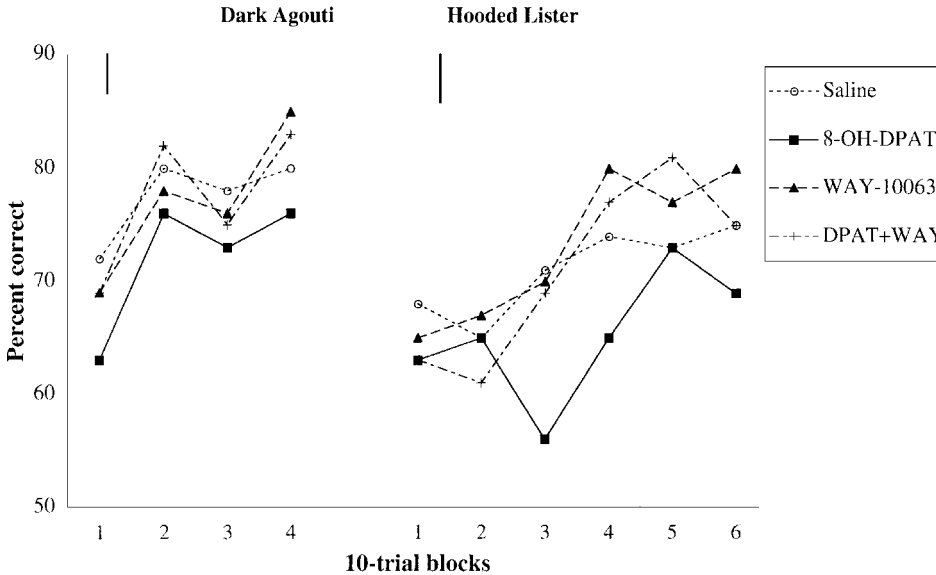

Figure 3. Effects of 8-OH-DPAT (0.15 mg/kg), WAY–100635 (0.3 mg/kg) and their combination (DPAT+WAY) on the accuracy of visual learning. The error bar shows the standard error of the difference (*SED*), based on the pooled error term for the main effect of drug.

effects simply echo the main effects of drug reported earlier in a less sensitive manner because they use only part of the data (the longer DT responses, see earlier). More important, the drug effect did not interact with blocks or group, Fs $\leqslant$ 1.07, so the drug effects were similar at all stages of learning each problem, in both DA and HL groups.

Discussion

The fact that 8-OH-DPAT impaired accuracy and performance in the constant-negative procedure and that these effects were reversible by pre-treatment with the 5-HT_{1a} receptor antagonist WAY–100635 provides confirmation that the 8-OH-DPAT effects are both robust (despite the differences between the groups of rats) and 5-HT_{1a} mediated. As the drug effect did not interact with group, neither strain nor training history prior to drug testing is relevant to the interpretation of the observed effects. Before discussing their psychological basis, we discuss problems that could arise from the treatment regime, the accompanying effects on DT, and pharmacological or behavioural non-specificity of the drug treatments.

We used a within-subjects design to minimize the number of animals used, as once rats are sophisticated in this task they readily provide data on new learning. It is unlikely that findings from one day's testing to the next would be affected by carry-over effects attributable to the drugs' half-life (see e.g., Dourish, Hutson, & Curzon, 1985; Evenden & Angeby-Moller, 1990; Osman et al., 1996; Perry & Fuller, 1989). In any case, the counterbalancing of the injection sequence would prevent any residual drug from having systematic effect on the data, as well as cater for secondary effects that might carry over from one day to the next (e.g., Kennett, Marcou, Dourish, & Curzon, 1987). We selected a single dose of 8-OH-DPAT because of the need to include additional treatment conditions. Dose–response data obtained within subjects with this compound anyway lack precision, as even a single dose can lead to lasting changes in receptor-mediated response (e.g., Kennett et al., 1987). Previously both 0.3 and 0.1 mg/kg 8-OH-DPAT impaired accuracy in the same task (Cassaday & Gaffan, 1996), so in the present study an intermediate dose of 0.15 mg/kg 8-OH-DPAT was used. Examination of our data gave no indication that drug effects showed systematic variation across the three or four replications of the treatments, so we can conclude that whatever level of 5-HT_{1a} activation was produced resulted in a stable impairment that was consistently reversible.

We have taken the conventional position that we should only claim that a drug has cognitive effects after first considering whether the findings could be due to "noncognitive" effects on speed of responding (cf. Stanhope et al., 1995). The doses of 8-OH-DPAT and WAY–100635 that we selected both increased the proportion of responses made at long latency. We have previously discussed the relationship between DT and accuracy. Short-latency responses always tend to be inaccurate (irrespective of drug treatment). However, once short-latency responses are excluded, there is no obvious correlation between DT and accuracy (Cassaday & Gaffan, 1996). After allowing for any effect that the latency changes might have had on accuracy, it was clear that 0.15 mg/kg of 8-OH-DPAT impaired accuracy but WAY–100635 on its own did not.

The fact that normally stimulus selections arrived at more slowly in the visual learning task are more accurate, whereas treatment with 8-OH-DPAT both lengthened DT and impaired accuracy in the longer DT bands, suggests that the effects on latency and accuracy are psychologically different. This suggestion is further supported by the finding that whereas treatment with WAY–100635 on its own increased DT there was, in the case of this treatment, no intrinsic effect on response accuracy. However, it remains possible that the increase in DT that we observed under 8-OH-DPAT, which was more marked than under WAY–100635, was itself partly a consequence of the cognitive impairment caused by the former drug. If the increase in response latency produced by 8-OH-DPAT in this experiment were specific to this task, there would be a logical problem in dissociating effects on response latency and accuracy (i.e., perhaps the rats take longer in this task only in consequence of their cognitive impairment rather than because 8-OH-DPAT decreases activity). This problem does not arise in that there are effects of 8-OH-DPAT on locomotor activity in other tasks. However, these effects are inconsistent: Sometimes activity is increased (Dourish et al., 1985) but in other test settings activity may be decreased, as here (see Evenden & Angeby-Moller, 1990; Mittman & Geyer, 1989).

The replication of the 8-OH-DPAT effect (Cassaday & Gaffan, 1996) against a saline control and its reversal by pre-treatment with 5-HT$_{1a}$ receptor antagonist confirm that the observed impairment was not because of some non-specific adverse effect of the injection treatment. Further non-specificity might result from actions at other serotonergic receptor sub-types (Shen et al., 1993). However, the fact that 8-OH-DPAT effects were reversible by treatment with the selective 5-HT$_{1a}$ receptor antagonist WAY–100635 provides confirmation that these were mediated through the 5-HT$_{1a}$ rather than the 5-HT$_7$ receptor site. Although drug actions confined to the 5-HT$_{1a}$ site still affect many physiological systems, non-specific behavioural effects provide a poor account of our results. For example, they find no ready explanation in terms of motivation to respond for food. If the rats were hyperphagic after this 8-OH-DPAT treatment (see e.g., Dourish, Clark, & Iversen, 1988), we would expect to see an increase in the number of short-latency responses. In fact the 8-OH-DPAT treatment resulted in significantly slower response times. Reduction in food intake after 8-OH-DPAT treatment can also occur at doses high enough to produce obvious signs of behavioural syndrome (e.g., Tricklebank, Forler, & Fozard, 1985). However, we saw no signs of behavioural syndrome in any of our 8-OH-DPAT-treated rats.

Although logically it is impossible to distinguish whether physiological changes that reduce choice accuracy do so through some cognitive, sensory, or motivational mechanism, we conclude that the likely non-specific effects of our treatments (and the consequent effects on DT) do not readily explain the impairment in visual learning produced by 8-OH-DPAT. Inspection of the averaged learning rates within problems might seem to suggest that the 8-OH-DPAT deficit nevertheless reflects a difficulty with the expression of learning (because the lines differ in level but not slope, see Figure 3). Certainly we saw no evidence that 8-OH-DPAT affected learning-set (Harlow, 1949) in that the rate of acquisition was not affected by the drug. However, the basis for improvement over time is anyway confounded in that it includes factors such as habituation to the apparatus and the overcoming of side preferences, the bias to attend to the lower half of the screens, as well

as acquiring the constant-negative rule (Simpson & Gaffan, 1999). Furthermore, under saline, both strains are well above chance in the first 10-trial block so the slope of accuracy against trial blocks is not a pure index of rate of learning. Rats treated with 8-OH-DPAT reached a lower level of accuracy than controls within the number of trials allowed, and we believe that this lowering in performance (at all stages of learning), finds its most natural account in terms of an impairment in the cognitive processes necessary to the task. In short, we have an effect on performance, which is not secondary to response slowing, but not conclusively on learning rate either.

We did not examine the effects of the same drug treatments on previously acquired discriminations because apparent visual or performance-based impairment would be confounded with state-dependent disruption in the expression of this prior learning. Conversely, the absence of any drug effect could be attributed to a ceiling effect in overtrained animals. The multiple scene stimuli presented were of varying luminance and complexity, so variations in luminance and contrast were irrelevant to task solution, and the rats would be likely to use a more effective strategy of encoding the stimuli in terms of a unique combination of cues (Gaffan & Woolmore, 1996). Moreover, variables like luminance have already been shown to provide no basis for discrimination in this paradigm (Simpson & Gaffan, 1999). Although the present finding confirms that the 8-OH-DPAT impairment in visual learning is not dependent on the use of moving stimuli (Cassaday & Gaffan, 1996), the possibility that it results from effects on perceptual discrimination or attention is untestable with the present procedure because discriminative responding itself usually requires learning.

Although in principle, similar problems of interpretation apply to other tasks with an attentional component, the hypothesis that sensory deficits generally account for such results seems implausible. For example, central serotonergic depletion can either impair or enhance learning about the same visual stimuli, depending on the parameters in use (Harrison, Everitt, & Robbins, 1999; Ward, Wilkinson, Robbins, & Everitt, 1999). Furthermore, although there is some evidence that 5-HT is involved in visual distractibility, these effects do not seem to be mediated through the 5-HT_{1a} receptor site (Boulenguez, Foreman, Chauveau, Segu, & Buhot, 1995; Carli et al., 1995). The interpretation of our behavioural effects in terms of learning is also consistent with in vitro findings that 8-OH-DPAT inhibits the induction of long-term potentiation in rat visual cortex (Edagawa, Saito, & Abe, 1998, 1999).

We therefore conclude that the 5-HT_{1a} receptor agonist 8-OH-DPAT impairs visual learning in otherwise normal rats. In general, systemic 8-OH-DPAT may produce cognitive effects mediated by its action at the 5-HT_{1a} receptor site that can be partialled out from its non-specific effects with appropriate procedures. In Alzheimer's disease the hypoactivity of cortical pyramidal neurones, produced by the hyperpolarizing effect of 5-HT and its agonists, can be reversed by treatment with 5-HT_{1a} receptor antagonists (Bowen et al., 1992; Dijk et al., 1995; Francis et al., 1993). A more direct test of this hypothesis would require an animal model that uses lesions of the relevant cortico-cortical glutamate neurones (Fletcher et al., 1996). Meanwhile, in the normal animal, the reversal of 8-OH-DPAT effects produced by pre-treatment with WAY–100635 suggests that the 5-HT_{1a} receptor site could also have a wider role in learning and memory. In general, the modulation of cortical pyramidal cell firing via the 5-HT_{1a} receptor site might provide a

way to impair or enhance learning. However, in our task, we saw no evidence that treatment with WAY–100635 could on its own produce cognitive enhancement.

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