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Buspirone differentially modifies short-term memory function in a combined delayed matching/non-matching to position task

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Abstract

This study investigated the action of 5-hydroxytryptamine (5-HT) mimetics on short-term memory function. The objective was to determine whether two closely related tasks could differentiate between partial 5-HT_{1A} receptor activation, full 5-HT_{1A} receptor activation and generalised enhanced serotonin (5-HT) activity. Male hooded Lister rats were trained to perform an operant-based combined delayed matching/non-matching to position task. Drugs used were: fluoxetine (3 mg/kg, i.p.), a selective 5-HT reuptake inhibitor; the full 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT; 0.3 mg/kg, s.c.); and the partial 5-HT_{1A} receptor agonist, buspirone (1 mg/kg, i.p.). Buspirone differentially disrupted response accuracy depending on the style of trial. There was no such difference in the case of 8-OH-DPAT, which impaired accuracy in both delayed matching/non-matching to position task, while fluoxetine affected neither. Thus, the findings suggest that partial 5-HT_{1A} receptor activation compromises cognitive function to a greater extent than full 5-HT_{1A} receptor activation, although a dopaminergic component cannot be excluded since buspirone possesses some dopamine D2 receptor antagonist activity. Furthermore, it suggests that there is a differential role for 5-HT in these two closely related behavioural tasks.

Keywords: Serotonin; 5-HT_{1A} receptor; 8-OH-DPAT; Buspirone; Fluoxetine; Short-term memory

1. Introduction

It is highly probable that the serotonergic system is functionally implicated in learning and memory processes (Hunter, 1989; Normile et al., 1990; Steckler and Sahgal, 1995; Robbins, 1997). Among the many different serotonergic receptor subtypes, hydroxytryptamine (5-HT)$_{1A}$ receptors appear to have the greatest potential to modulate learning and memory due to their high density in brain areas associated with cognition, e.g. limbic brain areas (hippocampus, cingulate and entorhinal cortices, and lateral septum) and mesencephalic raphe nuclei. Activation of 5-HT_{1A} autoreceptors located in the raphe is thought to be responsible for inhibiting serotonergic neuronal activity in rat hippocampus and frontal cortex (Barnes and Sharp, 1999). Furthermore, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), a full 5HT_{1A} receptor agonist (Hjorth et al., 1982), and buspirone, a partial 5-HT_{1A} receptor agonist (Coplan et al., 1995) with some dopamine D2 receptor antagonist activity (McMillen et al., 1983) have been shown to impair memory performance in both the passive avoidance (Carli and Samanin, 1992; Liang, 1999) and water maze tasks (Carli et al., 1992; Kant et al., 1998). This suggests that 5-HT_{1A} receptors play an important role in regulating the acquisition and retention components of mnemonic function and spatial memory. Fluoxetine, a selective 5-HT reuptake inhibitor that would lead to generalised 5-HT receptor activation, had no effect on either of these paradigms (Daws et al., 1998; Stewart and Reid, 2000). Contrary to this, Meneses and Hong (1995) found that fluoxetine improved cognitive performance.

As separate paradigms, the delayed matching to position and delayed non-matching to position tasks have become widely used as putative models for investigating drug effects on short-term memory function in rats (Dunnett, 1993). Briefly, these paradigms commence with the insertion of a single, sample, lever into an operant chamber. A response on this lever causes it to be immediately withdrawn and a delay period initiated during which time the animal is required to respond on a central panel flap. Once the delay expires, two choice levers are introduced into the

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chamber. In delayed matching to position, a correct response is reinforced with a small food pellet delivered behind the central panel flap when the animal presses the previous sample lever. In delayed non-matching to position, the animal must press the other, non-sample, lever to receive reinforcement. This constitutes a trial. Following an inter-trial interval, the process is repeated for a given number of trials or session duration. One advantage of these tasks is that they are positively motivated and may be less prone to effects on anxiety more associated with passive avoidance (aversive stimulus) or water maze (aversive situation).

The ability of these two paradigms to identify impairments or improvements in short-term memory function induced by serotonergic agents has been subject to controversy. For example, Warburton et al. (1997) argued that 8-OH-DPAT does not affect cognitive function in delayed matching to position despite reducing performance accuracy, while Herremans et al. (1995) reported that full 5-TH_{1A} receptor activation disrupted short-term memory function. No impairment on the performance of either delayed matching to position or delayed non-matching to position was observed following generalised enhanced 5-HT activity induced by fluoxetine (Janssen and Andrews, 1994). A combined form of delayed matching to position and delayed non-matching to position was chosen because there has been some conflicting data regarding the ability of certain drugs to influence delayed matching to position and delayed non-matching to position performance. We specifically used a combined form of these positional tasks to increase the apparent load on cognitive function through increased task complexity with the intention of: improving sensitivity, reducing the potential for ceiling effects at the lowest delay, and also to reduce the probability of a strategy-driven response (Chudasama and Muir, 1997).

Thus, our aim was to compare three different 5-HT mimetics, fluoxetine, 8-OH-DPAT and buspirone, on short-term memory function to: determine the relative importance of the $5HT_{1A}$ receptor against more generalised enhanced 5-HT activity and to investigate the potential for qualitative differences in the delayed matching to position and delayed non-matching to position short-term memory paradigms.

2. Methods

2.1. Animals

Eighteen male hooded Listers (UWC stock) weighing 120–150 g were used at the start of the study. Animals were housed in groups of three with a 12:12-h light–dark cycle and ambient temperature maintained at 21–23 °C, with water available at all times. Animals were maintained at 85–90% of their free-feeding weights by restricting food access to 1 h/day from Monday to Friday and ad libitum during weekends. All experiments were performed in accordance with a project licence issued under the authority of the Home Office Animals (Scientific Procedures) Act 1986 and approved by the local Ethical Review Process.

2.2. Apparatus

Six standard operant conditioning chambers (Campden Instruments, UK), equipped with two retractable levers and a central food panel accessed by a perspex flap, were used for this study. Two aluminium dividers, extending 4 cm into the operant chamber were sited between the levers and the central panel. Each box was equipped with four functioning lights: house light, sample light over each lever, and a panel light situated within the food hopper. All bulbs were rated at 1 V. Equipment was controlled by a BBC Master computer via a SPIDER interface (Paul Fray) with software written by D.M. Pache.

2.3. Procedure

The procedure used was adapted from the combined delayed matching to position and delayed non-matching to position paradigm described by Pache et al. (1999) which was based on the original, separate delayed non-matching to position and delayed matching to position tasks of Kesner and Bierley (1980) and Dunnett (1985). Animals were initially acclimatized to the operant chambers and to collecting 45 mg precision food pellets (Campden Instruments) from the central hopper by nose-poking the perspex panel. They were then trained to lever press for a food reward on a continuous reinforcement schedule. Once reliable lever-pressing activity was established, they were made to respond to one lever for reinforcement inserted into the operant chamber following a darkness stimulus (5 s of all lights in the operant chamber switched off) and to the opposite lever inserted after a light stimulus (5 s of flashing lights: 1 s all lights on; 1 s all lights off). Once asymptotic responding for the choice accuracy parameter was attained, delayed matching/non-matching to position trials were introduced. This involved pseudorandom presentation of a sample lever immediately after the stimulus. Delays were gradually increased from 1 s using an inter-trial interval of 8 s to the following range: 1, 4, 8, and 16 s with 32 s as the inter-trial interval. Trial sequences were randomised at the start of a session.

2.3.1. Task

A single trial consisted of four phases: stimulus, sample, delay and choice (see Fig. 1). The stimulus phase comprised 5-s darkness or 5-s flashing lights (switching on and off the house and lever lights simultaneously at 1-s intervals. The sample phase consisted of the houselight

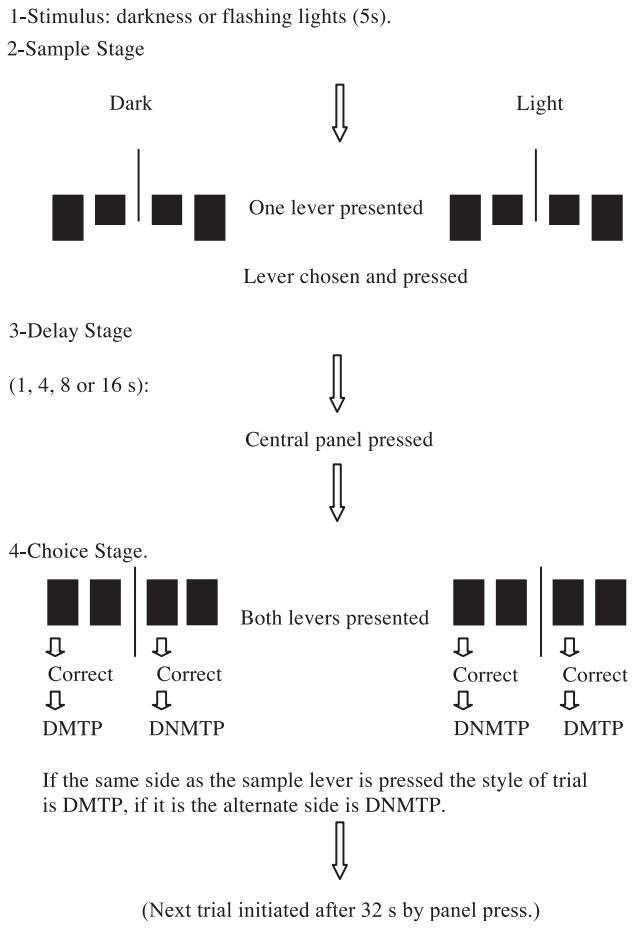

Fig. 1. The four-trial stages in the combined delayed matching/non-matching to position (DMTP/DNMTP) task.

being switched on and one of two levers (sample lever) randomly presented after the stimulus and immediately retracted when pressed by the animal. Thus, each stimulus had two potential sample lever presentations (dark, right or left; and light, right or left). When the sample lever was retracted, the delay phase began where subjects pressed the central panel flap until the randomly chosen delay expired: 1, 4, 8 or 16 s. The choice phase began immediately after the first panel press following the expiry of the delay. Both levers were presented and subjects required pressing the left lever if the stimulus was darkness or the right lever if the stimulus was flashing lights to gain a small food reward (45 mg precision food pellet). Thus, if the sample lever was the same as the correct lever, this represented a delayed matching to position style of trial, while a different sample and correct lever represented a delayed non-matching to position style of trial. Once the animal made the choice, the next trial was initiated after 32 s by the animal pressing the panel press. A session contained 64 trials. Thus, each possible trial was presented eight times. Sessions finished when the animal completed 64 trials or at 60 min, whichever was first.

2.4. Drugs

All drugs, calculated as salt, were dissolved in vehicle (normal saline). Fluoxetine (3 mg/kg, supplied by Sigma) and buspirone (1 mg/kg, Sigma) were injected intraperitoneally using a dose volume of 2 ml/kg. 8-OH-DPAT (0.3 mg/kg, Sigma) was injected subcutaneously using a dose volume of 1 ml/kg. Drugs were administered 10 min prior to behavioural testing. Experiments were started once asymptotic performance (80%) had been attained using 1-, 4-, 8- and 16-s delays and 32 s as the inter-trial interval. Training continued on Mondays and Thursdays, while experimental sessions were reserved for Tuesdays and Fridays. Wednesdays, Saturdays and Sundays were rest days.

2.5. Data analysis

Response accuracy was expressed as a percentage of correct responses against total number of trials conducted according to individual delays. Total response accuracy was calculated by collapsing, or pooling, the data across delays and expressing the total number of correct trials against total number of trials completed. Panel press activity was expressed as the rate per second during each delay.

Response accuracy in the combined task comparing saline with the three 5-HT mimetics was analysed using two-way analysis of variance (ANOVA) with treatment and delay as repeated factors (SPSS 10.0). A significant effect was followed up with one-way ANOVA and Dunnett's post hoc analysis on total response accuracy. If a given treatment affected response accuracy on the combined task, then a two-way ANOVA with style of trial and delay as repeated factors was conducted to determine whether treatment affected delayed matching or delayed non-matching performance differentially. To determine whether the response accuracy profile of a particular treatment was delay-dependent or delay-independent, a one-way ANOVA was performed with delay as the repeated factor. To include an animal in the data analysis, at least 20 trials must have been completed. Two animals failed to reach criteria and their data excluded from the analysis.

3. Results

3.1. Effect of drug treatment on total response accuracy in the combined task

Statistical analysis revealed a significant main effect of treatment and delay ($F(3,45)=23.8$, $P<0.001$ and $F(3,45)=13.0$, $P<0.001$, respectively; see Fig. 2). Subsequent post hoc analysis showed that the saline control differed from both buspirone and 8-OH-DPAT treatment, but not fluoxetine.

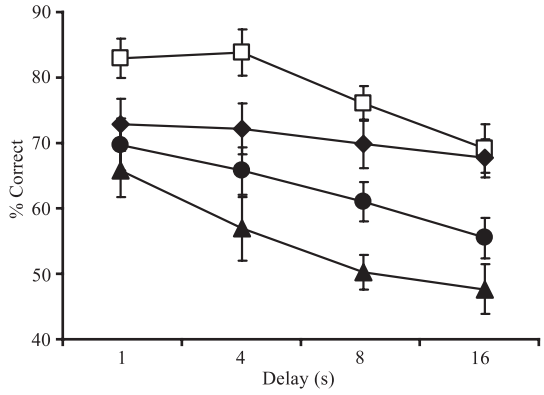

Fig. 2. Comparison of the combined task delayed matching/non-matching to position overall accuracy using saline (i.p.), buspirone (BSP; 1 mg/kg, i.p.), 8-OH-DPAT (DPT; 0.3 mg/kg, s.c.) and fluoxetine (FLX; 3 mg/kg, i.p.). ($n=16$). □, saline; ▲, buspirone (1 mg/kg); ●, DNMTP 8-OH-DPAT (0.3 mg/kg); ♦, fluoxetine (3 mg/kg).

3.2. Effect of style of trial on response accuracy according to drug treatment

3.2.1. Saline control

Statistical comparison, using within-subjects ANOVA with style of trial and delay as repeated factors, indicated no significant difference between the delayed non-matching to position and delayed matching to position styles of trial on response accuracy ($F(1,15)=2.3$, see Fig. 3A). No differences in panel press activity were observed between trial styles ($F(1,15)=0.1$). Subjects given saline as a treatment demonstrated a delay-dependent decrease in response accuracy for both delayed matching to position and delayed non-matching to position trials (within-subjects one-way ANOVA with delay as the single repeated factor, $F(3,45)=3.8$, $P<0.05$; and $F(3,45)=4.3$, $P<0.01$, respectively, see Fig. 3A).

3.2.2. Buspirone 1 mg/kg

A significant main effect of style of trial was observed following buspirone treatment on response accuracy ($F(1,15)=9.3$, $P<0.01$, see Fig. 3B), which showed a dissociation between both styles of trial; but no differences in panel press activity were identified between trial styles ($F(1,15)=3.0$). Within-subjects one-way ANOVA with delay as the single repeated factor showed a delay-dependent decrease in response accuracy for delayed non-matching to position ($F(3,45)=5.5$, $P<0.01$, see Fig. 3B). However, in delayed matching to position, the slope was delay independent ($F(3,45)=0.1$, see Fig. 3B).

3.2.3. 8-OH-DPAT 0.3 mg/kg

No significant main effect between the delayed non-matching to position and delayed matching to position styles of trial was identified in 8-OH-DPAT treatment on response accuracy or delay press activity ($F(1,15)=4.1$, and $F(1,15)=1.6$, respectively, see Fig 3C). However, within-

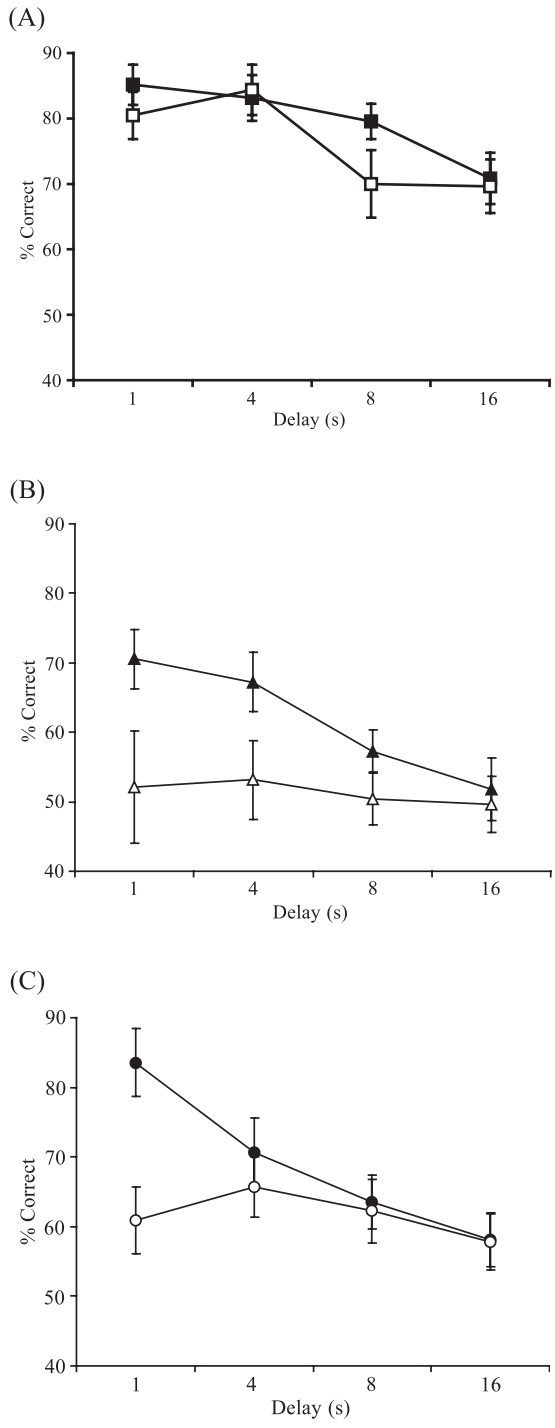

Fig. 3. (A) Comparison of delayed non-matching to position (DNMTP) and delayed matching to position (DMTP) trial accuracy following saline (i.p.) control ($n=16$). Key: ■, DNMTP saline; □, DMTP saline. (B) Comparison of delayed non-matching to position (DNMTP) and delayed matching to position (DMTP) trial accuracy following buspirone treatment (1 mg/kg, $n=16$). Key: ▲, DNMTP buspirone (1 mg/kg); △, DMTP buspirone (1 mg/kg). (C) Comparison of delayed non-matching to position (DNMTP) and delayed matching to position (DMTP) trial accuracy following 8-OH-DPAT treatment (0.3 mg/kg, $n=16$). Key: ●, DNMTP 8-OH-DPAT (0.3 mg/kg); ○, DMTP 8-OH-DPAT (0.3 mg/kg).

subjects one-way ANOVA with delay as the repeated factor conducted on each style of trial indicated a delay-dependent decrease in response accuracy in delayed non-matching to position ($F(3,45) = 8.8$, $P < 0.001$, see Fig. 3C), but a delay-independent impairment of response accuracy for delayed matching to position trials ($F(3,45) = 0.7$, see Fig. 3C).

4. Discussion

Numerous studies have been conducted using delayed matching and delayed non-matching to position in isolation as putative models for short-term memory function and have demonstrated significant effects with compounds that modify serotonergic function. This study differs from the previous studies in that it has evaluated the effects of serotonergic compounds on short-term memory function using a combined delayed matching to position and delayed non-matching to position task. The combined task is inherently more cognitively difficult than each single task conducted in isolation, and consequently, if a particular drug disrupts cognition, it may be more readily detected when response accuracy at the shortest delay is compared to that of the longest delay within a given treatment and not necessarily in comparison to saline control. It is arguable that rather than reflecting short-term memory per se; this combined delayed matching/non-matching to position task more accurately reflects cognitive performance as a whole, which would include additional behavioural functions relevant to the execution of the task such as recall and attention. It is important to note that control-treated animals were not differentially affected by the particular trial they were conducting at any one time (see Fig. 3A). It was only when drugs were introduced that the tasks became differentially affected (see Fig. 3B).

Buspirone and 8-OH-DPAT dramatically impaired performance in delayed matching to position trials such that accuracy was reduced to a level which was just higher than chance alone across all delays, i.e. response accuracy was delay independent (Fig. 3B and C). Although response accuracy was also disrupted in delayed non-matching to position, response accuracy was greater at the short delays than long delays, i.e. response accuracy was delay dependent. It is our contention that the response accuracy impairment observed in delayed non-matching to position style of trial must reflect some loss of cognitive function that was not as great as the deficit imposed by delayed matching to position trials. Thus, delayed matching to position trials prompted random responding, which would suggest that this task was more difficult for the subjects than the delayed non-matching to position task. This supports original indications identified by Dunnett et al. (1988), which suggested greater difficulty in training between delayed matching to position and delayed non-matching to position paradigms. Here we have described an effect following execution of a given task rather than acquisition of the task itself.

It is rather surprising how these two closely related paradigms could be so much dissociated by 5-HT_{1A} receptor agonists. One plausible explanation relies on the natural tendency of certain animals to switch, i.e. having received reinforcement following one instrumental response, turn to the other (lever in the case of an operant chamber; direction in the case of a T-maze) for the following reinforcement. Chiang et al. (2000) found that 8-OH-DPAT increased switching between levers in rats. Thus, the tendency of animals to switch following 5-HT_{1A} receptor activation might be one of the reasons why delayed non-matching to position is considered easier than delayed matching to position. However, the same laboratory a year later failed to repeat those results and reported that 8-OH-DPAT, at identical doses, did not affect switching (Body et al., 2001). Moreover, for the combined task, animals need to recall information stored at the flashing light/darkness stimulus stage, where there are no levers present, in order to identify the lever required for subsequent reinforcement. Thus, the fact that response accuracy is better in delayed non-matching to position trials cannot only be based on the tendency of 5-HT_{1A} receptor activation to increase switching as a mediating strategy.

Evidence that links 5-HT with increased task difficulty comes from the work of Beylin et al. (2001) who examined the role of the hippocampus in a classical conditioning context. They surmised that hippocampal involvement was a function of task difficulty. With normal levels of 5-HT, both matching and non-matching-to-position tasks would be performed equally well. In our study, it could be expected that 5-HT levels in the hippocampus would be lower due to the activation of both somatodendritic 5-HT_{1A} receptors located in the raphe nucleus (Casanovas et al., 1997). In this instance, with presumably reduced 5-HT, the more difficult task would be more severely affected as demands on hippocampal function are increased. This reflects the importance of the serotonergic system for the execution of such paradigms. It should be noted, however, that this argument contrasts with that presented by Mair et al. (1998). These workers found that the accuracy of delayed matching to sample responses was less impaired following hippocampal lesions than delayed non-matching to sample, although the nature of the task used was slightly different (matching-to-sample as opposed to matching-to-position). It should be noted that 5-HT levels would also be reduced in the prefrontal cortex (Casanovas et al., 1999), an area similarly recognized as being involved with working memory function. However, our study relates to the role of a specific neurotransmitter system rather than neuroanatomical issues, and in this respect, it can be said that generalised $5HT_{1A}$ receptor activation had differential effects on apparently similar behavioural tasks. This indicates that these tasks are not processed in the same way by the subject.

The significant interaction identified by two-way ANOVA on trial style and delay indicated that buspirone differentially affected response accuracy according to whether subjects were responding on a delayed matching or

delayed non-matching to position trial (Fig. 3B). However, no dissociation in panel press activity was observed, which suggests that this dissociation of trial style could not be easily attributable to sensorimotor deficits. On the other hand and by contrast with buspirone, there was no significant main effect between styles of trial following 8-OH-DPAT treatment. Thus, although it is difficult to establish dose equivalence between compounds, it could be tentatively suggested that buspirone imposes a greater deficit on performance than 8-OH-DPAT. This might well be related to the rapid conversion of buspirone to 1-(2-pyrimidinyl)-piperazine (1-PP), which has noradrenergic properties (Enberg, 1988). Nevertheless, Steckler et al. (1998) reported that noradrenaline did not affect any of the delayed tasks (matching or non-matching to position). Therefore, the differences observed between buspirone and 8-OH-DPAT treatments are possibly due to 5-HT_{1A} partial versus full receptor agonist activity (Coplan et al., 1995). Alternatively, the ability of buspirone to block dopamine D2 receptors (McMillen et al., 1983) and the close association of dopamine D2 inhibition with the impairment of working/short-term memory in the hippocampus may also explain the dichotomous effects of buspirone and 8-OH-DPAT (Wilkerson and Levin, 1999).

Previous work in this laboratory had demonstrated that higher dose fluoxetine treatment (10 mg/kg) in a delayed non-matching to position task inhibited responding to such an extent that not enough trials could be completed to satisfy statistical analysis (data not published). It was considered possible that the increased complexity inherent in a combined matching/non-matching to position task would be sufficient to determine whether a lower, less inhibiting, dose of fluoxetine is capable of modifying short-term memory function. However, as can be seen in Fig. 2, the generalised 5-HT receptor activation elicited by fluoxetine induced no significant effect on response accuracy. Neither was this dose effective in changing panel press activity (data not shown). Fluoxetine is known to raise the levels of not just 5-HT, but also dopamine and noradrenaline (Pozzi et al., 1999). Thus, despite the potential for fluoxetine to elicit widespread neurotransmitter change in brain areas involved with short-term memory function, no overt effect was observed. This result agrees with Janssen and Andrews (1994) who also failed to demonstrate an effect on short-term memory function. However, it has been shown that selective serotonin reuptake inhibitors facilitate memory consolidation in healthy volunteers (Harmer et al., 2002), and fluoxetine improves learning in rats (Meneses and Hong, 1995). It is clear that further work is required to establish which aspect of cognition is sensitive to SSRI treatment.

Thus, we conclude that it is possible to pharmacologically differentiate between delayed matching and delayed non-matching performance. That is, when conducted simultaneously, it is possible to have one task more significantly impaired than the other. In this case, it is possibly related to the magnitude of involvement within a given paradigm of a particular neurotransmitter system. Furthermore, it is also possible that partial 5-HT_{1A} activation compromises cognitive function to a greater extent than full 5-HT_{1A} activation. Since a dopaminergic component cannot be excluded from buspirone's pharmacological profile, the data may reflect a complex balance between the dopaminergic and serotonergic systems and their individual contributions to both matching and non-matching to position paradigms. Finally, we also conclude that the combined delayed matching/non-matching to position task allows a more detailed and sensitive differentiation of the ability of a drug to affect cognitive processes than either delayed matching to position or delayed non-matching to position conducted individually.

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