

Antidepressant Drugs Specifically Inhibiting Noradrenaline Reuptake Enhance Recognition Memory in Rats

Kristin Feltmann, Åsa Konradsson-Geuken, Dimitri De Bundel, Maria Lindskog, and Björn Schilström
Karolinska Institutet

Patients suffering from major depression often experience memory deficits even after the remission of mood symptoms, and many antidepressant drugs do not affect, or impair, memory in animals and humans. However, some antidepressant drugs, after a single dose, enhance cognition in humans (Harmer et al., 2009). To compare different classes of antidepressant drugs for their potential as memory enhancers, we used a version of the novel object recognition task in which rats spontaneously forget objects 24 hr after their presentation. Antidepressant drugs were injected systemically 30 min before or directly after the training phase (Session 1 [S1]). Post-S1 injections were used to test for specific memory-consolidation effects. The noradrenaline reuptake inhibitors reboxetine and atomoxetine, as well as the serotonin noradrenaline reuptake inhibitor duloxetine, injected prior to S1 significantly enhanced recognition memory. In contrast, the serotonin reuptake inhibitors citalopram and paroxetine and the cyclic antidepressant drugs desipramine and mianserin did not enhance recognition memory. Post-S1 injection of either reboxetine or citalopram significantly enhanced recognition memory, indicating an effect on memory consolidation. The fact that citalopram had an effect only when injected after S1 suggests that it may counteract its own consolidation-enhancing effect by interfering with memory acquisition. However, pretreatment with citalopram did not attenuate reboxetine's memory-enhancing effect. The D1/5-receptor antagonist SCH23390 blunted reboxetine's memory-enhancing effect, indicating a role of dopaminergic transmission in reboxetine-induced recognition memory enhancement. Our results suggest that antidepressant drugs specifically inhibiting noradrenaline reuptake enhance cognition and may be beneficial in the treatment of cognitive symptoms of depression.

Keywords: antidepressant drugs, dopamine, noradrenaline, recognition memory

Cognitive dysfunctions in several domains including attention, executive function, and memory (Airaksinen, Larsson, Lundberg, & Forsell, 2004) persist in patients suffering from major depres-

sion even after the remission of mood symptoms (Reppermund, Ising, Lucae, & Zihl, 2009; Weiland-Fiedler et al., 2004). Patients suffering from chronic major depression display volume reductions of both the hippocampus (Campbell, Marriott, Nahmias, & MacQueen, 2004; Koolschijn, van Haren, Lensvelt-Mulders, Hulshoff Pol, & Kahn, 2009) and the prefrontal cortex (Koolschijn et al., 2009), regions important for memory formation. Furthermore, abnormal activity in the hippocampus and the prefrontal cortex during memory formation has been shown in depressed patients (Bremner, Vythilingam, Vermetten, Vaccarino, & Charney, 2004; Fairhall, Sharma, Magnusson, & Murphy, 2010). However, deficits in hippocampus-dependent memory tasks can be found in depressed patients even without hippocampal volume reductions (MacQueen et al., 2003). Formation of long-term memory involves memory acquisition followed by memory consolidation, a process of strengthening of the acquired memory over time (for review see McGaugh, 2000). The cognitive deficits remaining in remitted patients are disabling and impair functional recovery (Jaeger, Berns, Uzelac, & Davis-Conway, 2006), and it is important to gain better understanding of the mechanisms by which antidepressant drugs affect cognitive function. Animal studies have revealed that several antidepressant drugs, such as the tricyclic antidepressants (TCAs) and the selective serotonin reuptake inhibitors (SSRIs), either impair or have no effect on memory performance (for review see Monleón, Vinader-Caerols, Arenas, & Parra, 2008). However, most of these studies investigated aversive memory (footshock-conditioned), and the knowl-

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Kristin Feltmann and Åsa Konradsson-Geuken, Department of Physiology and Pharmacology, Karolinska Institutet; Dimitri De Bundel and Maria Lindskog, Department of Neuroscience, Karolinska Institutet; Björn Schilström, Department of Physiology and Pharmacology, Karolinska Institutet.

Kristin Feltmann is now at the Department of Clinical Neuroscience, Karolinska Institutet.

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Correspondence concerning this article should be addressed to Kristin Feltmann, Centrum för psykiatriforskning Stockholm, Norra Stationsgatan 69, plan 7, 113 64 Stockholm, Sweden. E-mail: kristin.feltmann@ki.se

edge about how different classes of antidepressant drugs affect neutral memory and other types of cognition is limited.

A meta-analysis performed by Hindmarch (2009) concluded that TCAs impair cognition in healthy volunteers, probably due to their anticholinergic activity, whereas the selective SSRIs are less cognitive-impairing. However, several clinical studies have found cognitive-enhancing effects of other antidepressant drugs (Ferguson, Wesnes, & Schwartz, 2003; Harmer et al., 2009; Herrera-Guzmán et al., 2009; Jorge, Acion, Moser, Adams, & Robinson, 2010; Levkovitz, Caftori, Avital, & Richter-Levin, 2002; Roy et al., 2010). For example, Ferguson and coworkers (2003) have shown that chronic treatment with the selective noradrenaline reuptake inhibitor (NRI) reboxetine, but not the SSRI paroxetine, increased attention and working memory in depressed patients. Additionally, chronic treatment with the selective serotonin/noradrenaline reuptake inhibitor (SNRI) duloxetine as well as the selective allosteric serotonin reuptake inhibitor (ASRI) escitalopram improved visual and verbal episodic memory in patients with major depressive disorder. Reboxetine was able to improve emotional memory already after a single dose in the absence of subjective mood changes (Harmer et al., 2009). However, the different conditions and tests used in the studies mentioned earlier make it hard to compare the effects of different drugs.

On the basis of previous results showing that the NRI reboxetine increases dopamine in both the prefrontal cortex and hippocampus in rats (Borgkvist, Malmjöf, Feltmann, Lindskog, & Schilström, 2012; Linnér et al., 2001) and on the basis of the established role of dopamine in memory formation (Shohamy & Adcock, 2010), we hypothesized that inhibition of the noradrenaline transporter might be an important property for an antidepressant drug to enhance cognition. In addition to dopamine, noradrenaline by itself has been suggested to play a role in memory consolidation (Kobayashi & Yasoshima, 2001; Roozendaal, Castello, Vedana, Bars-egyan, & McGaugh, 2008). We recently showed that reboxetine enhances recognition memory in rats and that this effect could be attenuated by local injection of the dopaminergic D1/D5 antagonist in the prefrontal cortex but not the dorsal hippocampus (De Bundel et al., 2013). In the present study, we tested different classes of antidepressant drugs for possible memory-enhancing effects by using a delay of 24 hr in the novel object recognition task, when natural forgetting occurs.

Method

Animals

Male Sprague–Dawley rats (Charles River, Sulzfeld, Germany) were housed under standard laboratory conditions (21 °C, 50%–60% humidity) and maintained on a 12-hr light–dark cycle (lights on at 6:00 a.m.) with ad libitum access to food and water. The animals had been acclimatized to their environment for at least 5 days before they were used in any experiment. Prior to the experiment, each rat had been handled 5 min/day for a total of five times and had received a total of three saline injections (0.3 ml, subcutaneous), in order to habituate the animals to the experimenter as well as to systemic injections. All behavioral experiments were performed during the light phase of the light–dark cycle (8:00 a.m. to 4:00 p.m.). Experiments were approved by and conducted in

accordance with the Stockholm North Committee on Ethics of Animal Experimentation (ethical permits N28/09 and N239/10).

Novel Object Recognition Test

Apparatus. The novel object recognition test was performed in an open Plexiglas box (80 × 31 × 33 cm) primed with bedding from the animal's home cages. The walls of the box were covered with opaque gray plastic foil. As contextual cues, the walls on the short sides had different black-and-white patterns. The objects to be discriminated (A: plastic toy car, B: Lego brick cube, C: ceramic cup) were of similar size (11–12 cm) and made of materials that could not be gnawed by the rats and that could be cleaned easily with 70% ethanol. Weights or adhesive tape was used to secure the objects' position, so that they could not be moved by the rats. Identical copies of the objects were used to prevent recognition due to odor marking. There was no preference for the objects, as shown by exploration time during S1 (A: 16.4 ± 1.0 s, B: 15.0 ± 0.9 s, C: 14.6 ± 0.8 s), one-way analysis of variance (ANOVA), $F(2, 91) = 0.93$, *ns*, or to any side of the box (left = 7.5 ± 0.3 s, right = 7.3 ± 0.3 s), paired Student's *t* test, $t(106) = 0.75$, *ns*.

General test procedure. The test procedure was a slightly modified version of the novel object recognition task used by Ennaceur and Delacour (1988). Rats (260–360 g) were allowed to acclimatize to the test room for about 1 hr before each session started. During the first session (S0) rats were habituated to the test apparatus for 20 min. The following day rats were presented with two identical objects during the training session (S1). After a delay of 2 hr or 24 hr, rats were allowed to explore a copy of the previous, familiar object and a novel object during the 5-min testing session (S2; see Figure 1A). The novel object during the S2 session was placed in the position (left or right) where the rat spent the least amount of time exploring the object during S1. The object combinations were counterbalanced within animal batches and treatment groups. Both sessions (S1 and S2) were video-recorded

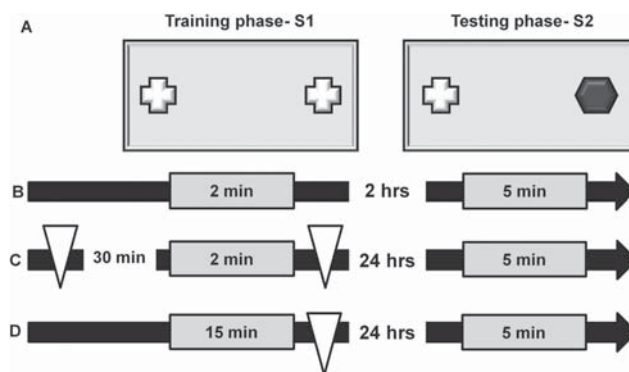


Figure 1. Experimental setup. Male Sprague–Dawley rats were presented with two identical objects during the training session (S1) and, after a delay, were tested for discrimination of the familiar and a novel object during the testing session (S2) A: The duration of the training session was either 2 min (B, C) or 15 min (D). Each testing session was 5 min. The interval between the sessions was either 2 hr (B) or 24 hr (C, D). White triangles symbolize subcutaneous injections either 30 min before (C) or directly after (C, D) the training sessions.

(HD Pro Webcam C910, Logitech), and the time rats spent exploring each object was scored blindly by a person who was not the experimenter (Xnote Stopwatch). Exploration of an object was defined as sniffing, biting, or licking the object. Sitting or climbing on the object, as well as leaning on the object without any sign of active exploration (e.g., facing the object), was not included. Because of the natural preference of rats to explore novel objects, predominant exploration of the novel object was regarded as remembrance of the familiar object. The number of times the rat crossed the midline of the box was counted and served as a measure for overall locomotor activity.

During the period of the experiments, construction work, including blasting, was performed in proximity to the building. Although it was ensured that no experiment was performed during scheduled blasting, some rats expressed signs of stress, including freezing behavior and fast running without exploring the objects. Thus, in order to standardize the test and obtain reproducible data on the basis of previous studies using the same test (De Bundel et al., 2013; Schilström et al., 2011), several exclusion criteria were applied. Rats were excluded if the total exploration time during either S1 or S2 was below 5 s, if only one object was explored in either session, and if the rat was immobile for more than 3 min during the 5-min S2 session. A total of 30 out of 165 rats were excluded from analysis on the basis of these criteria, but those excluded were evenly distributed between the different treatment groups, and therefore unusual behavior was in all likelihood not related to drug treatment.

Adapted designs of the novel object recognition test. In the first protocol, rats were allowed to explore the objects for 2 min during S1 and were tested for object discrimination 2 hr later in the 5-min S2. (see Figure 1B). In the second protocol, the delay between the sessions was increased to 24 hr (see Figure 1C). Rats expressed a significantly increased discrimination ratio if tested 2 hr compared to 24 hr post-S1, indicating remembrance of the objects, unpaired Student's *t* test, $t(10) = 2.47$, $p < .05$; see Figure 2A). Because rats did not recall the familiar object after 24 hr, the

second protocol (see Figure 1C) was used for testing different drugs for memory-enhancing effects. Doses were chosen on the basis of drug-induced monoamine increases in the prefrontal cortex and hippocampus. The following vehicles (veh) and drugs were injected 30 min prior to S1: saline (veh), 2-hydroxypropyl-beta-cyclodextrin (10%, veh), glucose (5.5%, veh), citalopram (10 mg/kg; Huang, Ichiwaka, Li, Dai, & Meltzer, 2006), paroxetine (10 mg/kg; Owen & Whitton, 2006), reboxetine (3 mg/kg; Borgkvist et al., 2012; Linnér et al., 2001), atomoxetine (3 mg/kg; Borgkvist et al., 2012), duloxetine (7 mg/kg; Kihara & Ikeda, 1995), mianserin (5 mg/kg; Wiker, Linner, Wadenberg, & Svensson, 2005) and desipramine (10 mg/kg; Bongiovanni, Kirkbride, Walmire, & Jaskiw, 2005). Saline, citalopram (10 mg/kg), reboxetine (3 mg/kg) and desipramine (10 mg/kg) were injected directly after S1 to test the drugs' effect on memory consolidation. To test whether SSRI pretreatment could attenuate reboxetine's effect, we injected citalopram (10 mg/kg) 35 min and reboxetine (3 mg/kg) 30 min before S1, respectively.

To test whether reboxetine's memory-enhancing effects would be dopamine-dependent, we aimed to combine reboxetine treatment with the D1/D5 antagonist SCH23390 at a dose that would not affect memory by itself. To identify this dose of SCH23390, we used a third protocol (see Figure 1D), in which rats were allowed to explore the objects for 15 min during S1 leading to a significantly higher discrimination ratio 24 hr post-S1 (see Figure 2B; unpaired Student's *t* test, $p < .01$) indicating remembrance of the objects. Two doses of SCH23390 (0.1 and 0.3 mg/kg) were injected immediately after the 15-min S1. Using the second protocol (see Figure 1C), dopamine dependency of reboxetine's effect was tested by injection of reboxetine (3 mg/kg) 30 min prior to S1 combined with injection of SCH23390 (0.1 mg/kg) directly after S1.

Drugs

Paroxetine, reboxetine, desipramine, atomoxetine, and SCH23390 were purchased from Tocris. Mianserin was purchased from Sigma-Aldrich. Citalopram and duloxetine were generously provided by H. Lundbeck A/S (Copenhagen, Denmark). Citalopram (10 mg/kg), reboxetine (3 mg/kg), atomoxetine (3 mg/kg), mianserin (5 mg/kg), and desipramine (10 mg/kg) were all dissolved in saline. Duloxetine (7 mg/kg) was dissolved in 10% 2-hydroxypropyl-beta-Cyclodextrin. Paroxetine (10 mg/kg) was dissolved in 5.5% glucose. All drugs were injected subcutaneously at a volume of 1 ml/kg, except for paroxetine, which was injected at 2 ml/kg.

Data Analysis

Data were expressed as discrimination ratio (exploration of the novel object divided by sum of exploration of both objects, mean $\pm$ SEM) and analyzed by Student's *t* test or one-way ANOVA followed by Dunnett's post hoc test, which is used to compare treatment groups to a control group. When combination treatments were used, data were analyzed by one-way ANOVA followed by Newman Keul's post hoc test in order to compare all treatment groups with each other. Total exploration during S1, that is, the sum of exploration of both objects, was analyzed by one-way ANOVA. Number of midline crosses

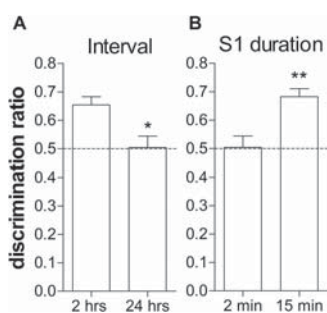


Figure 2. Effects of different protocol parameters on object recognition. A: Rats allowed to explore objects for 2 min in the training session (S1; $n = 8$) equally explored the novel and familiar object 24 hr later, indicating natural forgetting of the familiar object. Two hours post-S1, the discrimination ratio was significantly increased, indicating remembrance of the familiar object ($n = 4$). B: Increasing the training session from 2 min to 15 min ($n = 8$) significantly enhanced the discrimination ratio 24 hr post-S1, indicating a recall of the familiar object. Data are presented as mean plus or minus the standard error of the mean, * $p < .05$, ** $p < .01$, unpaired Student's *t* test. The horizontal dashed line at a discrimination ratio of 0.50 represents equal exploration of both the familiar and novel object, indicating forgetting of the familiar object.

during S1 after pretreatment with antidepressant drugs was analyzed by one-way ANOVA. All experiments were between-subjects designs, and rats were not tested multiple times.

Results

Drugs Specifically Inhibiting Noradrenaline Reuptake Improve Recognition Memory

Injection of saline 30 min prior to the 2-min S1 resulted in equal exploration of novel and familiar object 24 hr post-S1, as indicated by a discrimination ratio of 0.50. There was no significant effect from any of the different vehicles (saline = 0.50 ± 0.04 , $n = 8$; glucose = 0.51 ± 0.05 , $n = 5$; 2-hydroxypropyl-beta-Cyclodextrin = 0.52 ± 0.01 , $n = 5$), $F(2, 15) = 0.04$, ns , indicating that none of the vehicle groups remembered the objects 24 hr after the 2-min S1. Therefore, values of the different vehicle groups were pooled for further analysis. There was a significant main effect of treatment, $F(7, 58) = 5.22$, $p < .0001$ (see Figure 3). Treatment with the NRIs atomoxetine (3 mg/kg, $n = 7$, $p < .01$) and reboxetine (3 mg/kg, $n = 6$, $p < .001$), as well as the SNRI duloxetine (7 mg/kg, $n = 8$, $p < .001$) significantly increased the discrimination ratio compared to vehicle. In contrast, treatment with the SSRIs citalopram (10 mg/kg, $n = 7$) and paroxetine (10 mg/kg, $n = 7$) and the TCA desipramine (10 mg/kg, $n = 6$) had no effect on discrimination ratio. Although, some variation in total exploration during S1 occurred, $F(7, 58) = 2.98$, $p < .05$ (see Table 1),

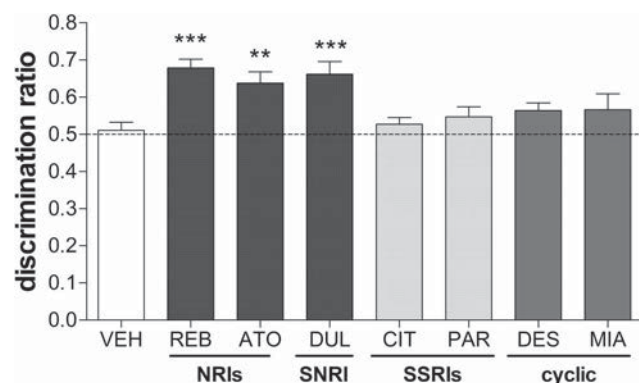


Figure 3. Effects of a single dose of antidepressant drugs or atomoxetine, injected prior to the 2-min training session (S1), on discrimination ratio 24 hr post-S1. The following antidepressant drugs were tested: the noradrenaline reuptake inhibitors (NRIs) reboxetine (REB; 3 mg/kg, $n = 6$) and atomoxetine (ATO; 3 mg/kg, $n = 7$), the noradrenaline serotonin reuptake inhibitor (SNRI) duloxetine (DUL; 7 mg/kg, $n = 8$), the selective serotonin reuptake inhibitors (SSRIs) citalopram (CIT; 10 mg/kg, $n = 7$) and paroxetine (PAR; 10 mg/kg, $n = 7$), and the cyclic antidepressants desipramine (DES; 10 mg/kg, $n = 6$) and mianserin (MIA; 5 mg/kg, $n = 7$). Data are expressed as mean plus or minus standard error of the mean discrimination ratio (exploration of novel object divided by exploration of both the novel and the familiar objects), ** $p < .01$, *** $p < .001$, versus vehicle (VEH), one-way analysis of variance followed by Dunnett's post hoc test. The horizontal dashed line at a discrimination ratio of 0.50 represents equal exploration of both the familiar and novel object, indicating forgetting of the familiar object.

post hoc analysis revealed that none of the drugs had a significant effect on total exploration time during S1 compared to vehicle treatment. Furthermore, the total exploration during S1 was not correlated with the effect on discrimination ratio, as indicated by correlation of mean exploration during S1 and discrimination ratio for all the treatments ($R^2 = 0.32$, ns). Similarly, antidepressant drugs had no significant effect on midline crossings compared to vehicle, $F(6, 57) = 1.29$, ns (see Table 1).

Antidepressant Drugs Injected Directly After the Training Session Improve Recognition Memory

In order to test whether the effects of norepinephrine transporter (NET) inhibition are memory-specific and not due to possible sensory, motor, or motivational effects, we injected reboxetine directly after S1, when memory consolidation occurs (McGaugh & Roozendaal, 2009). In order to compare the effects to other classes of antidepressant drugs, the SSRI citalopram, as well as the TCA desipramine, was also tested with this protocol. There was a significant main effect of treatment, $F(3, 23) = 4.63$, $p < .05$ (see Figure 4). Treatment with reboxetine (3 mg/kg, $n = 8$, $p < .1$) and citalopram (10 mg/kg, $n = 5$, $p < .01$) significantly increased the discrimination ratio compared to vehicle treatment. Although desipramine (10 mg/kg, $n = 7$) revealed no significant effect on discrimination ratio, the 95% confidence interval (0.50–0.77) of the discrimination ratio was above 0.50 indicating a trend for enhancement.

Pretreatment With an SSRI Does Not Attenuate Reboxetine's Memory-Enhancing Effect

The fact that citalopram enhanced memory when injected post, but not prior, to S1 suggests that this drug may inhibit memory acquisition. To test whether this possible inhibition, through functional antagonism, could interfere with a memory-enhancing effect produced by NET inhibition, we administered citalopram (10 mg/kg) 35 min and reboxetine (3 mg/kg) 30 min prior to S1. Upon a significant main effect of treatment, $F(2, 18) = 5.42$, $p < .05$ (see Figure 5), post hoc analysis revealed that reboxetine alone ($n = 6$, $p < .05$) and in combination with citalopram ($n = 7$, $p < .05$) significantly enhanced the discrimination ratio compared to saline, indicating that pretreatment with the SSRI did not attenuate reboxetine's memory-enhancing effect. The reboxetine- and the citalopram/reboxetine-treated group were not significantly different from each other.

Post-S1 Treatment With the D1/D5 Antagonist SCH23390 Attenuates Reboxetine-Induced Increase of Recognition Memory

To confirm that reboxetine's memory-enhancing effect involves dopaminergic transmission, we injected reboxetine 30 min prior to S1 and the dopamine D1/D5 antagonist SCH23390 directly after S1.

There was a significant main effect of treatment, $F(2, 19) = 4.39$, $p < .05$ (see Figure 6). Administration of reboxetine (3 mg/kg) in combination with the D1/D5 antagonist SCH23390 (0.1 mg/kg; $n = 8$) did not significantly increase the discrimination ratio compared to saline (ns), in contrast to reboxetine alone ($n = 6$). This result indicates that reboxetine's memory-enhancing effect was blocked by the D1/D5 antagonist. However, the reboxetine-

Table 1
Effects of Antidepressant Drugs on Locomotion and Object Exploration During Training Session (S1)

Antidepressant drug	Class	Dose (mg/kg)	Midline crossings	Total S1 exploration (s)
Vehicle			10 ± 1	19.1 ± 1.5
Citalopram	SSRI	10	8 ± 2	21.4 ± 1.5
Paroxetine	SSRI	10	10 ± 2	14.0 ± 1.3
Reboxetine	NRI	3	8 ± 1	15.1 ± 1.1
Duloxetine	SNRI	7	9 ± 1	14.9 ± .9
Mianserin	cyclic	5	12 ± 2	15.5 ± 1.4
Desipramine	cyclic	10	12 ± 2	14.5 ± 1.9

Note. Data are presented as midline crossings (mean ± standard error of the mean [SEM]) and the total exploration of the two identical objects (in s, mean ± SEM) during S1 following treatment with different classes of antidepressant drugs: selective serotonin reuptake inhibitor (SSRI), noradrenaline reuptake inhibitor (NRI), serotonin/noradrenaline reuptake inhibitor (SNRI), and cyclic antidepressants (tri- or tetracyclic). One-way analysis of variance followed by Dunnett's post hoc analysis revealed that none of the antidepressant drugs significantly altered midline crossings or total exploration time compared to vehicle treatment, indicating no drug-induced effects on locomotion or motivation to explore the objects.

and the SCH23390/reboxetine-treated group were not significantly different from each other.

The dose of SCH23390 used to block reboxetine's effect did not affect recognition memory itself. Using a 15-min S1 protocol, in which rats remember the familiar object 24 hr post-S1, we injected SCH23390 at 0.1 mg/kg ($n = 7$) and 0.3 mg/kg ($n = 8$) directly after S1, but it did not significantly decrease the discrimination ratio, $F(2, 17) = 0.20$, ns (vehicle: 0.68 ± 0.03 ; 0.1 mg/kg SCH23390: 0.66 ± 0.04 ; 0.3 mg/kg SCH23390: 0.64 ± 0.05).

Discussion

The main findings of this study are that acute administration of antidepressant drugs with selective inhibition of noradrenaline re-

uptake, but not antidepressant drugs selectively inhibiting serotonin alone, enhances recognition memory. Moreover, we showed that reboxetine's memory-enhancing effect could be attenuated by systemic injection of the D1/D5 antagonist SCH23390, furthering our previous findings that local injections of SCH23390 in the prefrontal cortex attenuated reboxetine's effect on recognition memory (De Bundel et al., 2013). Similar to the antidepressant drug reboxetine, the NRI atomoxetine, a drug approved for the treatment of attention-deficit/hyperactivity disorder, significantly increased recognition memory. Atomoxetine has previously been shown to enhance recognition memory in rats using a 3-hr delay (Tzavara et al., 2006). Together these data indicate that noradrenaline reuptake inhibition is sufficient for enhancement of recognition memory.

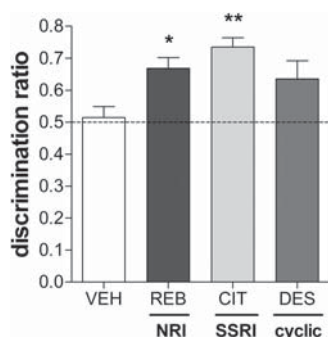


Figure 4. Effects of a single dose of antidepressant drugs injected after the 2-min training session (S1) on discrimination ratio 24 hr post-S1. The following antidepressant drugs were tested: the noradrenaline reuptake inhibitor (NRI) reboxetine (REB; 3 mg/kg, $n = 8$), the selective serotonin reuptake inhibitor (SSRI) citalopram (CIT; 10 mg/kg, $n = 5$), and the tricyclic antidepressant desipramine (DES; 10 mg/kg, $n = 7$). Data are expressed as mean plus or minus standard error of the mean discrimination ratio (exploration of novel object divided by exploration of both the novel and the familiar objects), * $p < .05$, ** $p < .01$, versus vehicle (VEH), one-way analysis of variance followed by Dunnett's post hoc test. The horizontal dashed line at a discrimination ratio of 0.50 represents equal exploration of both the familiar and novel object, indicating forgetting of the familiar object.

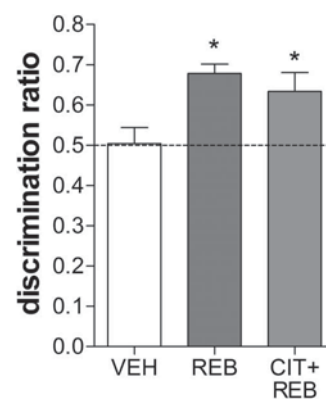


Figure 5. Effect of pretreatment with citalopram on reboxetine-induced increase of discrimination ratio. Pretreatment with citalopram (CIT; 10 mg/kg, 35 min prior to training session [S1], $n = 7$) did not abolish the effect of reboxetine injection (REB; 3 mg/kg, 30 min prior to S1, $n = 6$) on discrimination ratio. Data are expressed as mean plus or minus standard error of the mean discrimination ratio (exploration of novel object divided by exploration of both the novel and the familiar objects), * $p < .05$, versus vehicle (VEH; $n = 8$), one-way analysis of variance followed by Newman-Keul's post hoc test. The horizontal dashed line at a discrimination ratio of 0.50 represents equal exploration of both the familiar and novel object, indicating forgetting of the familiar object.

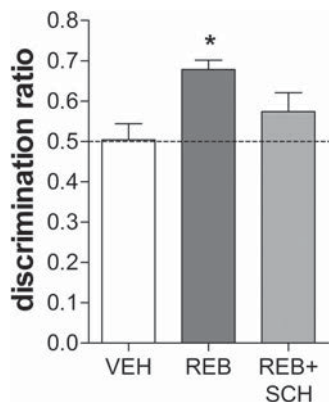


Figure 6. Effect of D1/5 antagonist SCH23390 on reboxetine-induced increase of discrimination ratio. Whereas a single injection of reboxetine (REB; 3 mg/kg, $n = 6$) prior to the 2-min training session significantly enhanced discrimination ratio, coinjection of SCH23390 (SCH; 0.1 mg/kg, $n = 8$) directly after the training session abolished this effect. Data are expressed as mean plus or minus standard error of the mean discrimination ratio (exploration of novel object divided by exploration of both the novel and the familiar objects), * $p < .05$, versus vehicle (VEH; $n = 8$), one-way analysis of variance followed by Newman-Keul's post hoc test. The horizontal dashed line at a discrimination ratio of 0.50 represents equal exploration of both the familiar and novel object, indicating forgetting of the familiar object.

A drug present during S1 could also enhance memory by affecting locomotion, motivation, or attention instead of a direct effect on memory consolidation. Antidepressant drugs injected prior to S1 did not significantly change midline crossings or increase total object exploration compared to vehicle during S1 in this study, suggesting no motoric or motivational effects. However, to further investigate whether enhancements were memory-specific, we injected the drugs directly after S1, so that the drug was present during memory consolidation but not memory acquisition. Using this protocol, we found that not only reboxetine but also citalopram enhanced recognition memory.

The contrasting effects of citalopram when injected prior to or post-S1 indicate that SSRIs may inhibit memory acquisition and thereby abolish their own effect on memory consolidation. This notion is supported by several preclinical studies showing that pre-training injections of SSRIs can impair, whereas posttraining injections do not affect or improve, memory in avoidance and spatial memory tasks (Majlessi & Naghdi, 2002; Monleón, Casino, Vinader-Caerols, & Arenas, 2001; Monleón et al., 2008). It is important to note that, although increased serotonergic transmission does not appear to be sufficient to improve object cognition, serotonin depletion impairs novel object recognition (Jensen et al., 2014), indicating that basal serotonergic transmission is necessary for recognition memory. Although inhibition of serotonin reuptake alone may impair memory acquisition, one can conclude that it does not interfere with the beneficial effect of noradrenaline reuptake inhibition, because both the SNRI duloxetine and the combined administration of citalopram and reboxetine improved recognition memory. Due to this lack of interference, the mechanisms involved in the SSRI-induced memory-inhibiting and memory-enhancing effects must be distinctly different from those involved in NRI-induced memory enhancement.

Several studies have suggested a role of the dopaminergic D1/D5 transmission in recognition memory. We have previously

shown that the novel object recognition task is dependent on dopaminergic D1/D5 transmission in the prefrontal cortex and dorsal hippocampus (De Bundel et al., 2013). Consolidation of recognition memory was recently shown to require D1/D5 receptors in the prefrontal cortex and amygdala but not the dorsal hippocampus (Rossato et al., 2013). Furthermore, injection of the dopamine D1/D5 agonist immediately after S1 improves recognition memory, and this memory improvement was blocked by a D1/D5 antagonist (de Lima et al., 2011). Reboxetine's memory enhancing might therefore be caused by its ability to increase dopamine output in areas of the brain where reuptake of dopamine depends mainly on the noradrenaline transporter including the prefrontal cortex (Linnér et al., 2001) and the ventral hippocampus (Borgkvist et al., 2012). In our recently published study, local injection of the D1/D5 antagonist in the prefrontal cortex but not the dorsal hippocampus blocked reboxetine's memory-enhancing effects (De Bundel et al., 2013), suggesting that the locus of the herein observed effects following systemic drug injections is likely to be the prefrontal cortex. Whereas the dorsal hippocampus in rodents has been associated with spatial memory, the ventral part of the hippocampus has been associated with emotional memory (for review see Gruber & McDonald, 2012). The dorsal hippocampus has recently been suggested to be important for single trials, such as in the present study, whereas the ventral hippocampus is involved in generalization of memory learned across events (Komorowski et al., 2013), which would argue against an involvement of the ventral hippocampus in this task. Nevertheless, we cannot rule out an involvement of the ventral hippocampus, and the dopamine elevations that reboxetine and atomoxetine cause in this area (Borgkvist et al., 2012) might be beneficial in other related memory types impaired in depression.

Further support that an enhancement of dopamine transmission in the prefrontal cortex might underlie the memory-enhancing effects observed herein can be found in the fact that duloxetine and atomoxetine increase dopamine outflow in the prefrontal cortex (Kihara & Ikeda, 1995; Li et al., 2012).

The antidepressant drugs desipramine and mianserin, which do not significantly affect recognition memory (discrimination ratio: 0.56 ± 0.02 for desipramine, 0.56 ± 0.04 for mianserin), have been shown to increase dopamine release in the prefrontal cortex (Bongiovanni et al., 2005; Wiker et al., 2005). However, these antidepressant drugs possess anticholinergic and/or antihistaminergic properties known to be cognitive-impairing or sedative (Hindmarch, 2009; Peretti, Judge, & Hindmarch, 2000). Similarly, although paroxetine increased cortical dopamine (Owen & Whiston, 2006), paroxetine-induced impairments of long-term memory in healthy volunteers was suggested to be caused by its anticholinergic effects (Schmitt, Kruizinga, & Riedel, 2001). In addition, a direct role of noradrenaline in consolidation of long-term memory of emotionally arousing events has been established (McGaugh & Roozendaal, 2002). Moreover, performance in the emotionally neutral task novel object recognition has been improved by increasing noradrenaline (Nirogi et al., 2012; Roozendaal et al., 2008), an effect that was attenuated by the beta-adrenergic antagonist propranolol (Roozendaal et al., 2008). Therefore, NRI-induced increased noradrenaline transmission might contribute to the memory-enhancing effects observed in this study. The two SSRIs tested in this study did not enhance recognition memory; however, we have previously reported that the SSRI escitalopram

increases recognition memory if injected prior to S1 (Schilström et al., 2011), and it has also been shown to enhance cognitive function in depressed patients (Wroolie et al., 2006) and in patients recovering from stroke (Jorge et al., 2010). It is important to note that escitalopram (the S-enantiomer of the racemic mixture citalopram) binds to the allosteric site of the serotonin transporter (therefore renamed ASRI; Sánchez, 2006), leading to a variety of different effects compared to citalopram (Schilström et al., 2011), including an increased burst firing of dopamine neurons in the ventral tegmental area. Although reboxetine increased burst firing of dopamine cells in the ventral tegmental area as well (Linnér et al., 2001), the SSRIs used in the present study (citalopram and paroxetine) decreased the firing rate of these neurons and did not affect burst firing (Di Mascio, Di Giovanni, Di Matteo, Prisco, & Esposito, 1998; Prisco & Esposito, 1995). In our study, the effects of certain antidepressant drugs on recognition memory may therefore be related to their effect on burst firing of dopamine neurons in the ventral tegmental area. However, given the complexity of interactions between the monoamines and the fact that they have all been shown to affect memory, further studies investigating the specific roles of noradrenergic and serotonergic receptors in the found memory-enhancing effects are needed.

The present study showing that NRIs and SNRIs are superior to SSRIs in terms of increasing recognition memory is the first to suggest differences in effects of antidepressant drugs on cognition on the basis of their pharmacology. Further studies in both animals and humans are needed to investigate the effects of available drugs on different types of cognition. This approach might ultimately help to choose drugs that treat cognitive deficits occurring in a variety of psychiatric disorders, including depression.

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