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The α_{2A}-Adrenergic Agonist Guanfacine Improves Visuomotor Associative Learning in Monkeys

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Two monkeys were trained on two-problem visuomotor associations: if the cue was a circle pattern, move a handle to the left ('go-left'), and if it was a triangle pattern, move the handle to the right ('go-right'). These two visuomotor associations were unchanged throughout all the experiments and therefore were very familiar to the monkeys. For learning of new visuomotor associations, each monkey was presented with a new set of four novel patterns in each and every daily session, two of which instructed 'go-left' response and the other two 'go-right' response. Systemically administered guanfacine, a selective α_{2A}-adrenergic agonist, improved the monkeys' learning ability: trials and errors to the learning criterion of 90% correct decreased significantly. The monkeys showed an enhanced capability of using at least three response strategies: win-stay on 'repeat trial', change-stay and change-shift on 'change trial'. The beneficial effect could be reversed by the coadministered idaxozan, an α_2-adrenergic antagonist, which had no effect when administered alone. Similar treatment with guanfacine had no beneficial effect on visual discriminative learning, a task that involves the inferotemporal cortex. The present results indicate that stimulation by guanfacine of α_{2A}-adrenoceptors improves visuomotor associative learning, probably through actions at α_{2A}-adrenoceptors in the prefrontal cortex.
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INTRODUCTION

It is known that norepinepherine (NE) exerts an important, beneficial influence on prefrontal cortical functions (Coull, 1994; Arnsten *et al*, 1996). It has been well documented that α_{2A}-adrenoceptors in the dorsolateral prefrontal cortex (PFdl) play an important role in regulating spatial working memory (Arnsten *et al*, 1996). For example, stimulation of α_{2A}-adrenoceptors in the PFdl improves spatial working memory performance (Arnsten and Goldman-Rakic, 1985; Arnsten *et al*, 1988; Arnsten and Leslie, 1991; Cai *et al*, 1993; Mao *et al*, 1999; Rama *et al*, 1996) and facilitates PFdl neuronal activity related to it (Li *et al*, 1999). Conversely, blockade or mutation of α_{2A}-adrenoceptors in the PFdl impairs spatial working memory performance (Arnsten and Goldman-Rakic, 1985; Li and Mei, 1994; Franowicz *et al*, 2002) and suppresses PFdl neuronal activity related to it (Li *et al*, 1999).

The ventral/orbital prefrontal cortex (PFv+o) plays an important role in nonspatial working memory (Courtney *et al*, 1996; Goldman-Rakic, 1996; Wilson *et al*, 1993) and in reversal learning of visual object discrimination (Dias *et al*, 1996; Iversen and Mishkin, 1970; Ridley *et al*, 1993). Steere and Arnsten (1997) reported that systemically administered guanfacine, the selective α_{2A}-adrenergic agonist, improves the reversal of an object discrimination task in monkeys. Avery *et al* (2000) reported that guanfacine increases regional cerebral blood flow (rCBF) in the PFv of monkeys (see Figure 2 of Avery *et al*, 2000).

In addition to nonspatial working memory and reversal learning of object discrimination, PFv+o also plays an important role in visuomotor associative learning (Murray *et al*, 2000; Passingham *et al*, 2000; Wang *et al*, 2000; Bussey *et al*, 2001, 2002). It is expected that stimulation of α_{2A}-adrenoceptors would have a beneficial influence on visuomotor associative learning. Indeed, Scahill *et al* (2001) showed that guanfacine improves the performance of children with Attention Deficit Hyperactivity Disorder (ADHD) on the Connor's Continuous Performance Task, a task that has a component of visuomotor association. Li and Kubota (1998) reported that the α_2-adrenergic agonist clonidine enhances PFv cortical neuronal activity related to a visual discrimination task with 'go' and 'no-go' performances, a task of visuomotor associations. The present study aims to demonstrate the role of α_{2A}-adrenoceptors in regulating visuomotor associative learning in monkeys.

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MATERIALS AND METHODS

Four monkeys (*Macaca mulatta*, male) were used. Monkeys #1 and #2 (10.0 and 11.0 kg, respectively) were used for examining the effect of guanfacine on visuomotor associative learning and Monkeys #3 and #4 (8.0 and 6.5 kg) for investigating the effect of guanfacine on visual discriminative learning. The monkeys were cared for in accordance with the *Guide for the Care and Use of Laboratory Animals* issued by the National Institutes of Health, USA (1996). The present study was approved and monitored by the *Ethical Committee of Animal Experiments* at the Institute of Neurobiology, Fudan University.

Performance of Familiar Visuomotor Associations

Monkeys #1 and #2 were trained on two-problem visuomotor associations. Each monkey was seated in a primate chair and faced a square panel placed 40 cm away. On the panel, there was a window (10 cm in width and 8 cm in height), behind it a food well, and under it a wooden handle which could be moved to the left or right. The experimenter sat behind the panel and could not be seen by the animal.

Each trial was initiated by the experimenter's inserting a card with a visual pattern (*circle* or *triangle*) on it into the window. The monkey was required to move the handle to the left ('go-left' response) if the pattern was the circle or to the right ('go-right' response) if it was the triangle. The card was removed from the window immediately after the monkey made a response. A piece of apple or peanut was delivered into the food well if the monkey made a correct response. The monkey released the handle and used its performing hand to pick the reward up. The handle automatically returned to its original position after being released. The next trial did not begin until the monkey released the handle after a response. The circle- and triangle-trials were presented in a random, but balanced, order (Gellermann schedule). The intertrial interval (ITI) was usually 10 s, but if the monkey touched or moved the handle during this interval it was prolonged for another 10 s. This procedure was continued until the monkey refrained from touching the handle during the ITI. A rerun correction procedure was introduced in case the monkey made an error response: the same pattern was presented again, giving the monkey a chance to change its response. The monkey received as many correction trials as necessary, that is, the same pattern was presented until the monkey emitted a correct response.

Training of this task took about 4 weeks for each monkey. The two visuomotor associations (ie 'circle, go-left' and 'triangle, go-right') were kept unchanged throughout all the experiments. Thus, the *circle* and *triangle* patterns were very familiar to the monkeys.

Learning of New Visuomotor Associations

After the monkey had learned the two familiar visuomotor associations (with $\geqslant$90% correct in 10 consecutive daily sessions), learning of new visuomotor associations was introduced. Each daily learning session began with the performance of 20 familiar-pattern (FP) trials (10 circle-trials and 10 triangle-trials; 'FP Block 1'), continued with new-pattern (NP) learning ('NP Block'), and ended with another block of 20 FP trials (10 circle-trials and 10 triangle-trials; 'FP Block 2'). The two FPs were not presented in the 'NP Block'.

For each and every session, the monkey was required to learn a new set of four NPs (we used X1, X2, X3, and X4 to represent them, respectively). The four patterns were presented to the monkey in a random, but balanced, order. The patterns were two-dimensional figures, with height and width of approximately 40 mm, and were drawn from a pool of over 400 patterns at random. A pattern was no longer used if it had been used in a previous learning session. The behavioral significance of X1 and X3 was arbitrarily defined as 'go-left' and that of X2 and X4 'go-right'. Learning criterion was defined as 18 correct out of 20 consecutive NP trials (90% correct). The same rerun correction procedure was used as described above. Once the criterion of 90% correct was reached, 'FP Block 2' was started immediately.

Systemic Administration of Guanfacine

After the monkey learned 10 sets of four NPs in 10 consecutive sessions with $\geqslant$90% correct, the experiments with drug administration began. Guanfacine hydrochloride (Wyeth-Ayerst Research, Princeton, NJ, USA; 0.0001, 0.001, or 0.1 mg/kg, dissolved freshly in sterile saline each experimental day) or sterile saline (equal volume) was injected intramuscularly 2 h prior to testing in each daily session. Monkey #1 received two doses of guanfacine (0.001 or 0.1 mg/kg) and Monkey #2 received three doses of guanfacine (0.0001, 0.001, or 0.1 mg/kg). In order to determine if guanfacine acted at α_2-adrenoceptors to produce its effect, the α_2-adrenergic antagonist idazoxan (Research Biochemical Inc., Natick, MA, USA; 0.1 mg/kg, prepared freshly each experimental day) was coadministered with guanfacine (intramuscular injection, 30 min prior to testing). The sequence of drug treatment was as follows: guanfacine (0.1 mg/kg; six sessions), guanfacine (0.1 mg/kg) plus idazoxan (0.1 mg/kg; six sessions), saline (six sessions), guanfacine (0.001 mg/kg; six sessions), guanfacine (0.001 mg/kg) plus idazoxan (0.1 mg/kg; six sessions), idazoxan (0.1 mg/kg; six sessions), and finally guanfacine (0.0001 mg/kg; six sessions). A 3-week washout was interposed between two treatments.

Visual Discrimination Learning

Monkeys #3 and #4 were trained on a visual discrimination task. Each monkey was seated in front of a touch screen. Each trial was initiated by the monkey's touching a filled *square* pattern (starting signal) displayed on the middle bottom of the screen. At 0.5$\sim$1.0 s after the monkey touched the *square* pattern, a pair of visual patterns (*circle* and *triangle*) were presented simultaneously. The *circle* pattern was defined as a positive one and the *triangle* pattern as a negative one. The monkey was trained to touch, within 2 s after presentation, the positive but not the negative pattern to obtain a drop of water as reward. The two patterns were changed randomly between the left and right positions. The ITI was 10 s. After the monkey had been well trained on the *circle* and *triangle* patterns (with 100% correct in 10 consecutive daily sessions; the two patterns

were then very familiar to the monkeys), visual discriminative learning was started.

In each daily learning session, the monkey was required to learn a pair of novel patterns, one of which was positive and the other negative. The novel patterns were two-dimensional figures, with height and width of approximately 40 mm, and were drawn from a pool of over 400 patterns. A pattern was no longer used if it had been used in a previous session. The monkey learned to touch the positive but not the negative pattern in order to obtain reward. Each daily session began with a block of 20 trials with the two FPs, continued with learning of a pair of novel patterns, and ended with another block of 20 trials with the two FPs.

Learning criterion was nine correct out of 10 consecutive trials (90% correct). On reaching the criterion, the monkey was allowed to perform the novel patterns for an additional block of five trials. After the monkey successfully learned eight pairs of novel patterns in eight consecutive daily sessions (normal control sessions), the experiment with guanfacine treatment (0.1 mg/kg; eight consecutive daily sessions) began, followed by the experiment with saline (eight consecutive daily sessions). Guanfacine or saline was administered intramuscularly 2 h prior to testing in each daily session.

Data Analysis

Trials and errors to the learning criterion were the main behavioral measures analyzed, along with reaction time. These measures in saline, guanfacine, and guanfacine plus idazoxan sessions were compared statistically using the Mann–Whitney *U*-test.

In order to compare the effects of guanfacine on visuomotor associative learning in Monkeys #1 and #2, we calculated the savings score using the following formula: (mean errors in saline sessions − mean errors in guanfacine sessions)/(mean errors in saline sessions + mean errors in guanfacine sessions) × 100. The higher the savings score was, the more effective guanfacine was.

RESULTS

General

Monkeys #1 and #2 performed the two familiar visuomotor associations ('*circle*, *go-left*' and '*triangle*, *go-right*') with 100 ± 0% correct (mean ± SD) in normal control sessions ($n = 10$ for each monkey). The reaction times of Monkey #1 to the *circle* and *triangle* patterns were 337 ± 22 and 333 ± 26 ms, and those of Monkey #2 were 352 ± 35 and 340 ± 42 ms, respectively.

Monkeys #1 and #2 needed 150 ± 19 and 202 ± 32 trials, with 42 ± 5 and 68 ± 11 errors, respectively, to learn a new set of four novel patterns in the normal control sessions ($n = 10$ for each monkey). For Monkey #1, the reaction time to X1 and X3 (instructing 'go-right' response) was 717 ± 102 ms, and that to X2 and X4 (instructing 'go-right' response) was 732 ± 105 ms. For Monkey #2, the reaction time to X1 and X3 was 715 ± 92 ms and that to X2 and X4 was 720 ± 85 ms. Therefore, each monkey spent significantly longer time on selecting a response when a novel pattern was presented.

Guanfacine has no Effect on Performance of Pre-Established Visuomotor Associations

In each daily session, the monkeys were required to perform the two familiar visuomotor associations before and after learning a new set of four novel patterns. The monkeys performed the familiar visuomotor associations 100% correct, leaving no room for improvement following treatment with guanfacine.

The reaction times to the two FPs were not changed following guanfacine treatment. The reaction times of Monkey #1 to the *circle* and *triangle* patterns were 318 ± 13 and 324 ± 22 ms, and those of Monkey #2 were 329 ± 13 and 334 ± 19 ms, respectively, in guanfacine sessions with the 0.1 mg/kg dose ($P > 0.05$ for guanfacine *vs* normal control).

Guanfacine Produces Improvement in Learning of New Visuomotor Associations

As shown in Figure 1, the trials and errors to the criterion of 90% correct decreased significantly after 0.1 or 0.001 mg/kg dose guanfacine ($P < 0.001$ for 0.1 or 0.001 mg/kg dose guanfacine *vs* saline), but not after the 0.0001 mg/kg dose. Monkeys #1 and #2 needed 131 ± 24 and 217 ± 38 trials, with 35 ± 7 and 70 ± 12 errors, respectively, to learn a new set of four novel patterns in saline sessions ($n = 6$ for each monkey). The same measures changed to 63 ± 15 and 89 ± 36 trials, with 14 ± 5 and 22 ± 13 errors, in guanfacine sessions with the 0.001 mg/kg dose ($n = 6$ for each monkey), and 63 ± 21 and 77 ± 37 trials, with 14 ± 5 and 17 ± 8 errors, respectively, in guanfacine sessions with the 0.1 mg/kg dose ($n = 6$ for each monkey).

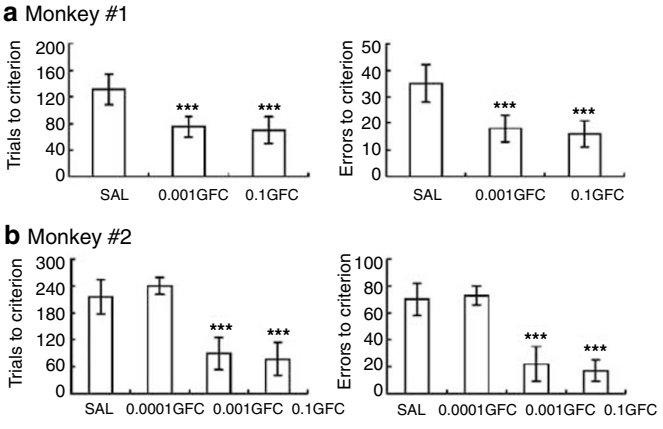

Figure 1 Guanfacine improved visuomotor associative learning. The trials and errors to the learning criterion decreased significantly in the guanfacine sessions with the 0.001 or 0.1 mg/kg dose in both monkeys, but were unchanged in the guanfacine sessions with the 0.0001 mg/kg dose (this dose was tested only in Monkey #2). Data are represented as mean ± SD. ***$P < 0.001$ *vs* saline, the Mann–Whitney *U*-test. SAL, saline; 0.0001GFC, 0.001GFC, and 0.1GFC represent 0.0001, 0.001, and 0.1 mg/kg dose guanfacine, respectively.

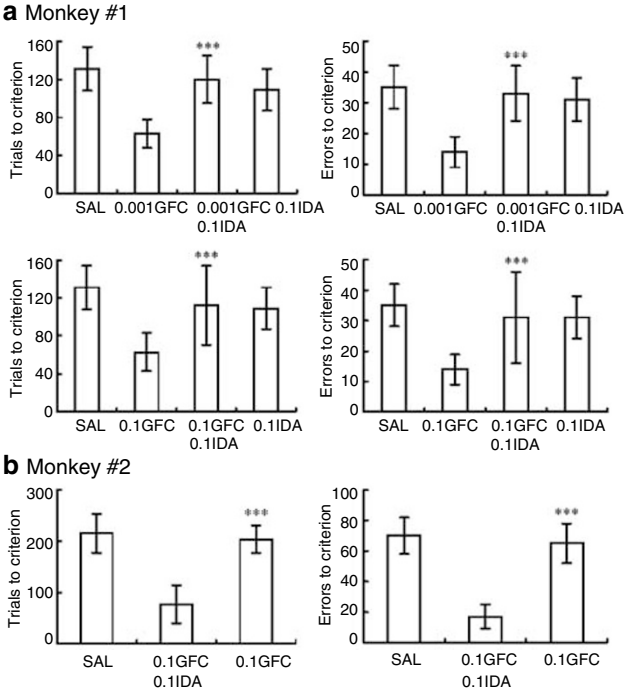

Figure 2 Idazoxan blocked the beneficial effect of guanfacine on visuomotor associative learning, but was without effect on its own. Idazoxan (0.1 mg/kg) was coadministered with 0.001 or 0.1 mg/kg dose guanfacine in Monkey #1 and with 0.1 mg/kg dose guanfacine in Monkey #2. The same dose idazoxan was tested alone in Monkey #1. Data are represented in mean ± SD. ***$P<0.001$ *vs* 0.001 or 0.1 mg/kg dose guanfacine, the Mann–Whitney *U*-test. SAL, saline; 0.001GFC and 0.1GFC represent 0.001 and 0.1 mg/kg dose guanfacine, respectively, and 0.1IDA 0.1 mg/kg dose idazoxan.

However, the reaction times to novel patterns were not altered. For Monkey #1, the reaction time to X1 and X3 (instructing 'go-left' response) was 708 ± 140 ms and that to X2 and X4 (instructing 'go-right' response) was 738 ± 123 ms in saline sessions ($n=6$). The same measures were 692 ± 106 and 710 ± 86 ms, respectively, in guanfacine sessions ($n=6$) with the 0.1 mg/kg dose ($P>0.05$ for guanfacine *vs* saline). For Monkey #2, the reaction time to X1 and X3 was 728 ± 130 ms and that to X2 and X4 was 725 ± 115 ms in saline sessions ($n=6$). The same measures were 704 ± 118 and 695 ± 125 ms, respectively, in guanfacine sessions ($n=6$) with the 0.1 mg/kg dose ($P>0.05$ for guanfacine *vs* saline).

By analyzing savings score, we found that the beneficial effect of guanfacine was more evident in Monkey #2 than in Monkey #1. The savings scores for Monkey #2 were 52.6 in the 0.001 mg/kg guanfacine sessions and 58.2 in the 0.1 mg/kg guanfacine sessions, while the same measures for Monkey #1 were 42.0 and 43.0, indicating that guanfacine was more effective in Monkey #2 than in Monkey #1.

There were two types of errors on *repeat trials* and *change trials*, respectively. *Repeat trial* refers to a trial in which the pattern was the same as on the previous trial, and *change trial* a trial in which the pattern was different from on the previous trial. In a *repeat trial*, it was possible for the monkey not to repeat a correct response (*Win-Stay failure*) or repeat an incorrect response (*Lose-Shift failure*). In a *change trial*, it was possible for the monkey to change a response when X1 (X2) was changed to X3 (X4), or *vice versa* (*Change-Stay failure*), or not to change a response when X1 (X3) was changed to X2 (X4), or *vice versa* (*Change-Shift failure*).

Table 1 Errors in Visuomotor Associative Learning in Saline and Guanfacine Sessions

	Number of errors		
	Saline	**Guanfacine (0.001 mg/kg)**	**Guanfacine (0.1 mg/kg)**
Monkey #1			
Total	210	84	84
Win-Stay failure	28	11***	13***
Lose-Shift failure	12	5	5
Change-Stay failure	55	23***	27***
Change-Shift failure	115	45***	39***
Monkey #2			
Total	420	132	102
Win-Stay failure	62	18***	15***
Lose-Shift failure	20	6	8
Change-Stay failure	133	46***	34***
Change-Shift failure	205	62**	45***

Each value represents a sum of errors to the learning criterion of 90% correct for six sets of novel visuomotor associations in six daily sessions. ***$P<0.001$ *vs* saline.

Table 1 shows the numbers of the four types of error in saline and guanfacine sessions. As shown, both monkeys were very good at applying a *Lose-Shift* strategy. The errors were mainly expressed as *Win-Stay*, *Change-Stay*, and *Change-Shift failures*, both in saline and guanfacine sessions. Guanfacine treatment significantly enhanced the monkeys' ability to use the *Win-Stay*, *Change-Stay*, and *Change-Shift* strategies, as the number of each of the three types of error decreased significantly following treatment with guanfacine.

Each monkey was given as many correction trials as necessary after it selected an incorrect response in a novel-pattern trial (error trial). That is to say, if the monkey made an incorrect response to a novel pattern, that pattern was presented again in the next trial (first correction trial), and if the monkey repeated the error again, the pattern was presented again (second correction trial). This correction procedure was continued until the monkey selected a correct response. In most cases, both monkeys were able to change its response in the first correction trial. For example, Monkeys #1 and #2 changed response in the first correction trial for 95.5 and 93.8% of error trials in saline sessions, respectively, and they did so for 100% of error trials in guanfacine sessions with the 0.1 mg/kg dose.

The beneficial effect of guanfacine could be reversed by coadministered idazoxan (0.1 mg/kg), the α_2-adrenergic antagonist (Figure 2; $P<0.001$ for guanfacine + idazoxan *vs* guanfacine; $P>0.05$ for guanfacine + idazoxan *vs* saline). The same dose idazoxan was without effect on visuomotor associative learning when administered alone (Figure 2a, $P>0.05$ for idazoxan *vs* saline), indicating that idazoxan blocked the effect of guanfacine by competing at α_{2A}-adrenoceptors. Thus, guanfacine produced its effect through actions at α_{2A}-adrenoceptors.

Guanfacine has no Beneficial Effect on Visual Discriminative Learning

Monkeys #3 and #4 performed the FPs (*circle* and *triangle*) 100% correct, either in the normal sessions ($n=8$), the saline sessions ($n=8$), or in the guanfacine sessions ($n=8$, with the 0.1 mg/kg dose). For Monkey #3, the reaction time to the familiar positive pattern (*circle*) was 425 ± 33 ms in the normal sessions, 423 ± 32 ms in the saline sessions, and 414 ± 23 ms in the guanfacine sessions ($P>0.05$ for guanfacine *vs* normal or saline). For Monkey #4, the same measure was 522 ± 23 ms in the normal sessions, 529 ± 24 ms in the saline sessions, and 517 ± 38 ms in the guanfacine sessions ($P>0.05$ for guanfacine *vs* normal or saline).

Both monkeys showed no improvement in visual discriminative learning following treatment with 0.1 mg/kg dose guanfacine. The trials and errors to the learning criterion in the guanfacine sessions were not significantly different from those in the normal or saline sessions (Figure 3; $P>0.05$ for guanfacine *vs* normal or saline). The reaction time to novel positive patterns was also not changed following treatment with guanfacine. For Monkey #3, the reaction time to novel positive patterns was 709 ± 18 ms in the normal sessions, 713 ± 19 ms in the saline sessions, and 706 ± 15 ms in the guanfacine sessions ($P>0.05$ for guanfacine *vs* normal or saline). For Monkey #4, the same measure was 724 ± 33 ms in the normal sessions, 728 ± 24 ms in the saline sessions, and 710 ± 13 ms in the guanfacine sessions ($P>0.05$ for guanfacine *vs* normal or saline).

Thus, guanfacine produced no beneficial effect on visual discriminative learning, a task that is dependent on the inferotemporal cortex.

DISCUSSION

The present study shows that systemically administered guanfacine significantly improved the monkeys' ability to learn novel visuomotor associations. As guanfacine had no beneficial effect on visual discriminative learning, the improvement of visuomotor associative learning was not due to enhancement of visual discrimination or pattern information processing, which requires the inferotemporal cortex.

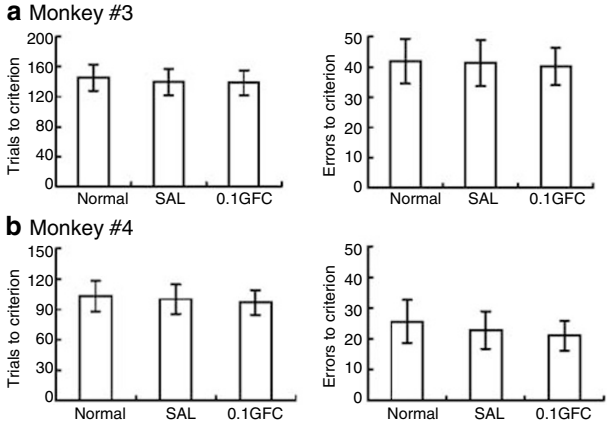

Figure 3 Guanfacine had no beneficial effect on visual discriminative learning. The trials and errors to the learning criterion in the guanfacine sessions were not significantly different from those in the normal or saline sessions in both monkeys. Data are represented in mean ± SD. 0.1GFC represents 0.1 mg/kg dose guanfacine.

The PFv + o is a cortical area critical for the acquisition of arbitrary visuomotor associations. For example, inactivation of or damage to this cortical area dramatically impaired a monkey's capability to acquire new visuomotor associations (Murray *et al*, 2000; Wang *et al*, 2000; Bussey *et al*, 2001, 2002). Neurons in the ventral prefrontal cortex showed an evolution in activity during learning of new visuomotor associations (Asaad *et al*, 1998; Li *et al*, 1997). Using fMRI and PET imaging techniques, Toni and his colleagues found that the ventral prefrontal cortex was activated during learning of visuomotor associations in humans (Toni and Passingham, 1999; Toni *et al*, 1999). Thus, the beneficial effect of guanfacine was most likely to be mediated by α_{2A}-adrenoceptors in the PFv + o.

It has been demonstrated that the PFdl is necessary for spatial working memory (Goldman-Rakic, 1996), whereas there is evidence that the ventral prefrontal cortex is involved in nonspatial working memory (Wilson *et al*, 1993; Courtney *et al*, 1996). During learning of novel visuomotor associations, the monkeys needed to keep track of the correctness or error of a response made in the previous trial, or of the visuomotor association *per se*, during the ITI, in order to maintain or change a response selection in the next trial. It was possible that guanfacine enhanced visuomotor associative learning by facilitating working memory or short-term memory for this task information and consequently improved the *Win-Stay/Lose-Shift* strategies on *repeat trials* and the *Change-Stay/Chang-Shift* strategies on *change trials*.

It was also possible that guanfacine improved the monkeys' attention and thus resulted in an improvement of the learning ability. It is known that the prefrontal cortex plays an important role in attention regulation. Poor attention regulation is a typical phenomenon seen after damage to the prefrontal cortex. Arnsten *et al* (1996) reported that systemically administered guanfacine could protect aged monkeys from distractions during the performance of a delay-response task.

The dorsal premotor cortex (PMd) is essential not only for the acquisition but also for memory mechanisms of visuomotor associations. Damage to the PMd produced a severe deficit in learning novel visuomotor associations and relearning pre-established ones (Murray *et al*, 2000; Wise, 1996; Wise and Murray, 2000). The PFv + o is insufficient to support visuomotor associative learning without the PMd. Therefore, it cannot be excluded that guanfacine produced its beneficial effect through actions at α_{2A}-adrenoceptors in the PMd.

Guanfacine has been used experimentally or clinically for the treatment of human psychiatric disorders such as schizophrenia, Korsakoff's syndrome, and especially ADHD (Chappell *et al*, 1995; Horrigan and Barnhill, 1995; Hunt *et al*, 1995; Scahill *et al*, 2001). Patients with these psychiatric disorders show prominent cognitive deficits of the prefrontal cortex. The present study provides evidence that guanfacine can enhance visuomotor associative learning, in which the PFv + o plays a key role. The present study provides an important expansion on an emerging field

demonstrating that α_{2A}-adrenoceptor stimulation can strengthen a variety of cognitive functions dependent on the prefrontal cortex, both in animals and humans (Arnsten *et al*, 1996; Steere and Arnsten, 1997; Jakala *et al*, 1999).

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