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Research report

Enhanced visuomotor associative learning following stimulation of α_{2A}-adrenoceptors in the ventral prefrontal cortex in monkeys

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Abstract

The present study investigated the effect of locally infused guanfacine, an α_{2A}-adrenergic agonist, into the ventral prefrontal cortex (PFv) on visuomotor associative learning. Two monkeys were well trained on a two-problem visuomotor associative task: the monkeys performed movement A if presented with a circle pattern, or movement B if presented with a triangle pattern. For learning of new visuomotor associations, the monkeys were presented with a new set of four patterns in each and every daily session, two of which instructed movement A and the other two movement B. Bilaterally infused guanfacine (2.5 μg/μl; 3 μl on each side) improved the monkeys' ability to learn new visuomotor associations: trials and errors to learning criterion of 90% correct decreased significantly. The monkeys showed an enhanced capability to use *win–stay/lose–shift* strategy on 'repeat trials' and *change–stay*/*change–shift* strategy on 'change trials.' The present results indicate that α_{2A}-adrenoceptor in the PFv is involved in regulating visuomotor associative learning.

Theme: Neural basis of behavior
Topic: Learning and memory: pharmacology

Keywords: Guanfacine; α_{2A}-Adrenoceptor; Ventral prefrontal cortex; Visuomotor associative learning; Monkey

1. Introduction

The prefrontal cortex (PFC) receives noradrenergic projections from the locus coeruleus (LC). Low to moderate levels of norepinephrine (NE) have a beneficial effect on PFC functions through actions at α_2-adrenoceptors (α_2-ARs). There are three subtypes of α_2- AR: the A, B, and C subtypes. Both α_{2A}- and α_{2B}-ARs can be found in the PFC, with α_{2A}-AR predominating. In the monkey PFC, α_{2A}-ARs are localized both presynaptically on NE terminals and postsynaptically (over the postsynaptic density) on dendritic spines of pyramidal neurons [1].

NE exerts its beneficial effect on PFC functions through actions at postsynaptic α_2-ARs. The α_2-AR agonist, clonidine or guanfacine, has been shown in mice [11], rats [28], monkeys [4,24], and humans [15,16] to improve PFC functions such as working memory. Clonidine or guanfacine becomes more potent and more efficacious when the presynaptic NE terminal is destroyed or depleted of NE [3,9].

Postsynaptic α_{2A}-ARs play a critical role in mediating the beneficial effect of NE. α_{2A}-AR mutant mice exhibit weaker working memory ability than wild-type mice [11]. The α_{2A}-AR agonist, guanfacine, loses its beneficial effect in mice with a functional knockout of the α_{2A}-AR [11]. In contrast, mice with a knockout of the α_{2C}-AR show normal cognitive enhancement following treatment with α_2-AR agonist [29]. Evidence shows that guanfacine acts directly in the PFC to enhance PFC functions. For example, systemic administra-

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tion of guanfacine increases regional cerebral blood flow in the dorsolateral PFC [6], a cortical area that is critical for working memory. Local infusions of guanfacine into this same cortical area produce a delay-related improvement in working memory in monkeys [21], while similar treatments with the α_2-AR antagonist, yohimbine, have an opposite effect [17].

α_2-AR stimulation in the PFC facilitates working memory at the cellular level. Iontophoresis of clonidine onto PFC neurons in monkeys increases delay-related firing—the cellular representation of working memory [19]. Systemic administration of clonidine similarly increases delay-related firing in PFC [19]. The strengthening of delay-related firing by either systemically or iontophoretically applied clonidine can be blocked by iontophoretically applied yohimbine [19].

In addition to working memory, α_2-ARs in the PFC are also involved in regulating attention and response inhibition. α_{2A}-AR stimulation by guanfacine reduces distractibility [2] and enhances behavioral inhibition [27]. Our recent study in monkeys indicate that some typical symptoms of attention deficit and hyperactivity disorder (ADHD) can be produced by blockade of α_2-ARs in the PFC. Chronic administration of yohimbine into the PFC increases monkeys' impulsivity [20]. Monkeys tested on a go/no-go task showed increased errors of commission, with no change in errors of omission, following treatment with yohimbine in dorsolateral PFC [20]. Consistently, patients with ADHD also show errors of commission on the go/no-go task, and these errors can be ameliorated by methylphenidate [32].

Thus, α_{2A}-ARs in the PFC play an important role in regulating fundamental cognitive abilities that subserve the so-called executive function of the PFC: the ability to represent information online in mind (i.e., working memory), to regulate selective attention, and to inhibit inappropriate behaviors. The α_{2A}-AR agonists like guanfacine act directly in the PFC to enhance this executive function.

Animals and humans have a fundamental ability to establish arbitrary associations between sensory stimuli and motor responses. If stimuli are visual ones, this kind of learning is termed 'conditional visuomotor learning,' 'visuomotor associative learning,' or 'arbitrary visuomotor mapping.' It is known that visuomotor associative learning also requires the PFC, especially the ventral prefrontal cortex and orbital prefrontal cortex (PFv+o) [7,8,22,23,33]. Recently, we reported that systemically administered guanfacine enhances monkeys' ability to acquire new visuomotor associations [34], well consistent with a previous study showing that similarly administered guanfacine improves reversal learning of object discrimination in monkeys [27]—a task that is also dependent on the PFv+o [14,25]. As systemically administered guanfacine acts at α_{2A}-ARs in the whole central nervous system, it is unknown if α_{2A}-ARs in the PFv+o are indeed involved in regulating visuomotor associative learning. To address this question, we investigated in the present study how visuomotor associative learning would be affected following stimulation of α_{2A}-ARs in the PFv.

The PFv was focused on investigation because our previous study showed that inactivation of the PFv significantly impairs learning of novel visuomotor associations, with no effect on performance of preestablished ones [33]. Monkeys with inactivation of the PFv need significantly more errors to acquire a new set of visuomotor associations [33]. Moreover, individual neurons in the PFv demonstrate an evolution in activity when monkeys learn novel visuomotor associations [5,18]. In humans, the PFv is significantly activated during learning of visuomotor associations [30,31].

2. Materials and methods

Two rhesus monkeys (males, 11.0 and 9.0 kg, respectively) were employed, one of which had been used in our previous study showing that systemically administered guanfacine improved visuomotor associative learning [34]. 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 monkeys were trained on two-problem visuomotor associations: they were required to perform movement A (for monkey 1, moving a handle leftward; for monkey 2, moving a handle forward) if presented with a circle pattern, or perform movement B (for monkey 1, moving a handle rightward; for monkey 2, moving a handle backward) if presented with a triangle pattern. For learning of new visuomotor associations, the monkeys were presented with a new set of four patterns in each and every daily session, two of which instructed movement A and the other two guided movement B. The behavioral procedures were controlled manually in monkey 1 and automatically by a personal computer in monkey 2, as described as follows.

2.1. Performance of familiar visuomotor associations

Monkey 1 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 leftward or rightward. The experimenter sat behind the panel and could not be seen by the animal. Each trial was initiated by the experimenter's inserting into the window a card with a visual pattern (circle or triangle) on it. The monkey was required to move the handle to the left ('go-leftward' response) if the pattern was a circle, or to the right ('go-rightward' response) if it was a triangle. The card was removed from the window immediately after the monkey made a response. A 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.

Monkey 2 was seated in a primate chair, but faced a computer display, which was placed 40 cm away. On the chair was installed a metal handle, which could be moved forward or backward. Each trial was initiated by the monkey's holding the handle to a central position. The monkey was required to move the handle forward ('go-forward' response) if a circle pattern was displayed, or move the handle backward ('go-backward' response) if a triangle pattern was presented. The circle or triangle pattern disappeared immediately upon the monkey's response. A drop of water was delivered to the monkey after a correct response. The circle-and-triangle trials were presented according to the Gellermann schedule. The ITI was randomly determined between 5 and 15 s.

For both monkeys, a rerun correction procedure was introduced in case they made an error response: the same pattern was presented again, giving the monkeys a chance to change their response. The monkeys received as many correction trials as necessary (i.e., the same pattern was presented until a correct response was emitted).

Training of the visuomotor associative task needed about 4 weeks for both monkeys. The two visuomotor associations (i.e., 'circle, go leftward or forward; triangle, go rightward or backward') kept unchanged throughout all experiments. Thus, the circle and triangle patterns were very familiar to the monkeys.

2.2. Learning of new visuomotor associations

After the monkeys acquired the two familiar visuomotor associations (with $\geq$90% correct in 10 consecutive daily sessions), learning of new visuomotor associations was introduced. Each daily 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 did not appear in the 'NP block.'

For each and every session, each monkey was required to learn a new set of four patterns (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 4.0 cm, and were drawn from a pool of over 400 patterns at random. A pattern, once used, was no longer employed again. The behavioral significance of X1 and X3 was arbitrarily defined as 'go leftward or forward' and that of X2 and X4 as 'go rightward or backward.' Learning criterion was defined as 18 correct out of 20 consecutive trials (90% correct). The rerun correction procedure was used, as described above. Once the learning criterion was reached, 'FP block 2' was started immediately.

2.3. Surgery for implantation of cylinders

Each monkey was subjected to surgery under anesthesia (sodium pentobarbital, 35 mg/kg) and aseptic conditions. The skin over the skull was removed and a few stainless steel screws were implanted on the skull. The skull surface and the screws were covered with dental cement. Two stainless steel tubes (8 cm in length, 0.6 cm in ID, and 0.8 cm in OD) were attached with dental cement to the anterior and posterior portions of the skull. The two tubes were used for fixation of the monkey's head.

Three weeks later, the monkey underwent a second surgery, also under sodium pentobarbital anesthesia (35 mg/kg), for implantation of two stainless steel cylinders (19 mm in ID) over the left and right PFC. The skull bone under each cylinder was removed and the dura matter was exposed. The arcuate sulcus and the principal sulcus could be identified after the bone was removed. This helped us to determine roughly the location of the PFv. The cylinders were covered with plastic covers to protect the exposed dura.

Postoperatively, the skin wound was bathed with sterile saline, treated with xylocaine jelly to reduce pain, and sprinkled with sulfanilamidum powder once a day for 6 days. The monkey was injected antibiotics (gentamycini sulfatis or streptomycini sulfatis) twice a day for 3 days. Postoperative recovery took about 7–10 days.

2.4. Administration of guanfacine into the PFv

After recovering completely from the second surgery, the monkey was retrained on the familiar and novel patterns for a few sessions. Thereafter, experiments with infusion of guanfacine began. The monkey was seated in the primate chair with its head fixed rigidly and received bilateral infusions of guanfacine into the PFv (2.5 μg/μl, 3 μl on each side). Bilateral infusions were performed simultaneously with two Hamilton syringes and aimed at two symmetric sites in the left and right PFv. Infusions were completed within 15–20 min (at a rate of about 1 μl every 5 min). Then, the syringe needles were withdrawn, the monkey's head was released, and task performance was started. The schedules of guanfacine treatment sessions and normal control sessions were alternated. The monkeys did not receive saline treatment in normal control sessions.

2.5. Histological examination of infusion sites

After all experiments were completed, each monkey was given an overdose of pentobarbital anesthesia (50

mg/kg) and perfused with saline, followed by 10% formalin solution. The monkey's brain was exposed and the cortical locations of guanfacine infusions were reconstructed according to the coordinate readings of the infusions.

The monkey's brain was then removed from the skull and fixed in 10% formalin solution for several days. The frontal lobes were cut into sections with 50 μm in thickness. The brain sections were stained by the Nissl method for histological confirmation of the infusion sites.

2.6. Statistical analysis of data

Trials and errors to the learning criterion were the main behavioral measures analyzed, along with reaction times. These measures in the normal control sessions and the guanfacine treatment sessions were compared statistically, using Mann–Whitney *U* test or unpaired *t* test.

3. Results

3.1. Guanfacine has no effect on performance of familiar visuomotor associations

Monkeys 1 and 2 performed the two familiar visuomotor associations 100% correct, either before or after learning of a new set of novel patterns, leaving no room for improvement following treatment with guanfacine.

For both monkeys, the reaction times to the familiar *circle* and *triangle* patterns in the guanfacine treatment sessions were similar to those in the normal control sessions (Table 1), indicating that guanfacine treatment exerted no influence on response speed.

Table 1
Reaction times (RTs) to familiar and novel patterns in the control and guanfacine sessions

	Normal control		Guanfacine	
	Mvt A	Mvt B	Mvt A	Mvt B
Monkey 1				
Familiar patterns	352±35	340±42	340±30	360±55
Novel patterns	715±92*	720±85*	695±85*	705±96*
Monkey 2				
Familiar patterns	385±53	362±34	377±41	355±58
Novel patterns	645±68*	622±63*	618±56*	607±43*

Data are represented as mean±S.D. (ms). Each value for the familiar patterns was the average of RTs from 120 trials in six daily sessions (20 trials each session), and that for novel patterns was the average of RTs from 120 to 300 trials in six daily sessions (20–50 trials each session).
Mvt, movement; Mvt A, moving the response handle leftward or forward; Mvt B, moving the response handle rightward or backward.
* $P<0.01$ vs. familiar patterns; unpaired *t* test.

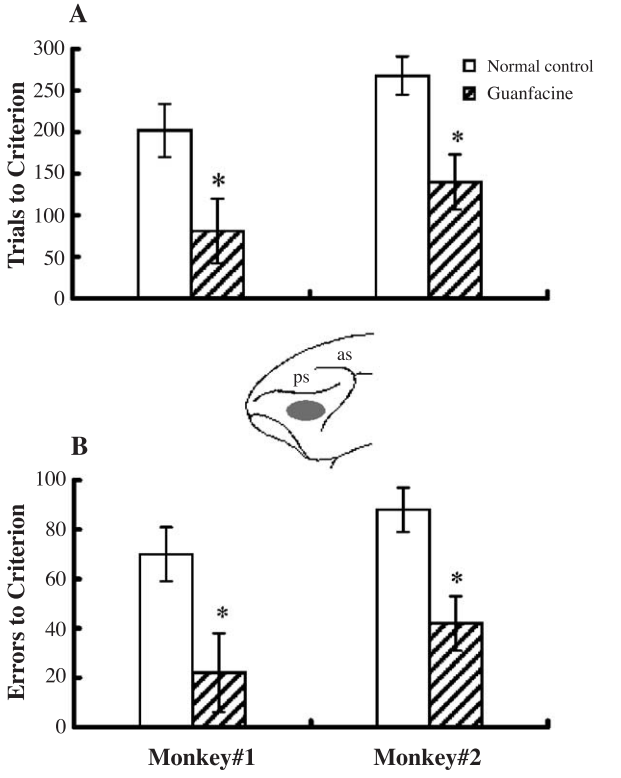

Fig. 1. Guanfacine improves visuomotor associative learning. Numbers of trial (A) and error (B) for each monkey to acquire a set of novel visuomotor associations were significantly reduced following infusion of guanfacine into the ventral prefrontal cortex. Data are represented as mean±S.D. (n=6 sessions for each bar). *$P<0.05$ vs. normal control, Mann–Whitney *U* test. Shown in the inset is the cortical area for infusion of guanfacine (shaded area). as, arcuate sulcus; ps, principal sulcus.

3.2. Guanfacine significantly improves learning of new visuomotor associations

Fig. 1 shows trials and errors for the monkeys to reach the criterion of 90% correct in learning novel visuomotor associations. Each monkey needed significantly less trials and made significantly less errors to acquire a set of novel visuomotor associations in the guanfacine treatment sessions ($P<0.05$ for guanfacine vs. normal control).

When presented with novel patterns, the monkeys spent a significantly longer time on selecting a response (Table 1; $P<0.01$ for novel patterns vs. FPs). Nevertheless, the reaction times to novel patterns kept unchanged following treatment with guanfacine (Table 1; $P>0.05$ for guanfacine vs. normal control). Fig. 2 shows the change in reaction time for novel patterns in control and guanfacine sessions, respectively, as learning progressed.

3.3. Guanfacine improves win–stay/lose–shift and change–stay/change–shift strategies

There were two types of error on *repeat trial* and *change trial*, respectively. *Repeat trial* refers to a trial in which the

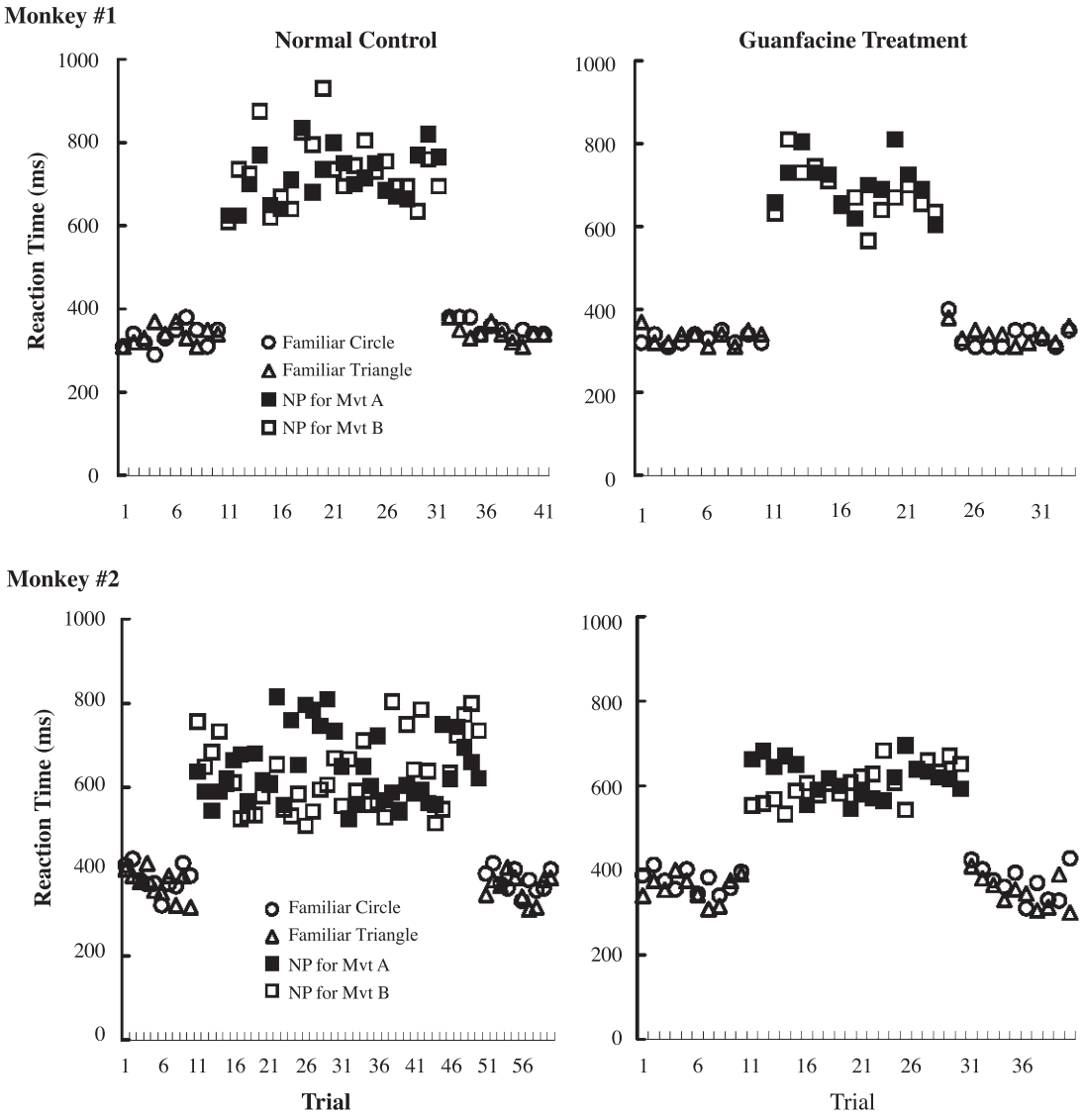

Fig. 2. Change in reaction times for novel patterns as learning progressed. The upper and lower panels show the reaction times (RTs) of monkeys 1 and 2, respectively, and the left and right ones the RTs in the normal control and guanfacine sessions. As shown, both monkeys spent much longer time to select a response when presented with novel patterns. The RTs for novel patterns exhibited no obvious decrease with progress of learning. NP, novel pattern; Mvt, movement; Mvt A, moving the response handle leftward or forward; Mvt B, moving the response handle rightward or backward.

pattern was the same as on the previous trial, and *change trial* refers to a trial in which the pattern was different from on the previous trial. On *repeat trials*, it was possible for the monkey not to repeat a correct response (*win–stay failure*) or repeat an incorrect response (*lose–shift failure*). On *change trials*, it was likely 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*).

As shown in Table 2, both monkeys were relatively good at applying *lose–shift* strategy. The errors were mainly expressed as *win–stay*, *change–stay*, and *change–shift failures*. All types of error (except for *lose–shift failure* in monkey 1) decreased significantly in the guanfacine treatment sessions, indicating an enhanced ability for the monkeys to employ the *win–stay/lose–shift* and *change–stay/change–shift* learning strategies.

4. Discussion

The present study demonstrates that stimulation of α_{2A}-ARs in the PFv improves the monkey's ability to acquire novel visuomotor associations, the first report of guanfacine improving cognitive performance when infused in the PFv.

The PFv in monkeys is a critical area for acquisition of arbitrary visuomotor associations. Inactivation of, or damage to, this cortical area impairs visuomotor associative learning [7,8,22,23,33]. Neurons in the PFv exhibit a learning-dependent change in activity when monkeys learn novel visuomotor associations [5,18]. Functional imaging studies in

Table 2
Types of error during learning of novel visuomotor associations in the control and guanfacine sessions

	Number of error	
	Normal control	Guanfacine (% of control)
Monkey 1		
Win–stay failure	14.8	19.4 (40.3)**
Lose–shift failure	4.8	14.0 (90.0)
Change–stay failure	31.6	24.8 (24.1)***
Change–shift failure	48.8	41.9 (26.3)***
Monkey 2		
Win–stay failure	18.1	12.7 (33.3)***
Lose–shift failure	10.4	11.1 (50.9)*
Change–stay failure	29.1	34.1 (55.8)*
Change–shift failure	42.4	42.1 (47.1)**

The monkeys needed a total of 420 and 530 errors, respectively, in the normal control sessions (n=6), and a total of 129 and 252 errors in the guanfacine sessions (n=6), to acquire six sets of novel visuomotor associations, one set each session. Each value represents percent of total errors. Value in parentheses represents percent of normal control.

* P<0.05 vs. normal control; Mann–Whitney U test.

** P<0.01 vs. normal control; Mann–Whitney U test.

*** P<0.001 vs. normal control; Mann–Whitney U test.

humans show that the PFv is activated during learning of novel visuomotor associations [30,31]. The present study provided the first evidence that α_{2A}-ARs in the PFv are involved in regulating acquisition of visuomotor associations.

Activation by guanfacine of α_{2A}-ARs in the PFv may enhance the mapping mechanisms between visual patterns and motor responses. Based on a large number of neuropsychological and neurophysiological studies, Murray et al. [22] have proposed a network that underlies the rapid acquisition and performance of visuomotor associations. This network consists of the premotor cortex (PM), PFC, hippocampal system (HS), and basal ganglia (BG), each having specialized contributions and operating largely in parallel. Specifically, the PM_BG and PFC_BG *modules* compute specific stimulus-to-action associations, where the network learns to associate a given input with a given action, serving as specific solutions to arbitrary visuomotor problems. Furthermore, the PFC_BG *module* subserves abstract rules and problem-solving strategies, and provides PM_BG *module* with pertinent sensory information. The HS plays a role parallel to that of both PFC_BG *module* and PM_BG *module*, but it may operate mainly in pending the consolidation of relevant information in the two cortical BG modules. Thus, stimulation of α_{2A}-ARs in the PFv may facilitate information processing in the PFC_BG *module*, producing a beneficial effect on the neural mechanisms underlying rule abstraction and problem-solving strategies. In the present study, the *win–stay/lose–shift* strategy on repeat trials may reflect the monkey's ability to select a response in accordance with experience of success or failure, whereas the *change–stay/change–shift* strategy on change trials may reflect the animal's capability to keep or avoid a previously executed response. Indeed, these problem-solving strategies were all enhanced following treatment with guanfacine in the PFv.

During learning of novel visuomotor associations, the monkeys needed to keep track of the correctness or incorrectness 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. This was important, especially at the very early stage of the learning. It might be possible that guanfacine facilitated short-term memory for this task information. In addition, it was likely that guanfacine improved the monkey's vigilance or attention that is also important for visuomotor associative learning.

The reaction times for novel patterns were not different between normal control and guanfacine conditions in both monkeys. After reaching a learning criterion of 90% correct, the monkeys were no longer allowed to perform novel patterns. Thus, it was likely that, during the learning, the monkeys' efforts were predominantly focused on mapping the 1:1 relationships between novel patterns and motor responses, instead of speeding up response, both under the control and guanfacine conditions. This might be the reason why guanfacine treatment did not shorten reaction times.

Guanfacine has been used for the treatment of human psychiatric disorders such as schizophrenia, Korsakoff's syndrome, and especially ADHD [10,12,13,26]. Patients with these psychiatric disorders show prominent cognitive deficits of the PFC. The present study provides evidence that stimulation of α_{2A}-ARs in the PFC strengthens PFC cognitive function other than working memory or executive function [16,27,34], and has an immediate clinical relevance to neuropsychiatric disorders associated with PFC dysfunction that may be treated with guanfacine.

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