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Short communication

Higher dopamine release induced by less rather than more preferred reward during a working memory task in the primate prefrontal cortex

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HIGHLIGHTS

- Prefrontal (PFC) dopamine (DA) is essential for working memory (WM) task performance.
- Preferred reward may facilitate WM task performance through enhanced PFC DA.
- Less preferred reward was found to induce higher WM-related dorsolateral (DL) PFC DA.
- Performing a WM task for less preferred reward may be mildly stressful for monkeys.
- Mild stress-induced DLPFC DA may be beneficial for coping with stressful situations.

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ABSTRACT

An optimal level of dopamine (DA) in the mammalian prefrontal cortex (PFC) is critical for higher cognitive control of behavior. Too much or too little DA in the PFC induces impairment in working memory (WM) task performance. PFC DA is also concerned with motivation. When reward is anticipated and/or delivered, an increase in PFC DA release is observed. In the primate, more preferred reward induces enhanced WM-related neuronal activity in the dorsolateral PFC (DLPFC). We hypothesized that there would be more DA release in the primate DLPFC when more preferred, as compared with less preferred, reward is delivered during a WM task. Contrary to our hypothesis, we found higher DA release in the DLPFC when less rather than more preferred reward was used during a WM task, while unpredictable free reward delivery induced an increase in DLPFC DA release irrespective of the difference in the incentive value of the reward. Behaviorally, the monkey was more motivated with preferred than with less preferred reward, although it performed the task almost without error irrespective of the difference in the reward. Considering that mild stress induces an increase in DA release in the mammalian PFC, performing a WM task for less preferred reward could have been mildly stressful, and this mild stress may have induced more DLPFC DA release in the present study. The higher DA release in the DLPFC with less preferred reward may be beneficial for monkeys to cope with mildly stressful and unfavorable situations to achieve proficient WM task performance.

It has been well documented that an optimal level of dopamine (DA) in the mammalian prefrontal cortex (PFC) is critical for higher cognitive control of behavior [1,2]. Thus, too much DA caused by strong stress or amphetamine psychosis, or too little DA caused by aging in the PFC induces impairment in working memory (WM) task performance [1–3]. An inverted U-shaped function is observed between the DA concentration/DA D1 stimulation in PFC and WM task performance both in humans and non-human animals [1,3,4]. Microinjection of DA and stimulation of the DA D1 receptor in the PFC dose-dependently modulate (enhance or suppress) WM-related neuronal activity [5–7]. We previously reported an increase in DA release in the primate dorsolateral PFC (DLPFC) during a WM task as compared with during a non-WM control task and resting periods [8].

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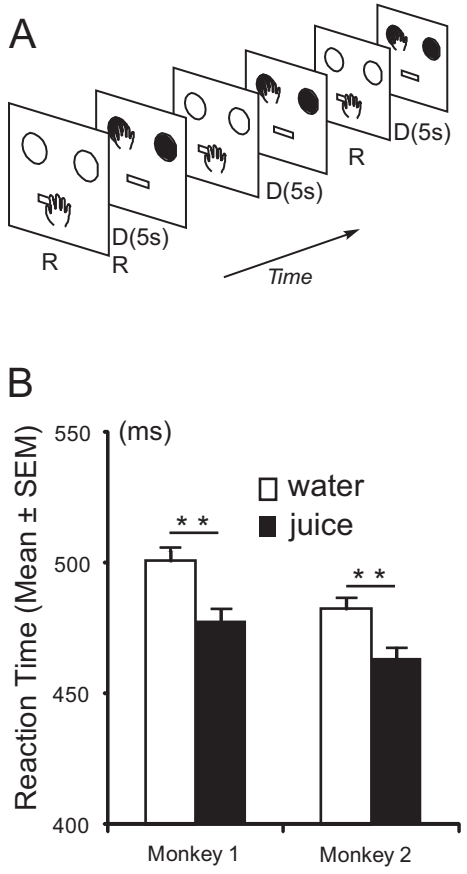

Fig. 1. (A) The sequence of events in the delayed alternation task. D, delay period; R, response. (B) Reaction times (RTs) of the monkeys (Monkey 1 and Monkey 2) from the time of the go signal presentation to the time of the key press response depending on the difference in the reward (water and juice). Bar graphs indicate the mean ± standard error (SEM): $n = 300$ for Monkey 1 and $n = 350$ for Monkey 2 for both kinds of reward. RTs were significantly different between the water and juice rewards ($P < 0.01$ for both monkeys, indicated by **, two-tailed t-test).

When reward is anticipated and/or delivered, an increase in DA release is observed in many areas of the mammalian brain, including the PFC [9–11]. It has also been indicated that the expectancy of a more preferred reward induces enhanced WM-related neuronal activity in the primate PFC [12–14]. The PFC is concerned with both cognitive and motivational functions, and especially the primate dorsolateral PFC (DLPFC) plays the most important role in the integration of cognitive and motivational operations [15]. Since motivational and cognitive operations appear to interact in the PFC through DA activity [16], we hypothesized that when more preferred, as compared with less preferred, reward is delivered during a WM task, there would be more DA release in the PFC, and such increased DA would work to enhance WM-related PFC neuronal activity. We thus examined DA release in the monkey during a WM task using rewards with different incentive values. Since we previously observed an increase in DA release in relation to a WM task in the DLPFC, but not in the orbital and arcuate prefrontal areas [8], we focused on DA release in the DLPFC in the present study.

Two male Japanese monkeys (*Macaca fuscata*: *Monkey* 1, 6.5 kg; Monkey 2, 5.8 kg) were trained in a delayed alternation task (Fig. 1A). In a sound-attenuated room, each animal, which was seated on a primate chair, faced a panel with two circular keys (4 cm in diameter, separated by 18 cm from center to center) and a holding lever (4 cm wide, protruding by 5 cm) below them. On each trial of the task, the animal depressed the holding lever for 5 s (delay period), after which time both keys were illuminated by a white light as a go signal. The animal obtained a liquid (0.3 ml of water or grape juice) reward by alternating key presses to the right and left, each key press being preceded by the delay period. The monkey had to retain the spatial information as a WM during the delay period for correct performance. On completion of training, the monkey was surgically prepared under ketamine (10 mg/kg, i.m.) and pentobarbital anesthesia (Nembutal, 20 mg/kg, i.v.) under sterile conditions. A 20 mm × 20 mm piece of bone above the DLPFC was removed. An acrylic resin-made rectangular platform (inner size, 20 mm × 20 mm) for a microdialysis guide cannulae was attached to the skull just above the exposed PFC area using dental acrylic. A hollow rod (15 mm in diameter) for head fixation was also attached to the skull with dental acrylic. Antibiotics were administered for 7 days postoperatively. Then, extracellular neuronal activities were recorded from the PFC using the rectangular platform as a microdrive receptacle to determine the target positions of microdialysis sampling. All experiments were conducted in accordance with the National Academies Press guidelines for animal experiments and were approved by the ethics committee of our institute. During the experiments, which were conducted on weekdays, the monkeys obtained all of their fluids during the experiment, but they were given *ad libitum* access to water during the weekend in the home cage. The microdialysis sampling was started after the animal was further trained for 2 weeks with its head restrained to the frame of the monkey chair. For each experimental session, four to six guide cannulae were fixed through the platform just above the target area (DLPFC, including both banks and lips of the principal sulcus) (Fig. 2A) for the subsequent microdialysis experiments. The tips of the guide cannulae were located 1 mm above the appropriate positions within the gray matter that had been determined by neuronal recording. One session of a sampling experiment consisted of 3 days. Microdialysis probes (Type A-I-02, Eicom, Kyoto) with a semipermeable membrane of 2 mm in length and 0.22 mm in diameter at their tips were inserted into the appropriate locations through the implanted guide cannulae about 20 h before the sampling to stabilize transient changes in neurotransmitters. The sampling experiment was performed between 9:00 and 13:00 on two consecutive days after the day of microdialysis probe insertion, during the animal's WM task performance and during a rest (REST) period when the animal was sitting quietly without task performance and without a liquid reward. On each day of the experiment, sampling was done from 4 to 6 locations. We obtained dialysate samples during the (1) WM task with a water reward (water WM), (2) WM task with a juice reward (juice WM) and (3) REST periods. On the first day of sampling, the order of events was REST (35 min)–water WM (35 min)–REST (35 min)–juice WM (35 min)–REST (35 min), whereas on the second day, it was REST (35 min)–juice WM (35 min)–REST (35 min)–water WM (35 min)–REST (35 min), thus counterbalancing the order of the water and juice rewards. On the second day, we further examined DA changes caused by unpredictable reward delivery as described below. Thus, after the last REST session, we obtained samples when the water reward was delivered (unpredictable water reward) for 35 min, followed by another REST period (35 min), and then when the juice was delivered (unpredictable juice reward) for 35 min. The interval of liquid delivery was randomly selected from 2, 4, 6, 8 and 10 s, and the mean inter-delivery time was about the same as 6 s of each trial of WM task performance. Microdialysis probes were perfused with aCSF (artificial cerebrospinal fluid) [8] at a flow rate of 2 μl/min. To prevent sample contamination between different conditions, dialysate sampling started 5 min after the beginning of each task, rest and unpredictable reward delivery period and continued throughout the remaining 30 min. Sixty microliters (2 μl/min × 30 min) of dialysate collected at 10 °C in polypropylene sample tubings during each period was kept under acidic conditions (pH 3.5). The specimens were frozen immediately and stored at −80 °C. The DA concentration in the perfusate