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Short communication

Dopamine and glutamate release in the anterior default system during rest: A monkey microdialysis study

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HIGHLIGHTS

- A default mode of brain activity is present in the monkey medial prefrontal cortex.
- We examined dopamine and glutamate release in the monkey medial prefrontal cortex.
- Dopamine level was higher during rest than during a cognitive task.
- Glutamate level was not different between the rest and cognitive task periods.
- Default mode of brain activity may be supported by increased dopamine release.

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ABSTRACT

Human neuroimaging studies have demonstrated the presence of a default system in the brain, which shows a default mode of brain activity, i.e., greater activity during rest than during an attention-demanding cognitive task. Our previous study on monkeys has revealed a default mode of brain activity in medial cortical areas. We have observed an increase in dopamine (DA) release during a working memory (WM) task compared with that during rest in the monkey lateral prefrontal cortex (LPFC). However, no previous study has examined DA release related to the default mode of brain activity. We used a microdialysis technique to investigate changes in DA release in the medial prefrontal cortex (MPFC), which constitutes the anterior default system, during the WM task and rest. Because DA and glutamate (Glu) release in the LPFC is interrelated, we also examined Glu release in the MPFC. We observed a significant increase in DA release, but no significant change in Glu release during rest compared with that during the WM task. We also observed an inhibitory relationship between the two transmitters in the MPFC. Considering that human default brain activity is related to internal thought processes and increased DA release in the LPFC plays an important role in executive control, increase in DA release during rest in the monkey anterior default system may be related to some form of internal thought process.

Human neuroimaging studies have demonstrated the presence of a default system in the brain, which shows a default mode of brain activity, i.e., greater activity during rest than during an attention-demanding cognitive task [1]. The human default mode of brain activity is observed in the medial prefrontal cortex (MPFC) and medial and lateral parietal cortices [1,2], and is considered to be related to internal thought processes [3]. In a positron emission tomography (PET) study, we identified default mode activity in the monkey brain and observed increased regional cerebral blood flow (rCBF) in the medial cortical areas, i.e., the MPFC including the anterior cingulate cortex and the posterior medial parietal cortex, during rest than that during a working memory (WM) task performance [4]. A subsequent functional magnetic resonance imaging (fMRI) study also revealed higher rest-related blood oxygenation level-dependent (BOLD) activity in these medial cortical areas [5]. Dopamine (DA) plays important roles in executive control in the lateral prefrontal cortex (LPFC) [6,7]. We previously reported an increase in DA release in the monkey LPFC during a WM task com-

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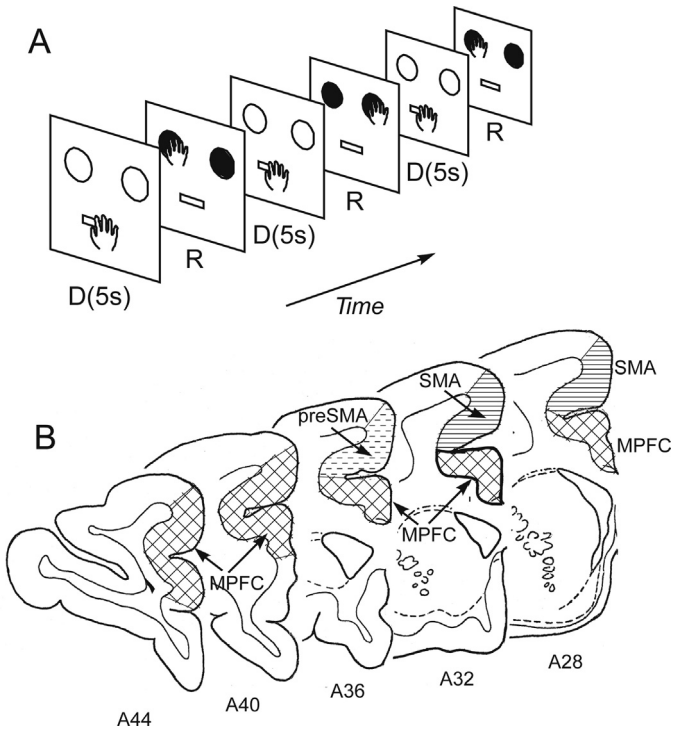

Fig. 1. Summary of the experimental procedure. (A) Sequence of events in the delayed alternation task. D, delay; R, response. (B) Coronal sections indicating areas of the primate frontal cortex where microdialysis sampling was conducted. MPFC, medial prefrontal cortex; SMA, supplementary motor area; preSMA, presupplementary motor area. A28–A44 indicate that the section is 28–44 mm anterior to the interaural plane.

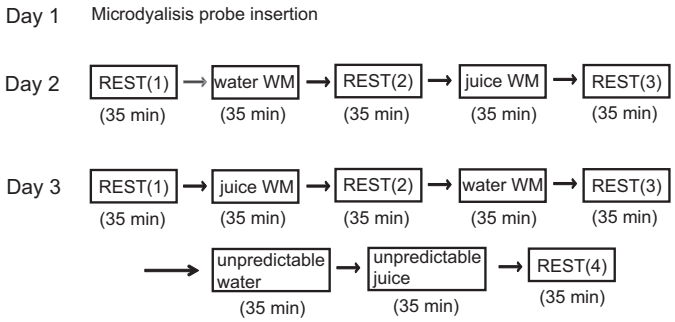

Fig. 2. Sequence of the events in a 3-day microdialysis experimental session.

pared with that during a non-WM control task and rest periods [8]. However, no previous study has investigated the release of DA, which plays important roles in cognitive operations, in the default system during a WM task and during rest. Therefore, we used a microdialysis technique to examine changes in DA release in the monkey MPFC, constituting the anterior default system, during the WM task compared with that during rest. We also examined DA changes in the medial premotor areas (supplementary motor and presupplementary motor areas: SMA/preSMA), which are not parts of the monkey default system. We previously identified a relationship between DA and glutamate (Glu) release in the monkey LPFC during task performance [9]. Therefore, to explore a possible relationship between DA and Glu release in the medial frontal areas, we also investigated Glu release in the MPFC and the SMA/preSMA during the WM task and rest.

Two male Japanese macaques (*Macaca fuscata*: Monkey 1, 6.5 kg; Monkey 2, 5.8 kg) were used. They had been trained to perform a WM (delayed alternation) task and had previously been used to investigate DA release in the LPFC during this WM task [10]. In the present study, DA release in the medial frontal areas (MPFC and SMA/preSMA) was examined during performance of this WM task. Although the main aim of the present study was to examine WM-task-induced changes in DA and Glu release in the anterior default system, changes with two different types of reward were also examined, as an extension to our previous study, which investigated DA release in the LPFC in response to different rewards [10]. 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.

Each animal was seated on a monkey chair facing a panel with two circular keys and a holding lever located below the keys (Fig. 1A). During 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 reward (0.3 ml of water or grape juice) by alternating key presses to the right and left, each key press being preceded by the delay period.

The monkeys were surgically prepared under ketamine (10 mg/kg, intramuscular) and pentobarbital anesthesia (Nembutal, 25 mg/kg, intravenous) under sterile conditions. First, a 20 × 20-mm piece of bone above the MPFC was removed and a rectangular platform composed of acrylic resin (inner size, 20 × 20 mm) for microdialysis guide cannulae was attached to the skull just above the exposed frontal area (center of the platform was aimed at $L = 0$ and $A = 35$) using dental acrylic. A hollow rod (15 mm in diameter) that had been attached to the skull with dental acrylic was used for head fixation. Next, using the brain atlas for the Japanese Macaque [11], extracellular neuronal activity was recorded from the MPFC and the SMA/preSMA to determine the target positions for microdialysis sampling.

Dialysates were sampled from the MPFC and the SMA/preSMA (Fig. 1*B*) of both hemispheres, as previously described [10]. For each experimental session, 4–6 guide cannulae were fixed through the platform just above the bone-free area. Each session of the sampling experiment lasted for 3 days (Fig. 2). Microdialysis probes (Type A-I-02; Eicom, Kyoto, Japan) 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 approximately 20 h before the sampling to stabilize transient changes in neurotransmitters. The sampling experiment was performed on the 2 consecutive days during the WM task and during rest (REST) (when the animals were sitting quietly without task performance and without a liquid reward). Dialysate samples were obtained under three conditions: (1) the WM task with a water reward (water WM), (2) the WM task with a juice reward (juice WM), and (3) the REST periods. On the first day of sampling, the order of events was REST 1 (35 min), water WM (35 min), REST 2 (35 min), juice WM (35 min), and REST 3 (35 min). On the second day, the order was REST 1 (35 min), juice WM (35 min), REST 2 (35 min), water WM (35 min), and REST 3 (35 min), thus counterbalancing the order of the water and juice rewards. In addition, on the second day, changes in neurotransmitter release caused by unpredictable reward delivery were examined. Thus, after REST 3, samples were obtained when a water reward was delivered for 35 min and when a juice was delivered (unpredictable juice reward) for 35 min. Finally, there was another rest period for 35 min (REST 4). The interval of liquid delivery was randomly selected from 2, 4, 6, 8, or 10 s, with the mean interval being approximately the same as the 6 s for each trial of the WM task.

The microdialysis probes were perfused with artificial cerebrospinal fluid 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 event, and continued throughout the remaining 30 min. A total of 60 μl