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STRIATAL DOPAMINE MODULATES TIMING OF SELF-INITIATED SACCADES

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Abstract—The ability to adjust movement timing is essential in daily life. Explorations of the underlying neural mechanisms have reported a gradual increase or decrease in neuronal activity prior to self-timed movements within the cortico-basal ganglia loop. Previous studies in both humans and animals have shown that endogenous dopamine (DA) plays a modulatory role in self-timing. However, the specific site of dopaminergic regulation remains elusive because the systemic application of DA-related substances can directly alter both cortical and subcortical neuronal activities. To investigate the role of striatal DA in self-timing, we locally injected DA receptor agonists or antagonists into the striatum of two female monkeys (*Macaca fuscata*) while they performed two versions of the memory-guided saccade (MS) task. In the conventional, triggered MS task, animals made a saccade to the location of a previously flashed visual cue in response to the fixation point offset. In the self-timed MS task, monkeys were rewarded for making a self-initiated saccade within a predetermined time interval following the cue. Infusion of a small amount of a D_1 or D_2 antagonist led to early saccades in the self-timed, but not the triggered MS tasks, while infusion of DA agonists produced no consistent effect. We also found that local administration of nicotinic but not muscarinic acetylcholine receptor agonists and antagonists altered the timing of self-initiated saccades. Our data suggest that the timing of self-initiated movements may be regulated by the balance of signals in the direct and indirect basal ganglia pathways, as well as that between both hemispheres of the brain. Published by Elsevier Ltd on behalf of IBRO.

Key words: self-timing, saccade, dopamine, acetylcholine, basal ganglia, primate.

INTRODUCTION

The ability to perform precisely timed actions is crucial in daily life. In many situations, we must make self-initiated movements in anticipation of forthcoming events. In laboratory conditions, scalp potential that is generated prior to an expected event (contingent negative variation; CNV) is known to reflect the prediction of timing for behavioral decisions (Macar and Vidal, 2003; Pfeuty et al., 2005; van Rijn et al., 2011). In experimental animals, a similar gradual ramp-up of neuronal activity before self-timed movements has been reported in the basal ganglia (Romo and Schultz, 1992; Lee and Assad, 2003; Turner and Anderson, 2005), thalamus (Tanaka, 2007), and the cortex (Okano and Tanji, 1987; Kurata and Wise, 1988; Murakami et al., 2014; Maimon and Assad, 2006), suggesting that the basal ganglia-thalamocortical pathways are responsible for the generation of the climbing neuronal activity. These activities appear to have a causal role in the adjustment of movement timing (van Donkelaar et al., 2000; Tanaka, 2006; Kunimatsu and Tanaka, 2012), and may partly reflect the subjective passage of time during motor preparation (Macar and Vidal, 2009; Wittmann, 2013).

To report or produce a certain time interval by making a self-initiated movement, the subjects need to suppress the movement until the time comes. Therefore, the impairment of self-timing could also reflect the level of patience, or alternatively, impulsivity could result from overestimation of time intervals (Wittmann and Paulus, 2008). Endogenous neuromodulators such as dopamine (DA) and acetylcholine (ACh) regulate signals in the basal ganglia (Calabresi et al., 2000; Surmeier et al., 2007), and have been shown to play a role in self-timing. For instance, patients with Parkinson's disease show reduced CNV (Ikeda et al., 1997), exhibit a difficulty in the self-initiation of actions (Kelly et al., 2002; Jones and Jahanshahi, 2009), and present impairments in the ability to report time interval in the range of seconds (Malapani et al., 1998; Jones et al., 2008; for review, see Allman and Meck, 2012). Pharmacological experiments have also shown that both DA and ACh are crucial for movement timing (for review, see Coull et al., 2011). For example, the systemic administration of DA-related and ACh-related substances altered the peak timing of temporal production in trained rats (Hinton and Meck, 1997; Matell et al., 2004; MacDonald and Meck, 2005), while in humans, the oral administration of DA antagonists disturbed time perception in the range of seconds (Rammsayer, 1993). However, because both DA and

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Abbreviations: ACh, acetylcholine; ANOVA, analysis of variance; CNV, contingent negative variation; DA, dopamine; FP, fixation point; mAChR, muscarinic acetylcholine receptor; MI, modulation index; MR, magnetic resonance; MS, memory-guided saccade; nAChR, nicotinic acetylcholine receptor.

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ACh are known to modulate neuronal processes within the frontoparietal cortices that also participate in temporal processing and decision making (Williams and Goldman-Rakic, 1995; Vijayraghavan et al., 2007; for reviews, see Arnsten, 2009; Noudoost and Moore, 2011; Thiele, 2013; Sarter et al., 2014), the specific roles of neuronal modulators in the basal ganglia remain elusive.

To address this issue, we manipulated DA signals in the striatum of monkeys by locally injecting DA receptor agonists and antagonists while they performed the oculomotor version of the self-timing task. We found that DA receptor antagonists altered the timing of self-initiated saccades, while DA receptor agonists did not produce any consistent effect. Importantly, the effects on timing were only slight for reactive saccades that were triggered immediately by visual stimuli. Furthermore, we found that agonists and antagonists of nicotinic but not muscarinic ACh receptors altered self-timing. These results suggest that the timing of self-initiated movements might be regulated according to the balance of signals between direct and indirect basal ganglia pathways, as well as that between both hemispheres.

EXPERIMENTAL PROCEDURES

We used two Japanese monkeys (*Macaca fuscata*, female, 7 and 8 kg, monkeys *B* and *G*) in the present experiments. All experimental protocols were evaluated and approved by the Hokkaido University Animal Care and Use Committee. Much of the experimental procedures were similar to those described previously (Tanaka, 2005; Kunimatsu and Tanaka, 2010).

Animal preparation

Using sterile procedures and general isoflurane anesthesia, the animals were subjected to two separate surgeries in which we implanted a pair of head holders and an eye coil. Analgesics were administered during each surgery and for several days afterward. Upon full recovery from the surgery, the monkeys were trained to perform oculomotor tasks. During training and the subsequent experimental sessions, the head of each monkey was secured to a primate chair located in a darkened booth, and horizontal and vertical eye position signals were recorded using the search coil technique (MEL-25; Enzanshi Kogyo). After completion of the eye movement training, we conducted a third surgery in which we placed a recording cylinder over the head-body junction of the caudate nucleus that was verified by means of magnetic resonance (MR) images taken before and after the surgery. Daily recording sessions began after full recovery from the surgery. Water intake was monitored regularly so that monkeys were motivated to perform the behavioral tasks.

Visual stimuli and behavioral tasks

The experiments were controlled by the TEMPO system (Reflective Computing). Visual stimuli were presented on a 24-inch cathode-ray tube monitor (refresh rate: 60 Hz) positioned 38 cm from the eyes, and subtended 64 × 44° of the visual angle. We used three saccade paradigms (Fig. 1). In the visually guided saccade task, the saccade target appeared at the time of the fixation point (FP) offset, and monkeys made an immediate saccade. In the conventional, triggered memory-guided saccade task (triggered MS task; Hikosaka and Wurtz, 1983), a visual cue was presented briefly (100 ms) during central fixation. Monkeys were required to remember the cue location, and maintain fixation for an additional delay interval which was random 1500 ± 900 ms and 1000 ± 200 ms for monkeys *B* and *G* respectively. The animals made a saccade to the cue location within 400 ms of the FP offset. In the self-timed memory-guided saccade task (self-timed MS task; Tanaka, 2006, 2007; Ashmore and Sommer, 2013), the animals were required to make a saccade to the cue location within a predetermined time interval following the cue offset (1100 ± 300 ms and 1200 ± 300 ms for monkeys *B* and *G*, respectively). The FP disappeared only after the animals generated a self-initiated saccade, i.e., when eye position deviated > 3° from the FP. For all three tasks, the color of the FP was initially gray for 400 ms and then changed to red (triggered MS task and visually guided saccade task) or blue (self-timed MS task) to signal the trial type. The saccade target and visual cue were presented either 16° left or right of the FP. The size of the eye position window was 2° for initial fixation and 4° for the saccade target. Correct performance was reinforced with a drop of liquid reward at the end of each trial. Each trial was presented in a pseudo-random order within a block that consisted of six different trials (three different tasks in opposite directions). Detailed behavioral analyses for these saccade tasks have been previously performed (Kunimatsu and Tanaka, 2012).

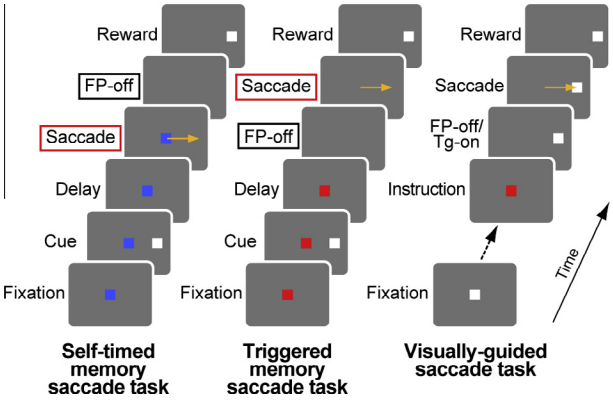

Fig. 1. Sequence of events in the three saccade tasks. In the self-timed memory saccade task, a cue in the peripheral visual field flashed briefly (100 ms) during central fixation. Monkeys were required to maintain fixation and remember the cue location. Animals made a memory-guided saccade to the cue location within a predetermined time window (900–1500 ms or 800–1400 ms) following the cue offset. In the conventional, triggered memory-guided saccade task, monkeys made a saccade to the previously presented cue location in response to the fixation point offset. In the visually guided saccade task, the animals were required to make a saccade toward a visible target within 400 ms. Different trial types were randomly interleaved within a block.

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