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# FACILITATION OF TEMPORAL PREDICTION BY ELECTRICAL STIMULATION TO THE PRIMATE CEREBELLAR NUCLEI

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**Abstract—The cerebellum is known to be involved in temporal information processing. However, the underlying neuronal mechanisms remain unclear. In our previous study, monkeys were trained to make a saccade in response to a single omission of periodically presented visual stimuli. To detect stimulus omission, animals had to predict the timing of each next stimulus. During this task, neurons in the cerebellar dentate nucleus exhibited a transient decrement of activity followed by a gradual increase in firing rate that peaked around the time of the next stimulus (Ohmae et al., 2013). In the present study, to address how these two components of neuronal activity contributed to omission detection, we applied electrical microstimulation to the recording site at different timing during the task. We found that electrical stimulation just before the stimulus omission shortened the latencies of both contraversive and ipsiversive saccades. Because the changes in saccade latency nonlinearly depended on the timing of stimulation in each inter-stimulus interval, and electrical stimulation just before the early stimulus in the sequence failed to evoke saccades, the neuronal activity in the dentate nucleus might regulate temporal prediction rather than facilitating saccade execution. Our results support the hypothesis that the firing modulation in each inter-stimulus interval in the dentate nucleus represents neuronal code for the temporal prediction of next stimulus.** **© 2017 IBRO. Published by Elsevier Ltd. All rights reserved.**

**Key words: temporal processing, electrical stimulation, dentate nucleus, cerebellum, primate.**

## INTRODUCTION

Temporal prediction is essential for both motor control and cognition. Although the involvement of the cerebellum in motor control has long been recognized, recent evidence shows that the cerebellum also plays a role in temporal prediction of sensory events (Coull and Nobre, 1998; O'Reilly et al., 2008; Roth et al., 2013; Avanzino et al., 2015). While much is known about the underlying neuronal mechanism of the cerebellar control of movements (for reviews, see Thach et al., 1992; Ito, 2011; Manto et al., 2012), how neuronal signals in the cerebellum regulate temporal prediction of external events remains elusive.

We recently found that neurons in the cerebellar dentate nucleus exhibited characteristic firing modulation for periodically presented audiovisual stimuli (Ohmae et al., 2013). In our "missing oddball" paradigm, monkeys predicted the timing of each next stimulus in the sequence so that they generated a saccade in response to a single omission of repetitive stimuli. Neurons in the posterior part of the dentate nucleus exhibited a transient decrement of firing rate for each stimulus presentation, which was followed by a gradual increase in firing rate. The degree of the initial decrement of activity was proportional to the inter-stimulus interval (i.e., the time from the preceding stimulus) and the neuronal firing rate reached a peak around the time of the next stimulus. Because pharmacological inactivation of the recording sites delayed the detection of stimulus omission but not the detection of stimulus change, the temporally specific signals found in the cerebellum likely regulated the temporal prediction of the periodic stimuli that was necessary for omission detection (Ohmae et al., 2013; Ohmae and Tanaka, 2016).

However, it remains uncertain how the signals in the cerebellar dentate nucleus regulate the detection of stimulus omission. Although the previous inactivation results clearly proved the causality, we were unable to associate patterns of neuronal activity with behavioral outcomes. Specifically, it was unclear whether the transient decrement or the gradual increment of firing rate played a role, or, alternatively, if neuronal modulation reflected the preparation of specific movements. Furthermore, because the gradual elevation of sensory gain in each trial and the firing modulation in each inter-stimulus interval had different time courses, they might play different roles in controlling the behavioral performance in the task. To address these issues, we applied electrical microstimulation to the recording sites in the dentate nucleus at various timing during the missing oddball task. Some of the present results have been reported in abstract form (Uematsu and Tanaka, 2015).

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*Abbreviations:* ANOVA, analysis of variance; FP, fixation point; MRI, magnetic resonance images; SOA, stimulus onset asynchrony.

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## EXPERIMENTAL PROCEDURES

### Animal preparation

Four Japanese monkeys (*Macaca fuscata*, 6–9 kg, two females, monkeys H, A, I and Hk) were used. All experimental protocols were evaluated and approved by the Hokkaido University Animal Care and Use Committee. Much of the experimental procedure was the same as those described previously (Tanaka, 2005). Monkeys were initially trained to sit in a primate chair. Animals were then implanted with a pair of head holders and an eye coil in two separate surgeries. All of the surgeries were executed under general isoflurane anesthesia using sterile procedures. Analgesics were also administrated during each surgery and several days later. After full recovery from the surgery, the animals were trained in the oculomotor version of the missing oddball detection task (Ohmae et al., 2013, see the following section). During the training and experimental sessions, animals' heads were secured to the primate chair in a darkened booth. Horizontal and vertical eye positions were recorded using the search coil technique (MEL-25, Enzanshi Kogyo). After sufficient training on the task, a recording chamber was placed to enable vertical electrode penetration, targeted at the cerebellar dentate nucleus. The chamber location relative to the dentate nucleus was verified using magnetic resonance imaging (MRI) after the surgery.

### Visual stimuli and behavioral task

Experiments were controlled by a Windows-based stimulus presentation and data acquisition system (TEMPO, Reflective Computing). Visual stimuli were presented on a 24-inch cathode ray tube monitor (refresh rate, 60 Hz) positioned 38 cm from the eyes. The monitor subtended 64 × 44° of visual angle.

In the missing oddball task (Fig. 1A; Ohmae et al., 2013), a fixation point (FP, red 0.5° square) was initially presented at the center of the screen. After the animals gazed at the FP, a saccade target (gray 0.5° or 1.0° square) appeared either 16° left or right of the FP. A brief visual stimulus (white unfilled 2° square, 35 ms or 2 video frames in duration) surrounding the FP was presented repeatedly at a fixed stimulus onset asynchrony (SOA) of either 150, 400, or 600 ms. An auditory tone (1500 Hz square wave, 35 ms) was also presented synchronously with the visual stimulus in all but six stimulation experiments in monkey H. After a random 3600- to 5200-ms period (2000–4800 ms for recording experiments), one stimulus in the series was omitted (missing oddball). The animals were required to make a saccade to the visible target in response to the stimulus omission within 600 ms. Successful performance was rewarded with drops of liquid reward. To compare the effects of electrical stimulation, we also presented the visually guided saccade task, in which a central FP (yellow 1.0° square) was replaced by a saccade target that was located 16° horizontally. Monkeys were rewarded for saccades within 700 ms following the target onset.

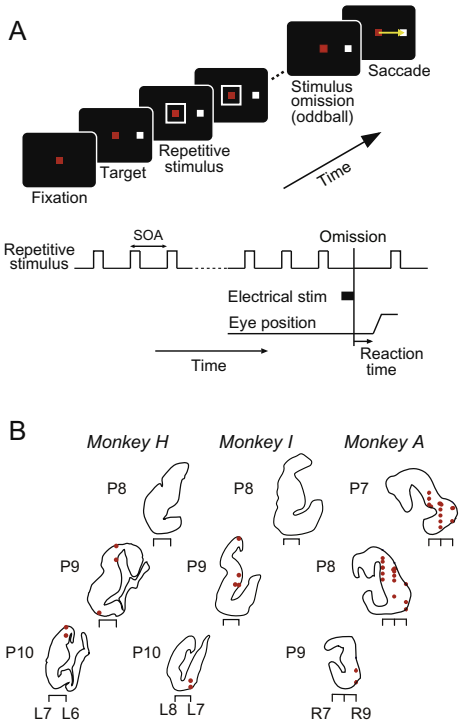


**Fig. 1.** (A) Sequence of events in the missing oddball detection paradigm. Monkeys made a targeting saccade in response to the single omission of repetitive stimulus that surrounded the fixation point. Electrical stimulation was applied before the stimulus omission in a fraction of trials. (B) Sites of electrical stimulation in three monkeys reconstructed from either histological sections (monkeys H and I) or MRI (A). For some penetrations, stimulation sites are jittered horizontally only for presentation purpose. Labels indicate the posterior locations of coronal sections (in millimeters) relative to the inter-aural line.

### Physiological procedures

Before each stimulation experiment, we recorded from neurons in the dentate nucleus of the cerebellum using single tungsten electrodes (Alpha Omega Engineering, Nazareth, Israel). The properties of the task-related neurons have been described previously in detail (Ohmae et al., 2013). The location of each electrode penetration was adjusted using the grid system (Crist Instruments, Hagerstown, MD, USA) attached to the recording chamber. During experiments, the electrode was inserted into the brain through a 23-gauge stainless steel tube and was advanced remotely using a micromanipulator (MO-97S, Narishige, Tokyo, Japan). Signals obtained from the electrodes were amplified, filtered, and analyzed online using a spike sorter with template-matching algorithm (MSD or ASD, Alpha Omega Engineering, Nazareth, Israel) to isolate single neurons.

We applied electrical stimulation to the recording sites at various timing during the task. Electrical stimulation was a train of 0.2-ms biphasic pulses delivered through the recording electrode. The frequency of stimulation pulses was either 200 or 333 Hz, and the duration was 100 or 200 ms. The intensity of stimulation current was monitored by measuring the voltage across a serially connected 1-kΩ resistor, and was adjusted within a range of 80–100 μA. According to the previous study

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