Temporal Information Processing in the Cerebellum and Basal Ganglia

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Abstract

Temporal information processing in the range of a few hundred milliseconds to seconds involves the cerebellum and basal ganglia. In this chapter, we present recent studies on non-human primates. In the studies presented in the first half of the chapter, monkeys were trained to make eye movements when a certain amount of time had elapsed since the onset of the visual cue (time production task). The animals had to report time lapses ranging from several hundred milliseconds to a few seconds based on the color of the fixation point. In this task, the saccade latency varied with the time length to be measured and showed stochastic variability from one trial to the other. Trial-to-trial variability under the same conditions correlated well with pupil diameter and the preparatory activity in the deep cerebellar nuclei and the motor thalamus. Inactivation of these brain regions delayed saccades when asked to report subsecond intervals. These results suggest that the internal state, which changes with each trial, may cause fluctuations in cerebellar neuronal activity, thereby producing variations in self-timing. When measuring different time intervals, the preparatory activity in the cerebellum always begins approximately 500 ms before movements, regardless of the length of the time interval being measured. However, the preparatory activity in the striatum persists throughout the mandatory delay period, which can be up to 2 s, with different rate of increasing activity. Furthermore, in the striatum, the visual response and low-frequency oscillatory activity immediately before time measurement were altered by the length of the intended time interval. These results indicate that the state of the network, including the striatum, changes with the intended timing, which lead to different time courses of preparatory activity. Thus, the basal ganglia appear to be responsible for measuring time in the range of several hundred milliseconds to seconds, whereas the cerebellum is responsible for regulating self-timing variability in the subsecond range. The second half of this chapter presents studies related to periodic timing. During eye movements synchronized with alternating targets at regular intervals, different neurons in the cerebellar nuclei exhibit activity related to movement timing, predicted stimulus timing, and the temporal error of synchronization. Among these, the activity associated with target appearance is particularly enhanced during synchronized movements and may represent an internal model of the temporal structure of stimulus sequence.

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We also considered neural mechanism underlying the perception of periodic timing in the absence of movement. During perception of rhythm, we predict the timing of the next stimulus and focus our attention on that moment. In the missing oddball paradigm, the subjects had to detect the omission of a regularly repeated stimulus. When employed in humans, the results show that the fastest temporal limit for predicting each stimulus timing is about 0.25 s (4 Hz). In monkeys performing this task, neurons in the cerebellar nuclei, striatum, and motor thalamus exhibit periodic activity, with different time courses depending on the brain region. Since electrical stimulation or inactivation of recording sites changes the reaction time to stimulus omission, these neuronal activities must be involved in periodic temporal processing. Future research is needed to elucidate the mechanism of rhythm perception, which appears to be processed by both cortico-cerebellar and cortico-basal ganglia pathways.

Keywords

Time production · Synchronized movement · Rhythm perception · Sensory prediction · Internal model · Cerebellar nucleus · Striatum · Motor thalamus · Nonhuman primate

Introduction

When we wait at a traffic light or ride to the beat of music, we unconsciously measure the elapsed time from the previous event and accurately predict the timing of the next event. Temporal information processing in the range of a few hundred milliseconds to several seconds is essential for our daily activities and involves multiple networks in the brain, including the cortico-basal ganglia-thalamocortical pathways and cortico-cerebellar-thalamocortical pathways (Buhusi & Meck, 2005; Coull et al., 2011; Merchant et al., 2013; Ivry & Schlerf, 2008). As experienced in everyday life, these processes are influenced by various internal and external factors (Wittmann, 2013; Lake et al., 2016). In recent years, the neural mechanisms of temporal information processing have been investigated in detail in laboratory animals that perform a variety of tasks, such as time production or reproduction (Jazayeri & Shadlen, 2015; Mita et al., 2009; Schneider & Ghose, 2012; Yumoto et al., 2011; Kunimatsu et al., 2018; Tanaka, 2007), temporal discrimination (Leon & Shadlen, 2003; Shimbo et al., 2021; Mendoza et al., 2018; Chiba et al., 2021), synchronized movement (Merchant et al., 2011; Gamez et al., 2019; Okada et al., 2022), and internalized rhythm (Cadena-Valencia et al., 2018; Ohmae et al., 2013; Kameda et al., 2019). In this chapter, we present the results of our behavioral experiments and neuronal recordings from the cerebellum, striatum, and motor thalamus of nonhuman primates, and discuss the roles of these subcortical structures. We first describe the neural mechanisms involved in measuring the time elapsed from external events, and then discuss the neural mechanisms involved in predicting the timing of periodic stimuli.

Production of Single Time Interval

Variability of Subjective Time Passage

One way to explore the mechanism of temporal information processing is to ask subjects to report the passage of a certain length of time by, for example, pressing a stopwatch at a specific time interval. Even for such a simple task, the length of the produced time varies from trial to trial, likely due to fluctuations in internal factors such as attention and arousal level. Suzuki et al. (2016) examined the relationship between the speed of subjective time passage and pupil diameter, an objective marker of internal state, in monkeys performing a time production task. In their task, a visual cue was presented briefly (0.1 s) while the animals looked at the fixation point on the screen (Fig. 1a). The animals were rewarded if they moved their eyes toward the location of the previous cue after a mandatory delay interval of 1 s. Since the fixation point disappeared only after

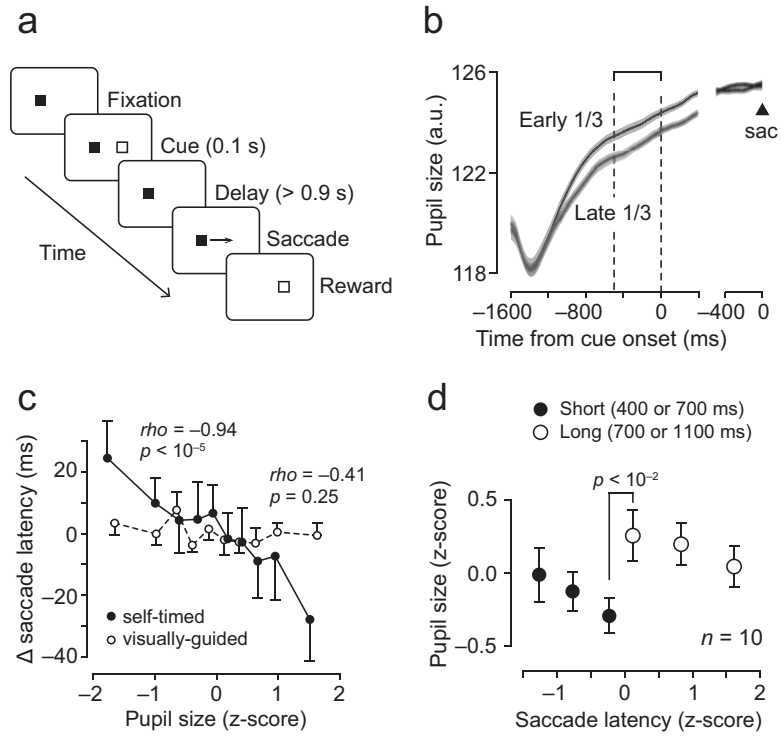

Fig. 1 Correlation between pupil size and the rate of subjective time lapse. (**a**) Self-timed saccade task. Monkeys made a memory-guided saccade to the location of a previously presented visual cue after a 1-second mandatory delay period. Since the fixation point disappeared only after the saccade, animals needed to measure the time elapsed from the visual cue. (**b**) Time courses of pupil size aligned with the cue onset. Trials are divided into three groups according to saccade latency, and the mean (± SE) pupil size for the earliest and latest saccade groups are shown. Two vertical dashed lines during eye fixation represent the time window for quantitative analysis. Note that the pupil size before the cue onset is larger for trials with shorter saccade latencies. (**c**) Relationship between pupil size and latency (relative to the mean) of self-timed (black circles) and visually guided (white circles) saccades. Error bars indicate ±95% CI. (**d**) Comparison between different mandatory delay intervals. Color of equiluminant fixation point indicated two different delay intervals. Data points represent the normalized mean (±95% CI) pupil size and saccade latency for each of the three saccade latency groups. Note that the pupil size is inversely correlated with the group-by-group variation in saccade latency under the same conditions, but not with actual saccade latency across conditions. Data summarize multiple experiments in two monkeys. (Adapted from Suzuki et al. (2016) under the terms of the Creative Commons Attribution 4.0 International License (CC-BY))

the saccade, the animals had to monitor the elapsed time in each trial. Data from several hundred trials were divided into three groups according to the length of the monkey's subjective 1-s (i.e., saccade latency), and the time course of pupil size during fixation was compared between the groups with the longest and shortest saccade latencies (Fig. 1b). In both groups of trials, pupils contracted immediately after the start of fixation and then gradually dilated, but interestingly, pupil diameters before the cue onset were clearly different depending on the subsequent self-timed saccade latency. Data from multiple experiments showed that pupil diameter before cue presentation was inversely correlated with the length of time the animals subsequently reported, with larger pupil diameters indicating shorter times (faster passage of time) and smaller pupil diameters indicating longer times (Fig. 1c). In contrast, pupil diameter did not correlate with the latency of visually guided saccades, where monkeys generated an immediate saccade toward the visual stimulus. Thus, internal factors influence temporal processing, and objective measures

such as pupil diameter could be used to infer how subjects perceive the passage of time.

Then, when measuring longer duration, does the pupil size become much smaller? Suzuki et al. (2016) further trained animals to report two different time intervals (0.7 and 1.1 s, for example) according to the color of equiluminant fixation point. When the relationship between production time and pupil diameter was examined, pupil diameter was different under different instructions, even if the self-timed saccade latencies were similar (Fig. 1d). Furthermore, while saccade latency and pupil size were inversely correlated within each condition, pupil size tended to be larger when the intended time length was long. These results indicate that internal factors fluctuate temporal processing during individual trials under the same condition but may have no relationship with the length of the intended time interval, or that the relationship to the intended timing is the opposite of the trial-by-trial variation. These results suggest that, when reporting elapsed time, there are two signals, one related to the length of time to be measured and the other related to trial-by-trial variability, and pupil diameter correlates well with the latter.

Preparatory Activity for Self-Timing

How is the trial-by-trial variation in self-timing controlled in the brain? It is widely accepted that the timing of self-initiated movement is determined by the time course of the preparatory activity, which gradually increases over time (Jazayeri & Shadlen, 2015; Maimon & Assad, 2006; Janssen & Shadlen, 2005; Merchant & Averbeck, 2017; Lee & Assad, 2003; Ashmore & Sommer, 2013; Xu et al., 2014; Parker et al., 2014; Dacre et al., 2021). During motor preparation, there are a variety of neural activities with different time courses, but integration of these signals leads to the generation of a gradual ramp-like activity (Murakami et al., 2014). This indicates that neurons exhibiting activity at different times cooperate to integrate information into the network and generate ramp-like activity that ultimately controls the timing of movement. Therefore, trial-by-trial variations in self-timing are likely to be reflected in the time courses of the ramping activity.

Previous studies have shown that neurons in the supplementary eye field (SEF), the motor thalamus, the cerebellar dentate nucleus, and the caudate nucleus of the basal ganglia exhibit a significant preparatory activity during the self-timed saccade task (Kunimatsu et al., 2018; Tanaka, 2007; Ohmae et al., 2017; Kunimatsu & Tanaka, 2012). Figure 2a illustrates a neuron recorded from the ventrolateral (VL) thalamus, which showed a gradual increase in activity before self-initiated saccades (Tanaka, 2007). The time course of neuronal activity differed from trial to trial, peaking at the time of saccade initiation and then declining rapidly. When the data for each neuron were divided into five groups according to saccade latency, and the population activity was computed for each group, the variation in saccade timing correlated well with the slope of ramping activity (Fig. 2b). In addition, the firing rate immediately before saccade initiation was comparable between the groups, which was in good agreement with the rise-to-threshold model of decision making. Indeed, these neuronal activities appear to be closely linked to self-timing, as pharmacological inactivation of the recording sites in the VL thalamus delays saccades (Tanaka, 2006).

Similar preparatory activity has also been recorded in the cerebellar dentate nucleus, which projects to the VL thalamus. Ohmae et al. (2017) trained monkeys to generate self-initiated saccades and varied the mandatory delay interval from 0.4 to 2.4 s in different trial blocks. For short delay intervals ($\leq$1.2 s), a significant correlation was found between the saccade latency and the rate of increase in preparatory activity (Fig. 2c). However, for the long delay interval (2.4 s), saccade latency did not correlate with the slope of the ramping activity (Fig. 2d). Instead, a correlation was found between saccade latency and the onset time of preparatory activity. These results suggest that during measurements of time interval shorter than ~1.2 s, trial-to-trial variations in response timing may reflect changes in the magnitude of cerebellar neuronal activity. On the other hand, during measurements of longer

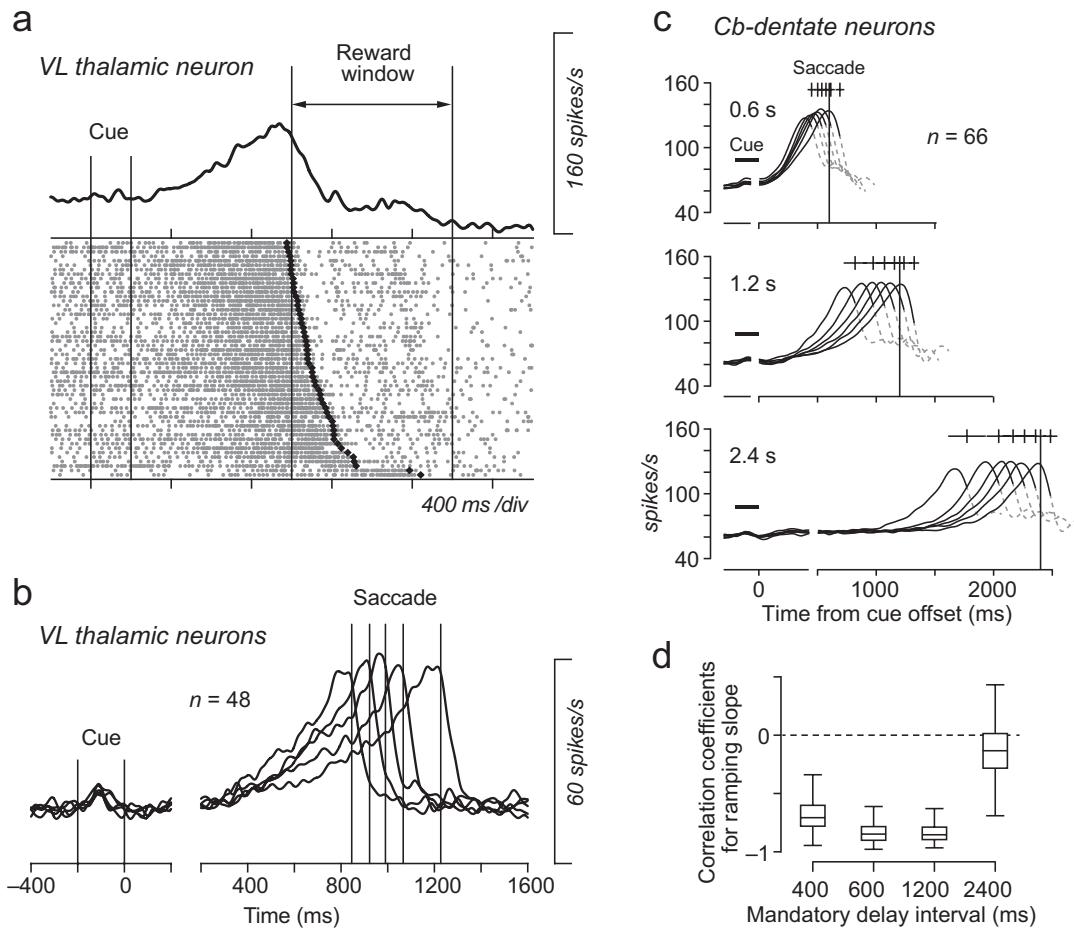

Fig. 2 Time courses of preparatory neuronal activity for self-timed saccades in the ventrolateral (VL) thalamus and the cerebellar dentate nucleus. (**a**) Activity of an example VL thalamic neuron during the self-timed saccade task. Data are aligned with the cue onset in the preferred direction, sorted according to saccade latency. Black symbol on each raster line indicates the time of saccade. Solid continuous line above the rasters indicates spike density. The animal received a reward for saccades generated within the reward window indicated by vertical lines. (**b**) Time courses of population activity of VL thalamic neurons. For each neuron, data were divided into five groups according to saccade latencies. Data were aligned either with the cue (left) or saccades (right), then were averaged across the population. In the right panel, traces are shifted in time so that the times of saccades (vertical lines) are placed at the means of the saccade latency relative to the cue offset. (**c**) Time courses of population activity of ramp-up neurons in the dentate nucleus of the cerebellum for different saccade latencies. For each neuron and mandatory delay interval, the data were divided into six groups according to saccade latencies. Crosses indicate the means and SDs of saccade latency for different groups. (**d**) Summary of correlation coefficients (Pearson's r) between the slope of ramping activity and saccade latency in the cerebellar dentate neurons. Box-whisker plots show the median, quartiles, and range of the results of the bootstrap analysis. (Adapted from Tanaka (2007) and Ohmae et al. (2017) under the terms of the Creative Commons Attribution 4.0 International License (CC-BY))

intervals, signals from the other areas that trigger preparatory activity in the cerebellum may be responsible for variations in self-timing.

One such candidate is the basal ganglia that are also involved in the generation of self-timed movements. In Parkinson's disease, the onset of self-initiated movements is delayed and the time measurements in seconds are inaccurate (Coull et al., 2011; Smith et al., 2007; Honma et al., 2016; Tokushige et al., 2018; Allman & Meck,

2012). Previous studies have suggested that the basal ganglia are mainly involved in measuring suprasecond time intervals, while the cerebellum is involved in subsecond timing (Buhusi & Meck, 2005; Lewis & Miall, 2003). The activities of single neurons in the cerebellar dentate nucleus and the striatum (caudate nucleus) were compared in monkeys trained to report 0.4, 1.0, and 2.2 s elapses according to the color of the fixation point (Fig. 3a), which varied from trial to trial (Kunimatsu et al., 2018). Neurons in both structures showed strong preparatory activity at all intervals, but their time courses were clearly different. The preparatory activity in the cerebellum started approximately 500 ms before the self-timed movements, while that in the striatum started at the onset of the delay period (i.e., immediately after the visual cue), and the rate of increase in neuronal activity depended on the length of time to be measured (Fig. 3b, c). Furthermore, when the time course of neuronal activity in each condition was compared across the three groups of trials sorted by saccade latency, the trial-by-trial variation started earlier in the cerebellum than in the striatum (Fig. 3d). Thus, for the measurements of the suprasecond interval, preparatory activity first started in the striatum, while the trial variation emerged earlier in the cerebellum. These results suggest that the striatum monitors the passage of time throughout

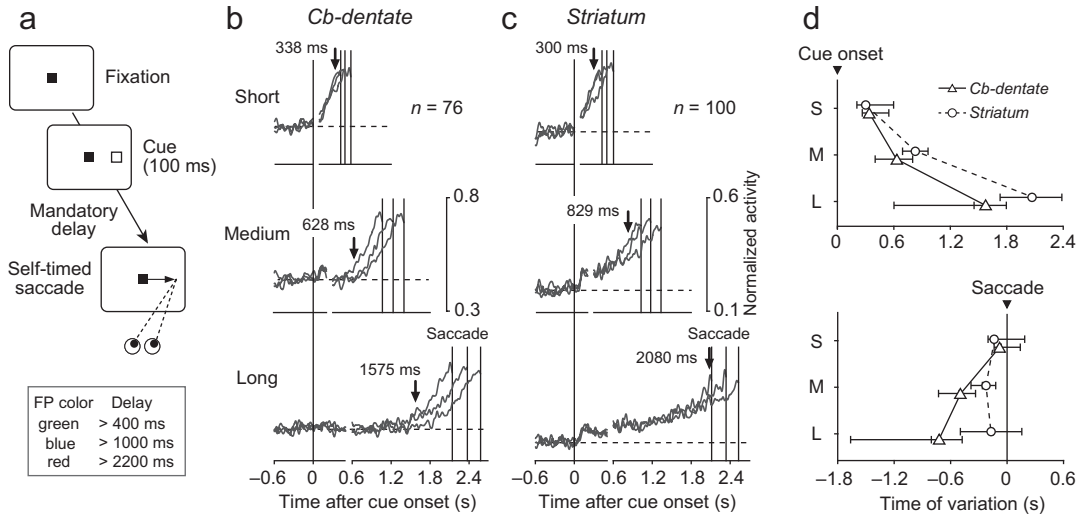

Fig. 3 Timing of trial-by-trial variation of ramping activity in the cerebellar dentate nucleus and the striatum (the caudate nucleus) during the self-timed saccade task. (**a**) Sequence of events in the self-timed saccade task. During central fixation, a cue flashed briefly (100 ms) in the peripheral visual field. Monkeys were required to remember the cue location and maintain fixation until expiration of the predetermined mandatory delay interval that was indicated by color of the fixation point (bottom inset). Animals received a reward if they correctly made a self-timed memory-guided saccade to the cue location after the mandatory delay period. (**b**, **c**) Time courses of population activity for neurons in the cerebellum (**b**) and striatum (**c**). For each delay condition, trials were divided into three groups according to saccade latency. Then, the data were normalized for each neuron, aligned with saccade initiation, and were shifted in time so that the times of saccades (vertical lines) were placed at the mean saccade latencies relative to the cue onset (right panels). On the left panels, data of the population activity were aligned with the cue onset (left vertical line). Downward arrows indicate the time when the traces of normalized neuronal activities started to diverge as detected by repeated measures ANOVAs ($p < 0.01$ for consecutive 40 ms, uncorrected for multiple comparisons). (**d**) Times of onset of trial-by-trial variation relative to the cue (upper panel) or saccade initiation (bottom). Each datapoint indicates the mean of the data derived from the analysis shown in b and c. Error bars with three tick marks denote 2.5, 50, and 97.5 percentiles obtained by the bootstrap analysis. Note that the trial-by-trial variation started earlier in the cerebellum than the striatum for medium and long delay intervals. (Adapted from Kunimatsu et al. (2018) under the terms of the Creative Commons Attribution 4.0 International License (CC-BY))

the delay period and reports the time relative to the entire interval. In contrast, the cerebellum may regulate movement timing within the range of several hundred milliseconds in each trial. Consistent with this, local inactivation of the cerebellar nucleus delayed only subsecond timing, whereas inactivation of the striatum altered both subsecond and suprasecond timing (Kunimatsu et al., 2018).

The recording studies described so far have examined only ramping activity, but other recent studies have examined the time course of neural trajectories in populations of neurons during timing behavior, under the assumption that individual neurons with different time courses are equally involved in timing. These studies showed that neurons in the medial frontal cortex and striatum flexibly change the shape and speed of neural trajectories depending on measured intervals (Wang et al., 2018; Gámez et al., 2019; Betancourt et al., 2023; Meirhaeghe et al., 2021). Striatal neurons with different slopes of ramping activity can be considered as part of the population producing these trajectory changes, and the sequential activity of many neurons may underlie the generation of ramping activity (Zhou & Buonomano, 2022). On the other hand, it is not yet known how the neural trajectories of cerebellar neuronal populations change in measurements ranging from several hundred milliseconds to a few seconds. Although a cerebellar model that generates ramping activity through learning has been proposed (Narain et al., 2018), its temporal limit has not been investigated. Future analysis is needed to determine how neural trajectory of population of cerebellar neurons can relate to subsecond fluctuations in self-timing.

Neural Correlates of Intended Timing

As mentioned above, in the striatum, the rate of increase in preparatory activity for different intervals varied from the beginning of the delay period (Fig. 3c). This indicates that neural excitability in the network including the striatum may flexibly change upon the instruction of the time length to be measured. Indeed, the response of striatal local field potentials (LFPs) to the peripheral visual cues (visual evoked potentials) scaled depending on the length of the mandatory delay interval (which was indicated at the trial start by the color of the fixation point), with large responses for short duration and small responses for long duration (Fig. 4a, b) (Suzuki & Tanaka, 2019). In addition, the LFP power of the low-frequency components (6–20 Hz) just before the cue presentation was proportional to the time interval to be measured, thereby indicating that the network state was altered during preparation of time measurement (Fig. 4c, d). However, when the data were analyzed separately by latency variation under the same conditions, no change in visual response or low-frequency power was found (Fig. 4e). Thus, the intention to measure a specific time interval alters the network state and excitability of striatal neurons, but the stochastic variation of the internal state under the same conditions may not.

The results are summarized in Table 1. When measuring time intervals, there are two sources of variation, one related to the intended length of time and the other to stochastic variation. The preparatory activity for self-timed movements began early in the striatum, regardless of the length of the intended time length, and began shortly (~500 ms) before the movement in the cerebellum. In contrast, the effects of trial-to-trial variability were first observed in the cerebellum and later found in the striatum. The visual response and the low-frequency power in the striatum scaled according to the length of the instructed time interval but not greatly by the stochastic variation of the produced interval. Pupil size, on the other hand, was strongly correlated with trial-to-trial variability in self-timing but not with the intended time interval to be measured.

These findings suggest that the cerebellum coordinates motor timing within a range of second or less, and that cerebellar activity has a significant influence on the intertrial variability of self-timing. The pupil diameter is known to correlate well with the activity of the central noradrenergic system (Murphy et al., 2014; Joshi et al., 2016; Aston-Jones & Cohen, 2005), and the noradrenergic neurons in the dorsal pons send pro-

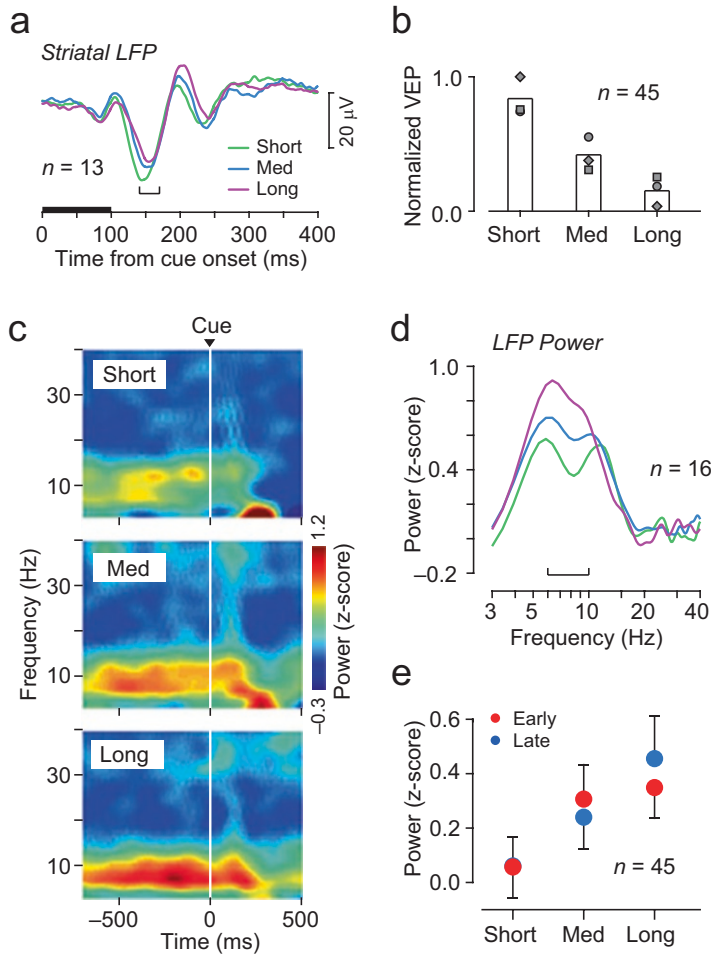

Fig. 4 Contextual modulation of local field potentials (LFPs) in the striatum during the preparation of time measurements. (**a**) Time courses of striatal LFPs aligned with the contralateral visual cue (horizontal black bar) in the self-timed saccade task. Colors indicate different interval conditions. Bracket denotes the time range of the maximum response in individual experiments. (**b**) Comparison of the magnitude of visually evoked response across conditions. Each bar summarizes the mean of normalized response obtained from 45 recording sites. Different symbols plot the data of different monkeys. (**c**) Color-coded power spectra of LFP for self-timed trials with different interval conditions. Vertical white line indicates the cue onset. Note that the power of the low-frequency component increases with longer delay intervals. (**d**) Spectral analysis of LFP during the precue period (500 ms). Bracket denotes the frequency range showing a significant difference across the interval conditions. (**e**) Power modulation associated with trial-to-trial variation in saccade latency. For each interval condition, data were divided into trials with early and late saccades, and the low-frequency power was computed for each. (Adapted from Suzuki and Tanaka (2019) under the terms of the Creative Commons Attribution 4.0 International License (CC-BY))

Table 1 Influence of variation of measured interval on neural and pupil response

	Striatum			Cerebellum	
Source of variation	Preparatory activity	Visual response	α-β power	Preparatory activity	Pupil size
Intended	Early	Scaled	Scaled	Late	–
Stochastic	Late	–	–	Early	Scaled

Minus sign indicates weak or no responsiveness to temporal variation

jections to many brain regions, including the cerebellum, with exceptionally few projections to the striatum (Baldo et al., 2003; Jones & Yang, 1985). This suggests that stochastic changes in internal states may be accompanied by changes in the activity of neuromodulators, such as noradrenaline. This contributes to behavioral variations via changes in neuronal activity in the cerebellum. In contrast, intentional changes in the measured time length were accompanied by changes in the neural excitability of the striatum. It is well known that the low-frequency component of striatal LFP is related to dopamine, and low beta power (8–30 Hz) within the basal ganglia circuitry is significantly increased in Parkinson's disease (Hammond et al., 2007). Since dopamine in the striatum is also known to be involved in interval timing (De Corte et al., 2019; Hamilos et al., 2021; Soares et al., 2016; Kunimatsu & Tanaka, 2016), dopamine may contribute to changing the network state in the cortico-basal ganglia pathways on each trial, depending on the length of time being measured. In fact, patients with Parkinson's disease have a difficulty in varying the measurement time from trial to trial according to instructions, thereby showing a stronger central tendency than normal subjects (so-called "migration effect") (Malapani et al., 1998). However, the role of dopamine during normal conditions still needs to be explored, as a recent study has shown that the suppression of beta power associated with movement is not temporally coupled with dopamine release (Schwerdt et al., 2020). In addition, acetylcholine signaling in the striatum has also been shown to be involved in self-timing (Kunimatsu & Tanaka, 2016), and the relationship between low-frequency oscillations and acetylcholine awaits further clarification.

Rhythmic Timing

Role of the Cerebellum in Synchronized Movement

In addition to self-timed single movements, a series of repetitive movements synchronized to an external rhythm, such as tapping, have been used to investigate the neural mechanisms of temporal processing (Merchant et al., 2013; Kotz et al., 2018; Chauvigne et al., 2014; Gámez et al., 2019; Betancourt et al., 2023). Synchronized movement requires the learning of stimulus tempo, generation of an internal model for periodicity, precise control of movement timing, detection of temporal error, and update of the internal model (Repp, 2005). Although predictive synchronized movements such as musical dance are frequently observed in everyday life, spontaneous synchronization is thought to be unique to species with vocal learning abilities (Patel et al., 2009; Merchant & Honing, 2013). However, some vocal nonlearners, including monkeys, can be trained to generate predictive synchronized movements for immediate rewards (Takeya et al., 2017; Gamez et al., 2018).

As evidenced by the inability to ride excessively slow rhythms, predictive synchronization has a time limit. This appears to be 2–3 s for tapping (Tokushige et al., 2018; Mates et al., 1994) and approximately 1.5 s for eye movements (Shelhamer & Joiner, 2003; Takeya et al., 2018). In monkeys, this is close to the aforementioned time limit at which the rate of increase in neuronal activity in the cerebellum can regulate the timing of self-initiated movements (Fig. 2d). The cerebellum is also involved in eye-blink conditioning with a temporal limit of ~2 s (Medina & Mauk, 2000; Mauk & Buonomano, 2004), and the cerebellar cortex is known to be important in controlling its timing (Perrett et al., 1993). These findings suggest that the cerebellum plays a role in the temporal control of synchronized movements. Indeed, neural activity in the cerebellum, along with motor-related cortical areas and the basal ganglia, increases during motor synchrony (Chauvigne et al., 2014; Aso et al., 2010; Lee et al., 2016; Witt et al., 2008), and damage to the cerebellum increases the temporal variability of discrete periodic movements (Spencer et al., 2003).

Okada et al. (2022) trained monkeys to perform synchronized saccades to alternating left and right targets at regular intervals (Fig. 5a) and examined neuronal activity in the dentate nucleus of the cerebellum. Many neurons showed increased activity before eye movements, half of

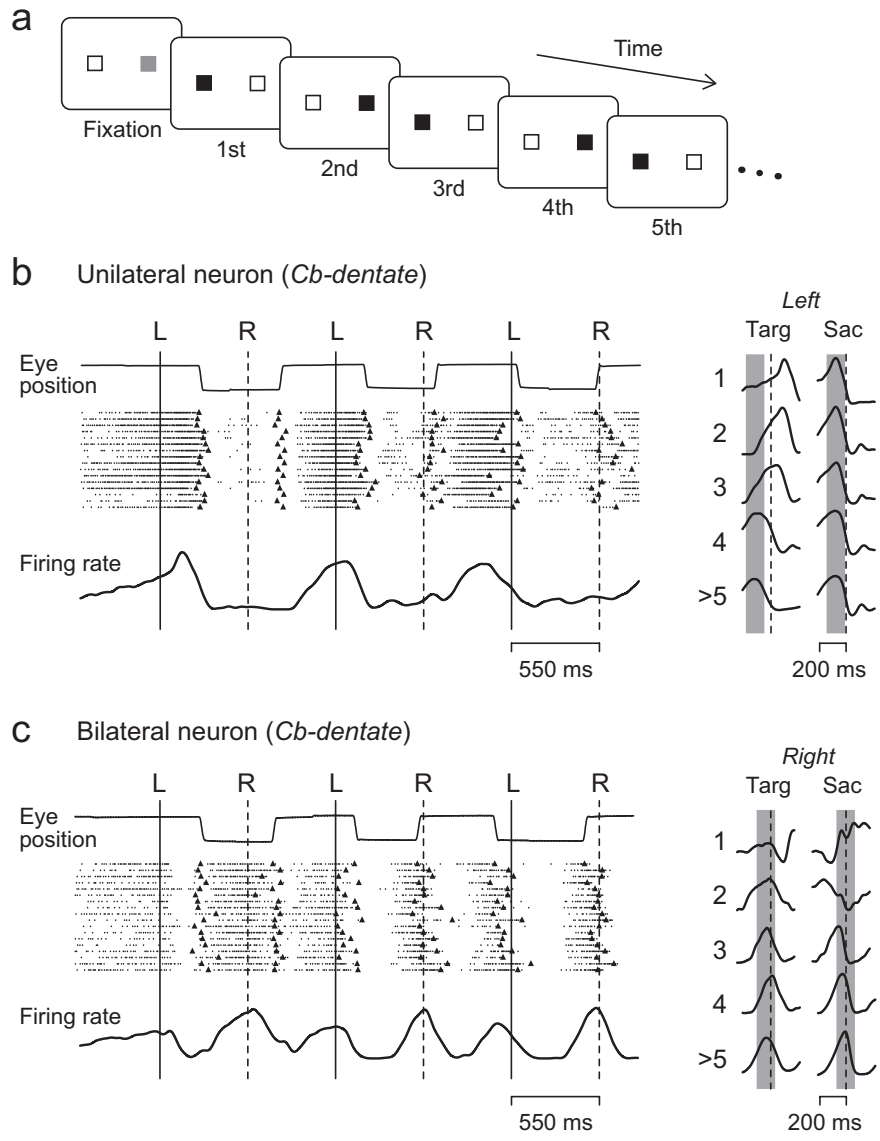

Fig. 5 Neuronal activity in the cerebellum during synchronized eye movements. (**a**) Saccade targets were presented alternately at landmark locations (white squares, 14° apart) for 400, 550, or 700 ms (constant in each trial). Monkeys were rewarded for every three predictive saccades. (**b**) Response of a unilateral neuron to the early stimulus sequence. Data are aligned with the target onset (solid and dashed vertical lines) in trials with a 550-ms stimulus interval. The black symbol on each raster line indicates saccade onset. Note that neuronal activity consistently precedes the leftward saccade. The right panel shows the traces of the mean firing rate aligned either to the target onset or saccade initiation (vertical dashed lines). Number on the left indicates the stimulus sequence. Shadings represent the 100 ms window centered at the peak activity during the later stimulus sequence. (**c**) Response of a bilateral neuron. Note that even during the initial few cycles of target presentation, the peak firing rate of the neuron roughly coincides with the target onset, whereas early saccades lag behind the target onset. (Adapted from Okada et al. (2022) under the terms of the Creative Commons Attribution 4.0 International License (CC-BY))

which had strong directional modulation, exhibiting a ramp-like preparatory activity mostly for ipsilateral synchronized saccades. However, these neurons also showed strong presaccade activity even when the animals made a series of reactive saccades to randomly timed targets. This suggests that they are involved in motor control, independent of the stimulus rhythm. In contrast, the remaining half of the presaccade neurons were active for eye movements in both directions, with enhanced activity during synchronized saccades compared with reactive saccades. These results indicate that neurons that are active in bilateral eye movements are important for motor synchrony.

Figure 5b, c illustrates examples of these neurons. The Unilateral neuron exhibited strong activity before saccades to the left, and the initial peak of activity and saccades occurred after the target onset. However, the timing of peak activity gradually advanced as saccade latency became shorter during the sequence. When neuronal activity was aligned with target onset or saccades in the order on each trial, the timing of peak activity varied with respect to the target onset, but consistently preceded saccades (Fig. 5b, right panel). This finding indicates that this unilateral neuron is related to motor control. In contrast, the representative bilateral neuron exhibited increased activity for saccades in both directions, and the timing of peak activity changed only slightly, although the saccade latency gradually shortened (Fig. 5c). When averaging neuronal activity in the order of target or saccade, the activity was more consistent with target onset, indicating that the neuron was activated in anticipation of stimulus timing rather than movement. Another class of neurons in the cerebellar nucleus showed increased activity immediately after saccades. About half of these neurons showed a significant correlation with saccade latency (or the time difference between target appearance and saccade), indicating that they detected temporal errors in synchronized saccades (Okada et al., 2022).

These results suggest that neurons in the cerebellar nuclei carry the signals necessary to predict the timing of alternating targets, adjust the timing of movements, and detect temporal errors to update the internal model of periodic events. Since these neurons were found in the output node of the cerebellum, the information was transmitted to the brainstem and thalamocortical pathways. Signals related to eye movements might be sent to the midbrain superior colliculus to regulate saccade timing (May et al., 1990; Prevosto et al., 2017), and those related to temporal errors might be sent to the inferior olive in the medulla to induce learning (De Zeeuw et al., 1998). Alternatively, these signals, along with those related to the stimulus timing, might be sent to different areas in the cerebral cortex via the thalamus. Future studies are needed to clarify how information is integrated within multiple cerebrocerebellar loops, including the dentate nucleus, during synchronized saccades. In addition, since the basal ganglia are also known to be involved in synchronized movements (Chauvigne et al., 2014; Witt et al., 2008; Hove et al., 2013; Rao et al., 1997; Bartolo et al., 2014), it is important to examine how the signals in the cortico-basal ganglia and the cortico-cerebellar loops cooperate and interact for synchronized movements. Signals processed in these subcortical loops must be integrated in the parietal and frontal cortices, which is key to a comprehensive understanding of the neural mechanisms of motor synchronization.

Temporal Limit of Sensory Prediction for Rhythmic Events

The premise of synchronized movements is to detect the periodicity of sensory events and predict their timing. As mentioned earlier, synchronized movement is difficult when the tempo is too slow, but it is easy to imagine that synchronization can also be impossible when the tempo is too fast. In the case of synchronized movements, this is largely due to the constraints of the motor system, but there is a paucity of information on the temporal limit of purely sensory rhythms. This has been examined using the missing (omission) oddball detection paradigm in healthy individuals (Ohmae & Tanaka, 2016). In this task, participants were asked to press a button as fast

as possible when they detected the omission of isochronous repetitive auditory stimulus (Fig. 6a). To detect stimulus omission, it is necessary to predict the timing of the next stimulus. Figure 6b shows that the relationship between reaction time and the interstimulus interval (or stimulus tempo) differed after ~250 ms (4 Hz, vertical dashed line), suggesting that different mechanisms may underlie the detection of stimulus omissions for different tempos.

When listening to isochronous sound sequences with a short interstimulus interval, it is impossible to predict the timing of each stimulus in advance; rather, there is an impression of a

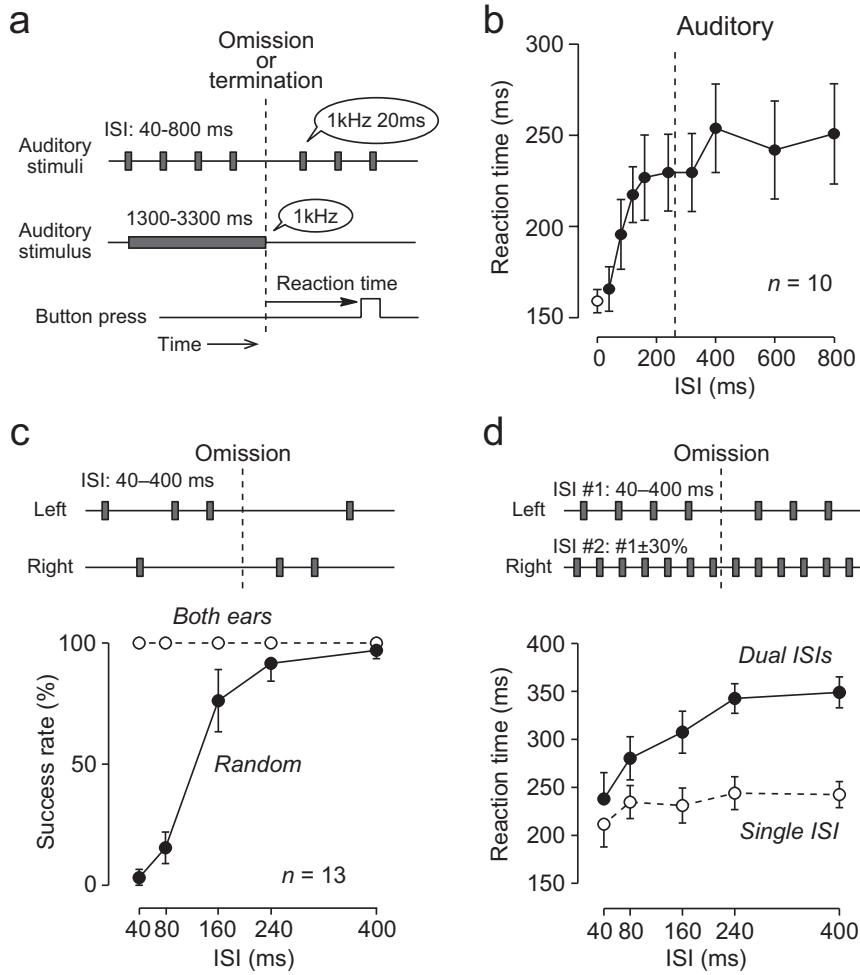

Fig. 6 Temporal limit of sensory prediction for rhythmic events. (**a**) Participants were asked to press the button as soon as possible in response to the omission of one repetitive auditory stimulus (upper) or the end of a continuous tone (middle). The interstimulus interval (ISI) ranged from 40 to 800 ms, and each repetitive sound lasted 20 ms. (**b**) Reaction time for different ISIs. Data for the continuous sound are shown at zero ISI (white circle). Error bars indicate 95% confidence intervals. Note that the reaction time highly depends on the ISI for the intervals shorter than 250 ms (vertical dashed line) but is relatively constant for longer intervals. (**c**) Each repetitive stimulus was randomly presented to either ear with a constant ISI (40–400 ms). Participants were asked to detect stimulus omission as accurately as possible. As a control, each sound was presented to both ears. The graph represents the proportions of correct trials in the random monaural (black circle) and binaural (white) conditions. (**d**) Repetitive stimuli with different ISIs were presented simultaneously to different ears. Stimulus omission occurred randomly in either ear. Black and white circles indicate the data for the dual- and single-ISI conditions, respectively. (Adapted from Ohmae and Tanaka (2016) under the terms of the Creative Commons Attribution 4.0 International License (CC-BY))

momentary interruption of a constant sound stream (Supplementary Audio files in (Ohmae & Tanaka, 2016)). This may be because auditory responses to regularly repeated sounds at a fast tempo are temporally grouped, and missing stimuli are detected as deviations from the steady state of neural activity. In fact, the data for responses to a pause in continuous sound are in line with the relationship between reaction time and stimulus tempo if the interstimulus interval of the continuous sound is assumed to be zero (Fig. 6b, white circle). When each sound in a sequence was presented randomly to each ear to prevent temporal grouping, the detection of stimulus omission became difficult only for stimulus intervals shorter than 250 ms (Fig. 6c). The same was true when sounds of different frequencies were presented at regular intervals (Ohmae & Tanaka, 2016).

On the other hand, the detection of stimulus omission for slower rhythms must rely on the temporal prediction of the next stimulus and may require higher-order cognitive processes that can be interfered with under dual-task conditions. To test this hypothesis, two sequences of sounds at different tempos were presented simultaneously to different ears so that attentional resources for temporal prediction were separately allocated to both ears. Even in this condition, the participants reliably detected the sound omission that occurred in either ear. However, compared to the response to a single sequence, the reaction time in the dual-task condition was prolonged, mainly for slower tempos (Fig. 6d). Taken together, these results suggest that a time window of approximately 4 Hz or slower is necessary to integrate auditory inputs from different sources to predict the next stimulus timing. Since a similar relationship between reaction time and interstimulus interval was also observed in sequences of visual and tactile stimuli (Ohmae & Tanaka, 2016), a 4-Hz limit of temporal prediction might be common to different sensory modalities. The 3–4 Hz limit for the integration of temporal information from different sources has also been demonstrated in simultaneity detection between different sensory modalities (Fujisaki & Nishida, 2010).

Subcortical Signals Underlying Rhythm Perception

Using a similar oddball detection paradigm with a visual metronome, neuronal activity during rhythm perception in the cerebellar nuclei, striatum, and motor thalamus has been examined in monkeys. In this task, a saccade target was initially presented either on the left or right side of the central fixation point (Fig. 7a). While maintaining eye fixation, visual stimuli surrounding the fixation point were repeatedly presented at an interstimulus interval that was constant in each trial but varied from trial to trial in the range of 100 to 600 ms. The animals were trained to make a saccade in response to an unexpected (random) omission of the repetitive stimulus to obtain a liquid reward (missing oddball condition). To detect stimulus omission, they were required to predict the timing of the next stimulus. In a variant of this task with a different color of the fixation point, the animals were required to detect the occurrence of color change in the repetitive stimulus (color oddball condition).

During this task, neurons in the posterior part of the cerebellar dentate nucleus, the head of the caudate nucleus, and the motor thalamus have been shown to exhibit periodic activity in the absence of movement (Fig. 7b) (Ohmae et al., 2013; Kameda et al., 2019, 2023; Matsuyama & Tanaka, 2021; Uematsu & Tanaka, 2022). Most of these neurons do not respond to the first few stimuli in sequence, but as repetition progresses, the firing modulation gradually increases, indicating neural entrainment to the stimulus rhythm. After several repetitions, the response to each stimulus reached a plateau, and at this moment the magnitude of the firing modulation was proportional to the interstimulus interval (Fig. 7c). Some neurons in the striatum also show preferences for a specific stimulus tempo (Kameda et al., 2019), indicating a tuned representation of interval timing (Heron et al., 2012; Protopapa et al., 2019). Importantly, periodic activity greatly decreases under the color oddball condition where temporal prediction is not needed but saccades are required, indicating that these activities are under top-down control and are involved in

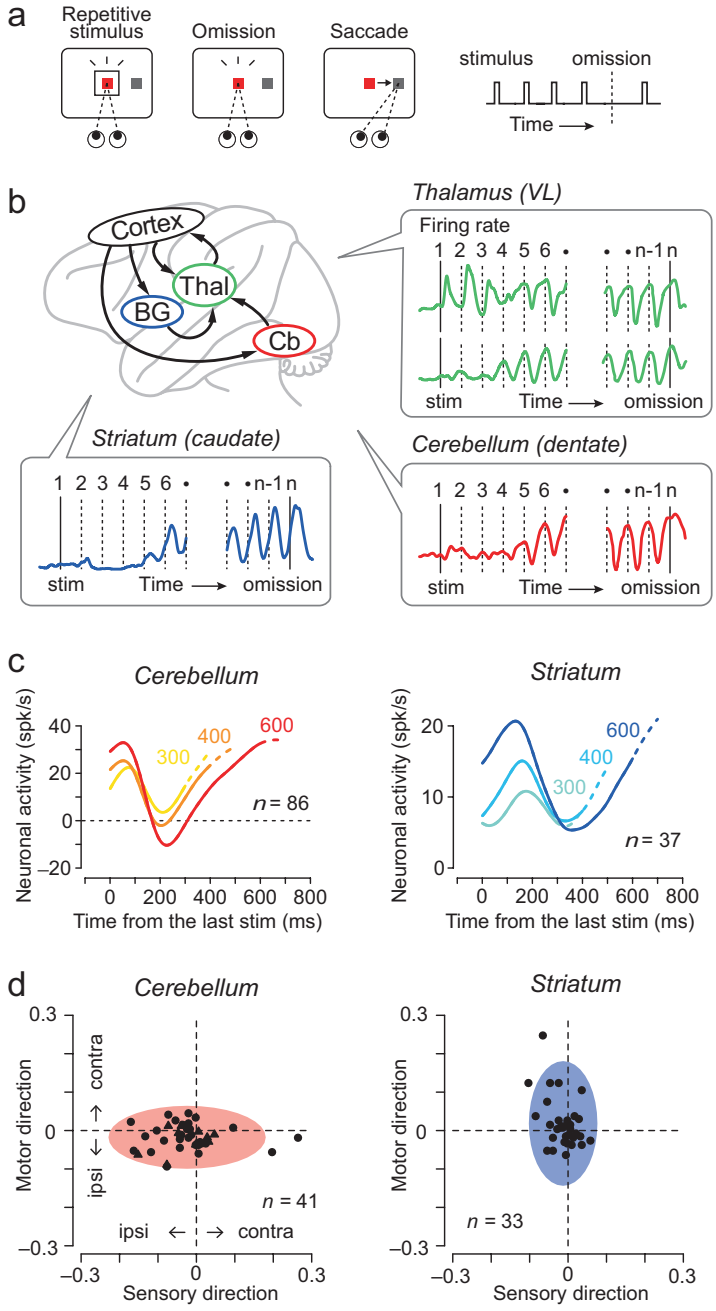

Fig. 7 Subcortical neuronal activities entrained to periodic visual stimuli. (**a**) In the missing oddball paradigm, a saccade target appeared horizontally during central fixation, and then a brief stimulus surrounding the fixation point was presented repeatedly at a fixed interstimulus interval (ISI). Animals were trained to make a saccade in response to the stimulus omission. (**b**) The colored solid line in the balloon represents the time course of neuronal activity recorded from the cerebellar dentate nucleus (red), striatum (caudate nucleus, blue), and motor thalamus (green), which showed periodic activity during eye fixation. In each panel, data are aligned with either the first stimulus (left) or stimulus omission (right). Note that most neurons gradually increase their periodic firing modulation with stimulus repetition. Also note that the timing of peak activity differs among brain regions. (**c**) The time courses of population activity in the cerebellum and striatum for three different ISIs aligned with the stimulus just

temporal processing. Indeed, neuronal activity at the time of stimulus omission correlates with reaction time in all three brain regions (Ohmae et al., 2013; Kameda et al., 2019; Matsuyama & Tanaka, 2021). Furthermore, electrical stimulation delivered to the cerebellar nuclei or the striatum shortened the reaction time to stimulus omission and inactivation prolonged it (Ohmae et al., 2013; Kameda et al., 2019; Uematsu et al., 2017). These effects disappeared under the color oddball condition or when the interstimulus interval was less than 200 ms, suggesting that these signals are important for predicting the timing of the next stimulus in advance.

Although the overall characteristics of neuronal activity are common in the cerebellum, striatum, and thalamus, the time course of periodic activity differs at each recording site. In the cerebellar dentate nucleus, most neurons show peak activity at the time of stimulus presentation, regardless of the stimulus interval, and cease firing during eye movements. Neuronal activity sharply decreases after the presentation of each stimulus, but its amplitude and the time course of recovery differs between stimulus intervals, resulting in anticipatory activity that peaks at the time of the next stimulus (Fig. 7b, c). In the striatum (caudate nucleus), on the other hand, neuronal activity increases after stimulus presentation and its peak remains constant at approximately 150–200 ms regardless of the stimulus interval, and the firing rate at the time of the next stimulus differed across intervals and the next stimulus timing cannot be accurately predicted from the time course of the population activity (Kameda et al., 2019). Furthermore, it has recently been shown that periodic neuronal activity in the cerebellum is modulated by the location of repetitive stimuli but not by the direction of prepared movements (Fig. 7d). Conversely, neuronal activity in the striatum is modulated by the direction of subsequent saccades but not by the location of the repetitive stimulus. These results suggest that the cerebellum is involved in the temporal prediction of sensory events while the striatum is involved in motor preparation during the task (Kameda et al., 2023). In the ventrolateral and the adjacent nuclei of the thalamus, which receive inputs from the cerebellum, many neurons exhibit anticipatory activity like those of the cerebellar nucleus. Some thalamic neurons reverse the direction of their response to each stimulus during repetition, showing the first reactive and later anticipatory activity (Fig. 7b). Since it has been suggested that the motor thalamus integrates information from subcortical and cortical sources (Galvan et al., 2016; Suzuki et al., 2021), the thalamic neurons showing such phase transitions may reflect signals from multiple input sources (Matsuyama & Tanaka, 2021; Sieveritz & Raghavan, 2021).

Thus, although subcortical networks are involved in rhythm processing, neural signals vary widely among brain regions, and further research is needed to clarify their specific roles. In particular, the time course of neural activity in the cerebellar nuclei during oddball tasks is similar to the activity that predicts target onset during saccade synchronization and may represent an internal model of periodic sensory events. Previous studies have shown that the cerebellum generates and updates internal models that predict sensory events even in the absence of movement (Cerminara et al., 2009; O'Reilly et al., 2008; Roth et al., 2013). Additionally, the time course of neuronal activity in the cerebellar nuclei during the oddball tasks closely resembles the time course of beta coherence in the cerebellum and the cerebral cortex during passive listening to isochronous sounds shown in humans (Fujioka et al., 2012), suggesting that the cortico-cerebellar loops may be essential for the generation of predictive signals. In relation to this, recent evidence suggests that the cerebellum is involved in temporal attention (Coull & Nobre,

Fig. 7 (continued) before omission. Dashed lines indicate the data during 100 ms following the stimulus omission. (**d**) Comparison of sensory and motor components of neuronal activity in the cerebellum and striatum. The repetitive visual stimulus and saccade target were independently placed either left or right of the fixation point, and the modulation of periodic activity in individual neurons due to stimulus location was evaluated using the generalized linear model. Each dot represents beta coefficient of each neuron calculated for the location of the repetitive stimulus (sensory direction) or saccade target (motor direction). (Panels (**c**) and (**d**) are adapted from Kameda et al. (2019, 2023))

1998; Nobre & van Ede, 2018; Breska & Ivry, 2021), which appears to be controlled by low-frequency neural oscillations in the sensory cortex during rhythm perception (Lakatos et al., 2008). Since attention is likely allocated to predicted stimuli, the cortico-subcortical network, including the cerebellum, may play a role in temporal attention during rhythm processing.

Relation to Other Studies

A well-known hypothesis in the study of temporal processing is that the basal ganglia are involved in beat-based or relative timing, whereas the cerebellum is involved in measuring single absolute time intervals (Teki et al., 2011a; Grube et al., 2010). In fact, it has been clearly demonstrated that poor performance on timing tasks in Parkinson's disease and cerebellar degeneration is double dissociated when processing periodic and single time intervals (Breska & Ivry, 2018). However, many previous studies in experimental animals have employed behavioral tasks that require the measurement of single time intervals to reveal the involvement of the basal ganglia (Lee & Assad, 2003; De Corte et al., 2019; Wang et al., 2018; Mello et al., 2015). Functional imaging studies have shown increased neural activity in the cerebellum and basal ganglia during both single and periodic time processing (Wiener et al., 2010), suggesting that these two subcortical systems interact strongly (Petter et al., 2016; Teki et al., 2011b). As described above, time-specific neuronal activity has been found in the cerebellum and striatum of monkeys during the self-timing task and the missing oddball detection task, which require single and periodic time processing, respectively. In both cases, manipulation of neuronal activity at the recording sites by electrical stimulation or pharmacological inactivation alters the task performance.

However, it is important to review these data in terms of relative and absolute timing to further understand the role of these subcortical regions. For example, the time course of preparatory activity in the striatum during self-timed tasks has been shown to be temporally scaled in the range of a few hundred milliseconds to seconds (Kunimatsu et al., 2018; Wang et al., 2018; Mello et al., 2015). This can be viewed as the neural activity encoding the passage of time relative to the length of time being measured. Similar temporal scaling has recently been shown for midbrain dopamine neurons (Hamilos et al., 2021) and hippocampus (Shimbo et al., 2021). In contrast, neurons in the cerebellum are also temporally scaled when the time length is less than a second (Okada et al., 2022; Ohmae et al., 2017), but at longer time intervals, they do not have information relative to the intended time length to be measured. Furthermore, in the missing oddball task, neuronal activity in the cerebellar nuclei for each repetitive stimulus appears to encode the absolute elapsed time from the previous stimulus, rather than the relative timing to the previous beat (Ohmae et al., 2013). This might mean that the cerebellum locally measures the time between immediately preceding events even when events have a periodic time structure.

Nevertheless, monkeys are capable of maintaining internalized rhythm, as they continue periodic saccades when targets are presented in conjunction with eye movements (error-clamp condition) during the synchronized saccade task (Takeya et al., 2017). Similarly, monkeys can continue predictive tapping even after periodic external stimuli have disappeared (Gamez et al., 2018) and can covertly shift the direction of motor preparation in the internalized rhythms (Cadena-Valencia et al., 2018; Garcia-Garibay et al., 2016). Further investigation is needed to understand how periodic time is encoded under these conditions, and how the roles of the cerebellum and basal ganglia are different.

Summary and Conclusions

This chapter presents recent studies in nonhuman primates that have examined neural mechanisms during the measurement of single and periodic time intervals. The series of studies described earlier in this chapter focuses on pupil diameter and subcortical preparatory activity during a self-timed saccade task and reveals two mechanisms that regulate movement timing. The trial-to-trial variation in the produced time interval under the

same conditions correlates well with pupil diameter (Suzuki et al., 2016), which reflects internal states such as attention and arousal level. When producing time intervals of 1.2 s or less, these timing variations can be explained by the rate of increasing activity in the cerebellum and motor thalamus, and inactivation of these areas delays self-timing. When measuring longer intervals, preparatory activity in the cerebellum begins approximately 500 ms before movement, and the stochastic variability in self-timing correlates well with the time of onset rather than with the slope of increasing activity (Fig. 2d, Ohmae et al., 2017).

On the other hand, when the length of time to be measured is explicitly indicated, the rate of increase in preparatory activity in the striatum changes accordingly. In the striatum, the preparatory activity persists throughout the delay period, but the effects of intertrial variations in self-timing appear only immediately before movement, following changes in the cerebellum (Fig. 3, Kunimatsu et al., 2018). This suggests that fluctuations in cerebellar activity are primarily responsible for the stochastic variation in timing. Because striatal inactivation changes self-timing regardless of the length of the mandatory delay, the striatum may measure elapsed time over the entire range from a few hundred milliseconds to several seconds.

In the striatum, the magnitude of the visual response to the cue was negatively correlated with the length of time to be measured, and the power of the low-frequency component before the cue was positively correlated (Fig. 4, Suzuki & Tanaka, 2019). This indicates that the length of the intended timing changes the state of the network, including the striatum, which may lead to changes in the time course of the preparatory activity. In Parkinson's disease, in which beta oscillation within the basal ganglia circuitry is abnormally enhanced, the central tendency is stronger when different time lengths are generated in each trial (Malapani et al., 1998). This may be because of the inability to flexibly change the state of the network according to the intended time length. In contrast, the trial-to-trial variation in self-timing is correlated with pupil diameter, which is known to reflect the activity of the central noradrenergic system. Strong noradrenergic innervation from the brainstem to the cerebellum may contribute in part to stochastic changes in self-timing. Thus, when producing time intervals, (1) intentional signals that depend on the length of time to be measured and, (2) stochastic signals that fluctuate according to the internal state, exist in the brain which might control self-timing by modulating neuronal activity in the basal ganglia and cerebellum, respectively.

The second half of this chapter discusses recent research on periodic timing. Stimuli that are regularly repeated on the order of hundreds of milliseconds produce rhythm perception, often accompanied by synchronized movements. Predictive synchronized movements are thought to be specific to vocal-learning species (Patel et al., 2009), but recent studies have shown that monkeys exhibit this ability when given immediate rewards (Takeya et al., 2017; Gamez et al., 2018). They can make predictive eye movements synchronized to alternating visual stimuli if the stimulus interval is 0.4 to 1.2 s. As movement becomes reactive when the stimulus interval is 1.8 s, the time limit for predictive synchronization may be approximately 1.5 s (Takeya et al., 2018).

When monkeys perform synchronized saccades, there are three types of neurons in the cerebellar nuclei that exhibit periodic activity related to movement timing, predicted target timing, and synchronization errors (Fig. 5, Okada et al., 2022). Of these, only neurons that show the peak activity at the target appearance is more active than during reactive saccades and may be particularly important in synchronizing movements. These neurons were active regardless of the target location, representing an internal model of periodic stimulation. To achieve synchronized movements, it is necessary to generate an internal model for periodic stimuli, adjust the movement timing, and update the internal model by detecting errors. The cerebellum contains all this information and may send signals to the brainstem and thalamocortical pathways, serving a part of the global network that enables motor synchrony. As it is also well known that the basal ganglia are

involved in synchronized movements, it is necessary to compare the roles of these subcortical regions in future studies.

When perceiving rhythm, we predict the timing of the next stimulus and focus our attention on that moment. Its time limit has been investigated using the missing oddball paradigm (Fig. 6, Ohmae & Tanaka, 2016). When detecting an omission of isochronously repeated sounds, the reaction time changes after about 0.25 s (4 Hz). At faster tempos, it is impossible to integrate temporal information from the opposite ear or from sounds of different frequencies. Conversely, at slower tempos, the reaction times to stimulus omission were significantly prolonged under dual-task condition. Taken together with the results of the synchronized movements, accurate temporal prediction is possible for periodic stimuli in the range of 0.25 to 1.5 s (0.6 to 4 Hz).

Periodic neuronal activity has been recorded from the cerebellum (Ohmae et al., 2013), striatum (Kameda et al., 2019), and motor thalamus (Matsuyama & Tanaka, 2021) in monkeys performing a similar task using a visual metronome (Fig. 7). At each site, the magnitude of neuronal modulation increased gradually with repeated stimuli, reaching a plateau within a few seconds. Under these conditions, the size of the response to each stimulus depended on the stimulus tempo. The time course of periodic neuronal activity varies between brain regions; in particular, many neurons in the cerebellar nuclei exhibit anticipatory activity that peaks at the stimulus timing and the magnitude of periodic modulation depends on the location of the repetitive stimulus (Kameda et al., 2023). The time course of neuronal activity in primates resembles the time course of beta-band coherence seen in the cortex and the cerebellum during passive listening to isochronous sound in humans (Fujioka et al., 2012), which may represent an internal model predicting the stimulus timing. Manipulation of neuronal activity in the cerebellum and striatum changes the reaction time of omission detection, suggesting that these areas are involved in periodic temporal processing. In the future, the neural mechanisms of the cortico-cerebellar and cortico-basal ganglia pathways in rhythm perception should be clarified.

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