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Roles of the cerebellum in motor preparation and prediction of timing

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Abstract

The cerebellum is thought to have a variety of functions because it developed with the evolution of the cerebrum and connects with different areas in the frontoparietal cortices. Like neurons in the cerebral cortex, those in the cerebellum also exhibit strong activity during planning in addition to the execution of movements. However, their specific roles remain elusive. In this article, we review recent findings focusing on preparatory activities found in the primate deep cerebellar nuclei during tasks requiring deliberate motor control and temporal prediction. Neurons in the cerebellum are active during anti-saccade preparation and their inactivation impairs proactive inhibitory control for saccades. Experiments using a self-timing task show that there are mechanisms for tracking elapsed time and regulating trial-by-trial variation in timing, and that the cerebellum is involved in the latter. When predicting the timing of periodic events, the cerebellum provides more accurate temporal information than the striatum. During a recently developed synchronized eye movement task, cerebellar nuclear neurons exhibited periodic preparatory activity for predictive synchronization. In all cases, the cerebellum generated preparatory activity lasting for several hundred milliseconds. These signals may regulate neuronal activity in the cerebral cortex that adjusts movement timing and predicts the timing of rhythmic events.

Keywords

proactive inhibition; self-timing; temporal prediction; predictive synchronization; eye movement; nonhuman primate

Introduction

The cerebellum assists movement execution, participates in generating large forces at movement initiation, and coordinates the timing of multiple muscle contractions. In cerebellar ataxia, the movement onset is delayed, the movement trajectory curves, and the timing of action termination varies to cause dysmetria (Holmes, 1939; Ito, 1984). These functions are subject to adaptive learning, and the cerebellum enables predictive motor control through practice. The cerebellum is thought to regulate movements by accessing the motor cortex and the brainstem motor generating circuitries. Anatomically, the output nodes of the cerebellum send massive projections to the ventrolateral thalamus. In turn, individual neurons in the thalamus send widespread projections to the primary motor cortex, which could be involved in the spatiotemporal coordination of distant muscles (Shinoda et al., 1993). A recent physiological study in nonhuman primates showed that the majority of neurons in the motor cortex receive inputs from the cerebellum via the thalamus (Nashef et al., 2018). These inputs are essential for strong transient activity at movement onset and mediate synchronized activity between neurons in the motor cortex (Hore and Flament, 1988; Nashef et al., 2019).

However, it is widely accepted that the function of the cerebellum goes beyond online adjustment of muscle activity during movements (Strick et al., 2009; Ito, 2011; Schmahmann et al., 2019). Nearly half a century ago, Allen and Tsukahara (1974) proposed that the medial and intermediate parts of the anterior cerebellum are involved in motor execution, and that the lateral and posterior parts of the cerebellum, together with the basal ganglia, are involved in motor intention and planning (Fig. 1). Anatomically, the cerebellum has reciprocal connections with association areas in the parietal and frontal cortices through the thalamus and the pontine nuclei, in addition to the motor-related areas in the frontal cortex (Middleton and Strick, 2000; Ramnani, 2006; Bostan et al., 2013). Recent functional imaging and clinical studies have revealed the cerebellar involvement in higher-order cognitive functions (Schmahmann and Sherman, 1998; Ito, 2008; Stoodley and Schmahmann, 2009; Bellebaum et al., 2012). Given that the number of neurons in the cerebellum is far more than all neurons in the cerebral cortex (Williams and Herrup, 1988; von Bartheld et al., 2016), it is not surprising that the cerebellum has a variety of functions. However, compared with the neuronal mechanisms of movement control and adaptive motor learning that have been studied with relatively simple reflexes, research in this field is limited. Because of the uniform circuit structure in the cerebellum, it is believed that the computational principles of

the cerebellum can be applied to various functions, but there is little available information on what neural representations are present in the cerebellum other than during the execution of movements. In this article, we review recent studies examining how the cerebellum is involved in motor intention and planning during behavioral tasks that have been mostly used for research in the cerebral cortex and the basal ganglia. Specifically, we discuss how the cerebellum plays a role in controlling deliberate actions, regulating the timing of self-initiated movements, and predicting the timing of periodic events.

Proactive control of volitional movements

The anti-saccade paradigm has been used to examine the neural mechanism of deliberate motor control (Munoz and Everling, 2004). In this task, subjects are asked to look away from the sudden appearance of a visual stimulus (Hallett, 1978; Fig. 2A). To accomplish this, they need to suppress reflexive (pro-)saccades to the target and generate motor commands for an eye movement to the opposite empty space. It has been widely accepted that anti-saccades are regulated by the cortico-basal ganglia pathways (O'Driscoll et al., 1995; Everling and Fischer, 1998). Indeed, subjects with basal ganglia diseases (Lasker et al., 1987; Briand et al., 1999; Chen et al., 1999; LeVasseur et al., 2001; Chan et al., 2005), developmental disorders (Barkley, 1997; Minshew et al., 1999; Munoz et al., 2003), and dysfunction of prefrontal cortex (Fukushima et al., 1988; Broerse et al., 2001) have difficulty in performing anti-saccades. The underlying neuronal mechanisms have been thoroughly examined in the relevant network in nonhuman primates (Johnston and Everling, 2008; Watanabe and Munoz, 2011).

However, the previous functional imaging studies often detected increased activity in the lateral cerebellum in addition to the cortico-basal ganglia pathways during anti-saccades (Luna et al., 2001; Tu et al., 2006), and clinical studies also show that the subjects with cerebellar degeneration exhibit moderate anti-saccade deficits (Hubner et al., 2007; Fielding et al., 2010). Furthermore, recent studies have shown that the error-related scalp potentials following erroneous pro-saccades in the anti-saccade trials are significantly reduced in subjects with focal cerebellar or thalamic lesions (Peterburs et al., 2011; Peterburs et al., 2012), and that the magnitude of the cortical potentials and error rate correlate with the gray matter volume of posterolateral cerebellum (including Crus I, II and VIIB) in patients with cerebellar degeneration (Peterburs et al., 2015). These results suggest that the cerebellum, especially the outer part of the posterior lobe, is responsible for generating anti-

saccades.

Recently, Kunimatsu et al. (2016) found that neurons in the caudal part of the cerebellar dentate nucleus (which receives inputs from the lateral cerebellum) exhibited increased activity for anti-saccades (Fig. 2B). The activities were greater for anti-saccades than pro-saccades, started during saccade preparation, peaked shortly before movements, and often decreased abruptly during saccades. The preparatory activity before target presentation was attenuated in error trials, but the same neurons exhibited a transient activity around the time of erroneous pro-saccades (Fig. 2C). These properties of neuronal activity suggest that the cerebellar output signals from the dentate nucleus are responsible for generating anti-saccades and the monitoring of error trials.

The causal role of the cerebellar nucleus in anti-saccades has been confirmed by inactivation experiments (Kunimatsu et al., 2016; Fig. 2D). Injection of a small amount of GABA agonist (muscimol) increased the proportion of error trials for anti-saccades, while the performance of pro-saccades remained unchanged. However, the inactivation effects were relatively mild compared with those reported in the motor thalamus (Kunimatsu and Tanaka, 2010) and the frontal cortex (Condy et al., 2007). Furthermore, inactivation of the cerebellar nucleus somehow improved the anti-saccade performance. The red data points in Figure 2E compare the changes in reaction time and endpoint error for successful anti-saccades during inactivation. The data show that while the accuracy of anti-saccades worsens, the reaction time is reduced during inactivation. Because these changes correlated, the size of both effects might have been solely determined by the extent of inactivation in the cerebellar nucleus. Although decreases in anti-saccade accuracy are commonly observed following lesions in the thalamus and cortex, the decrease in latency is unique to the cerebellum; local lesions in the other structures generally increases anti-saccade latency (Guitton et al., 1985; Rivaud et al., 1994; Peterburs et al., 2011; Chan et al., 2015, but see Condy et al., 2007). These results suggest that the thalamus and cortex are closely linked with the generation of anti-saccade motor commands, while the lateral cerebellum may play a role in the deliberate control enabling slow accurate anti-saccades. It has also been shown that pharmacological inactivation of the globus pallidus slightly increases the rate of error trials, but does not alter movement parameters in successful anti-saccade trials (Yoshida and Tanaka, 2009), suggesting that this structure is somewhat remote from the pathways directly regulating eye movements.

During inactivation of the dentate nucleus, anti-saccades become faster and

inaccurate, whereas pro-saccade performance remains unchanged. These results suggest that the lateral cerebellum may modulate the proactive, but not reactive, control signals for saccades that might be further processed in the thalamocortical and cortico-basal ganglia pathways. In behavioral tasks with multiple processes such as anti-saccades, the brain often adopts proactive control strategies (Braver, 2012). One such strategy is to globally suppress any reactive response to reduce inappropriate impulsive choice in face with difficult tasks (Frank et al., 2007; Isoda and Hikosaka, 2008; Chen et al., 2010). A recent study also suggests that proactive inhibition for anti-saccades has another component for specific movements (Abegg et al., 2012). The increased error rate and reduced anti-saccade latency during inactivation of the cerebellum might result from the impairment of these controls. Another well-known strategy of proactive control is to optimize the speed and accuracy of movements, and its neuronal correlates in the cerebral cortex have been recently explored (Heitz and Schall, 2012; Hanks et al., 2014). Because the cerebellum is essential for accurate movements, signals from the lateral cerebellum to the frontal cortex might mediate the tradeoff between the latency and accuracy of anti-saccades.

For deliberate control, error detection is a key element to optimize behavioral strategy (Jocham and Ullsperger, 2009). The cerebello-thalamo-cortical pathways have been shown to play a role in error detection and the subsequent behavioral adjustment in the stop-signal reaction time task (Stuphorn et al., 2000; Ide and Li, 2011; Zhang and Li, 2012; Sajad et al., 2019). As mentioned above, a role for the lateral cerebellum in generating error-related scalp potentials for anti-saccades has been suggested (Peterburs et al., 2015). Although several laboratories have recently started to explore neuronal activity in the cerebellum during anti-saccades (Avila et al., 2013; Kunimatsu et al., 2016) or the stop-signal reaction time task (Prevosto and Sommer, 2018) in monkeys, the functional linkage of these neuronal activities with error monitoring and behavioral adjustment remains to be elucidated.

Timing of self-initiated movements

Involvement of the cerebellum in action timing has been demonstrated in relatively automatic, sensory-triggered movements. For example, the cerebellar cortex plays a crucial role in the learning of time intervals between conditioned and unconditioned stimuli in the eye blink reflex in rabbits (Perrett et al., 1993; Medina and Mauk, 2000) and rodents (Heiney et al., 2014b; Steinmetz and Freeman, 2014; Johansson et al., 2015; ten Brinke et al., 2015). In monkey smooth pursuit eye movements, the cerebellum is involved in changing the direction

of eye motion in a predictable and timely manner in response to the alteration of target trajectory (Medina and Lisberger, 2008; Yang and Lisberger, 2014). The cerebellum appears to enable these controls by linking sensory inputs and motor timing in the range from few hundred milliseconds to a second (Mauk and Buonomano, 2004).

The cerebellum is also involved in the timing of volitional movements. It has been widely accepted that the motor cortices and the basal ganglia are involved in the generation of self-initiated movements (Okano and Tanji, 1987; Romo and Schultz, 1992; Schultz and Romo, 1992; Lee and Assad, 2003). In patients with Parkinson's disease, the event-related scalp potentials related to movement preparation have been shown to be greatly attenuated (Jahanshahi et al., 1995; Ikeda et al., 1997; Renfroe et al., 2016). A functional imaging study examining the correlation between the amplitude of event-related potentials (contingent negative variation) and the local cerebral blood flow has shown that in addition to the medial frontal cortex, multiple subcortical areas, such as the motor thalamus, cerebellum, and striatum, are involved in generating preparatory activity (Nagai et al., 2004). In the motor thalamus, which lies within the pathways transmitting subcortical information to the cortex, individual neurons exhibit significant preparatory activity prior to self-initiated movements (van Donkelaar et al., 1999; Tanaka, 2007; Wang et al., 2018), and inactivation of these neurons delays self-timing (van Donkelaar et al., 2000; Tanaka, 2006). Because the signals in the thalamus have been shown to be essential for the maintenance of the delay period activity in the premotor cortex (Guo et al., 2017), it is important to understand the signals arising from the subcortical regions that regulate information in the thalamocortical pathways.

Recent studies examined the preparatory activities in the cerebellum (Ashmore and Sommer, 2013; Ohmae et al., 2017) and the striatum (Kunimatsu et al., 2018) using the eye movement tasks in monkeys. In the self-timed saccade task, animals were trained to make a self-initiated memory-guided saccade to the location of a previously presented brief visual stimulus following a mandatory delay period, which was indicated by color of the fixation point in each trial (400, 1000 and 2200 ms, Fig. 3A). Because no immediate external trigger for the saccade was given, the animals had to monitor elapsed time from the visual cue to determine saccade timing. Therefore, this task can be viewed as an oculomotor version of the time production task. Previous studies have suggested that sub-second time measurement involves the cerebellum, while that of seconds involves the basal ganglia (Lewis and Miall, 2003; Buhusi and Meck, 2005). Other studies have also suggested that the cerebellum measures a single time interval, while the basal ganglia process rhythmic timing (Grube et

al., 2010; Teki et al., 2011; Breska and Ivry, 2018). Therefore, it was expected that the neural response might differ between the cerebellum and striatum depending on the length of the mandatory delay intervals.

However, both structures contained neurons exhibiting significant reparatory activity in all delay conditions (Fig. 3B). Neurons in the cerebellar dentate nucleus showed ramping activity approximately 500 ms before self-timed saccades in any condition, whereas those in the caudate nucleus started the preparatory activity immediately after the visual cue, and the rate of increase in the firing rate depended on the length of the mandatory delay interval (Kunimatsu et al., 2018). Furthermore, when the time course of neuronal activity in each condition was analyzed by dividing the data according to saccade latency, the trial-by-trial variation of neuronal activity started earlier in the cerebellum but appeared late in the striatum (Fig. 3B).

In another study that examined neuronal activity in the cerebellar nucleus in more detail, the latency of self-timed saccades showed a good correlation with the rate of increase in the preparatory activity when the delay period was 1 second or shorter, whereas it correlated with the onset time rather than the rate of rise of preparatory activity when the delay period was longer than 2 seconds (Ohmae et al., 2017). The time courses of neuronal activity suggest that, when initiating movements in time, the pathway that includes the lateral cerebellum is involved in the adjustment of self-timing in each trial within a range of several hundred milliseconds. In addition, the basal ganglia pathway that includes the striatum may play a role in monitoring the passage of time relative to the entire interval. Inactivation of the cerebellar nucleus delayed self-timing when the delay period was shorter than 1 second, but the effect was small or even absent when the delay period was longer than 2 seconds indicating that the signals outside of the cerebellum determined the movement timing. In contrast, inactivation of the striatum altered movement timing in all conditions, but the effect was more evident as the delay was longer (Kunimatsu et al., 2018). Thus, the cerebellum and basal ganglia show different neural activities during the preparation of self-timed movements, suggesting that at least two types of neural mechanisms exist. Neuronal activity in the cerebellar nucleus correlates well with variations in motor timing in a given condition, which could be involved in the fine adjustment of self-timing. Neurons in the striatum flexibly change the time course of preparatory activity according to the intended interval, which may continuously keep track of elapsed time in the range from hundreds of milliseconds to several seconds.

The existence of these two neural mechanisms for self-timing has also been suggested by other behavioral and physiological experiments that examined signals preceding the preparatory activity. In one study, the pupil diameter was measured during the self-timed saccade task (Suzuki et al., 2016). In trials with a delay of 1 second, the pupil diameter just before the visual cue was inversely correlated with the subsequent saccade latency (Fig. 4A). However, no significant correlation was found for the latency of reactive saccades to the visual stimulus, indicating that the correlation in the self-timing task was attributed to the preparatory state during the task. This was also true when the animals were trained to generate self-timed saccades with two different intervals following a visual cue depending on the color of the equiluminant fixation points; there was an inverse correlation of self-timing with the pupil diameter in each delay condition (Fig. 4B). However, comparing the pupil diameter in the trial that responded slowly under the short (400–700 ms) condition and the trial that responded quickly in the long (700–1100 ms) condition, the pupil diameter was clearly smaller in the former than the latter, although the saccade latency was almost the same. These results suggest that the pupil diameter is linked with the mechanism to implicitly bias trial-by-trial latencies in each condition, but not with the mechanism to flexibly change the movement timing based on the instruction.

Another study examining the local field potentials (LFP) in the caudate nucleus during the same task showed an opposite relationship to that discussed in the previous paragraph (Suzuki and Tanaka, 2019). When different mandatory delay lengths were informed with the color of the fixation point, both the magnitude of visual response to the target cue in the contralateral visual field and the power of low frequency components of the LFP just before the target cue onset correlated with the length of the instructed delay period (Figs. 4C and D). These results suggest that the network state in the pathways through the striatum changes according to the intended interval, which may be responsible for the above-mentioned difference in the time course of preparatory activities for different delay intervals. Despite the clear difference in low-frequency spectral modulation between the interval conditions, no consistent change was observed when the data were compared between short and long latency trials in each condition (Figs. 4E). In relation to these findings, previous studies have shown that pupil size strongly correlates with neuronal activity in the locus coeruleus (Aston-Jones and Cohen, 2005; Joshi et al., 2016). It is worth noting that the locus coeruleus sends massive projections to the cerebellum (Olson and Fuxe, 1971) but exceptionally sparse projections to the striatum (Swanson and Hartman, 1975; Jones and

Yang, 1985).

Recently, the preparatory activity for self-initiated movements in the cerebellum has also been examined in rodents. It is difficult to train rodents in complex behavioral tasks like those used in primates, but in rodents it is possible to combine physiological experiments with detailed network analyses using a variety of molecular tools (Luo et al., 2018). The preparatory activity in the cerebello-thalamo-cortical pathway during locomotion has been shown to directly regulate the timing of predictive licking for future reward (Chabrol et al., 2019). The ramping activity in the whisker discrimination task has also been shown to be maintained in the cerebello-thalamo-cortical network and regulate self-timing (Gao et al., 2018). Because the dentate nucleus and the fastigial nucleus are involved in the former and the latter studies, respectively, the pathways generating the preparatory activity within the cortico-cerebellar network may depend on the behavioral conditions. Another recent study in rats has shown that there are two components of preparatory activity for self-timing, each of which is related to the trial-by-trial variation or the intended timing, and that each component is represented in different areas in the frontal cortex (Murakami et al., 2017). Furthermore, the study examining the active whisking in mice showed that the lateral cerebellum is also involved in higher-order movement parameters (Proville et al., 2014).

Prediction of periodic event timing

In addition to the adjustment of movement timing, the cerebellum is also involved in the temporal information processing in the absence of movements. For example, previous functional imaging studies have reported the increased activity in the cerebellum when remembering of certain rhythms (Sakai et al., 1999; Teki and Griffiths, 2016). Clinical studies have shown that patients with cerebellar lesions have a difficulty in discriminating the length of time intervals between brief tones (Grube et al., 2010; Breska and Ivry, 2018). According to a recent study of magnetoencephalography, the coherence at low frequency between the cortical areas and the cerebellum exhibit predictive entrainment during passive listening to periodic sound without movements (Fujioka et al., 2012).

Recent studies in nonhuman primates further explored the underlying neuronal mechanism of rhythm processing (Ohmae et al., 2013; Uematsu et al., 2017; Kameda et al., 2019). In the oddball detection task, a brief visual stimulus was presented repeatedly around the fixation point, and the animals were trained to make a saccade in response to the changes in the stimulus sequence (Fig. 5A). The interstimulus interval varied from trial to trial but

was constant in each trial. In half of the trials with a red fixation point, one repetitive stimulus was omitted at a random timing, while in the other half of the trials with a green fixation point, one stimulus in the series altered its color (from white to red). To detect stimulus omission, monkeys needed to learn the interstimulus interval and predict the timing of each next stimulus. However, no temporal prediction was necessary to detect a change in stimulus color.

During this task, Kameda et al. (2019) compared neuronal activities in the cerebellar dentate nucleus with those in the caudate. Figures 5B and C illustrate representative examples of cerebellar and striatal neurons, respectively. Both neurons exhibited periodic activity when the animals maintained fixation in the presence of periodic visual stimuli. Importantly, the activity increased as the repetition progressed; the direction of firing modulation was opposed to that expected from sensory adaptation that attenuates sensory responses to repeated stimuli. Furthermore, in both brain regions, the neural activity increased under the missing detection condition rather than the change detection condition, suggesting that they were involved in predicting the stimulus timing. Most neurons in the cerebellar nucleus showed a transient decrement in activity for each stimulus, and the firing rate peaked around the stimulus timing. In the striatum, the response to each stimulus was excitatory, and the peak of neuronal activity was lagged behind the stimulus onset. Because electrical stimulation applied to each recording site shortened saccade latency for stimulus omission regardless of saccade direction, these neuronal activities appeared to be important for the detection of stimulus omission (Uematsu et al., 2017; Kameda et al., 2019).

Interestingly, in both structures the magnitude of neuronal response to each stimulus varied significantly with stimulus interval. When the interstimulus interval was altered between 100 and 600 ms, all cerebellar nuclear neurons and the majority of caudate neurons increased their activity proportional to the interval (Ohmae et al., 2013; Kameda et al., 2019). In the cerebellum, both the amplitude of transient decrease in activity for each stimulus and the time course of recovery changed with the interval, resulting in peaks of neuronal activity around the time of the next stimulus in all cases (Fig. 6A). In the striatum, the amplitude of the transient increase in activity changed with the interstimulus interval, but the response terminated in about 300 ms following the stimulus regardless of the interval, and the level of activity varied at the next stimulus timing (Fig. 6B). Prediction of stimulus timing based on the time courses of the population activity revealed that neurons in the cerebellar dentate nucleus carried more accurate temporal information than those in the caudate nucleus at any

interstimulus interval (Fig. 6C).

Some neurons in the cerebellar dentate nucleus showed increased activity for stimulus omission in trials with short interstimulus intervals (Figs. 7A and B). In the previous experiments in the cerebellum, the color of the fixation point was identical for different oddball conditions (i.e., missing or deviation), and therefore the time course of neuronal activity during fixation was essentially the same between the conditions (Ohmae et al., 2013; Fig. 7A). Because most cerebellar neurons exhibited decreased activity for each repetitive stimulus as well as the deviant stimulus with different color, the neuronal firing rate just before saccades was greater in the missing oddball than in the deviant oddball conditions. This tendency was more remarkable when the stimulus interval was short (Fig. 7C). Such a neuronal modulation might be useful to represent the prediction error signals when a regular stimulus is unexpectedly omitted. In fact, when the recording sites in the cerebellar nucleus were pharmacologically inactivated, the response time for omission detection was prolonged more than that for detection of color deviation (Fig. 7D). However, unlike the modulation of neuronal activity, the inactivation effects were greater for longer interstimulus intervals. These results suggest that the signals in the cerebellar nucleus are more important for omission detection, but that their role is to predict the timing of the subsequent stimulus, rather than to represent errors for the missing stimulus. Consistent with this, latency of saccades correlated with cerebellar neuronal activity just before stimulus omission, but only for longer stimulus intervals (Ohmae et al., 2013). More recent experiments in humans have shown that temporal prediction of each stimulus is needed to detect the stimulus omission when the stimulus sequence is slower than 4 Hz, but other mechanisms, such as temporal grouping of repeated stimuli, are necessary for faster sequences (Ohmae and Tanaka, 2016). The neural network involving the cerebellum might be important for the former prediction mechanism, which operates for the slower stimulus sequence. Thus, neurons in the cerebellar dentate nucleus play a role in predicting the stimulus timing during the task.

One question that arises is whether the system involved in the temporal prediction share a network with that involved in self-timing described in the previous section. To answer this question, it is necessary to record from the same neurons during the two different tasks. As in the example shown in Figure 8, some neurons in the dentate nucleus responding strongly to the oddball task do not respond to the self-timing task, indicating that different groups of neurons may mediate temporal information in these two behavioral conditions. Although there might be some overlap, separate functional modules for sensory prediction

and self-timing might exist in the cerebellar dentate nucleus that send information to different systems in the cerebro-cerebellar network. In this regard, quantitative analysis of neuronal activity is needed in future studies, including the clarification of brain regions receiving these cerebellar output signals. In addition, it is important to examine in future studies how the local cerebellar network contributes to the generation of temporal prediction signals in the dentate nucleus described so far. A possible involvement of the olivary input might be of particular interest.

Synchronized movements

Synchronized movements have also been used to investigate the underlying mechanism of timing prediction in the cerebellum. Although subjects with a mild cerebellar lesion can perform periodic continuous movements normally, they often exhibit greater variability in timing during discontinuous rhythmic movements such as finger tapping (Spencer et al., 2003), especially when the movements are fast (Bo et al., 2008). This is consistent with the fact that rhythmic continuous movements and discrete movements are regulated by different neural mechanisms (Schaal et al., 2004). Although the timing of continuous movements can be determined in a state-dependent manner using internal cues such as contraction of adjacent muscles and joint angles, the initiation of discontinuous movements like tapping requires an additional mechanism that explicitly determines the timing of subsequent movements (Spencer et al., 2003).

Predictive synchronized movements such as spontaneous dance and clapping to music are commonly observed in everyday life. When merely listening to a certain rhythm, entrained neural activity occurs not only in the auditory cortex but also in the motor areas in the frontal cortex, the cerebellum, and the basal ganglia, suggesting the possible underlying mechanism of spontaneous synchronization (Chen et al., 2008; Geiser et al., 2012; Nozaradan et al., 2012; Kung et al., 2013). However, it is difficult to understand the biological significance of riding music; how stamping on rhythm helps survival in nature? Indeed, even if monkeys are trained for several years to press a button in response to sounds or lights presented at regular beats, the response time does not become less than a few hundred of milliseconds, whereas humans easily predict the stimulus timing and immediately start predictive synchronized movements (with zero reaction time) (Zarco et al., 2009). This has also been reported in eye movements. In monkeys, periodic smooth tracking (i.e., continuous movements) can be performed with zero phase lag (Lisberger et al., 1987; Keller and Heinen,

1991), but periodic saccadic eye movements cannot be synchronized with regularly alternated visual stimuli (Fuchs, 1967). In contrast, some animals, such as parrots and elephants, exhibit spontaneous movements synchronized with periodic sounds, leading to the hypothesis that predictive synchronization might be relevant to the ability of vocal learning (Patel et al., 2009). However, given the difficulty of the behavioral tasks introduced so far, it is unlikely that monkeys lack the ability of predictive synchronization. Another possibility is that humans and other vocal learners may have an internal motivation for spontaneous synchronization, which monkeys and other vocal non-learners may lack. Consistent with this possibility, it has been shown that when humans generate periodic movements synchronized with external rhythms, neural activity in the reward system increases compared with when movements are randomly generated in time (Kokal et al., 2011; Trost et al., 2014). Indeed, clapping and dancing with music are certainly fun.

To examine the neural mechanism of synchronized movements, Takeya et al. (2017, 2018) trained monkeys to track alternately presented visual stimuli with their eyes (Fig. 9A). The duration of stimulus presentation was chosen randomly for each trial but was constant within the trial. To induce synchronized movements, a drop of juice reward was given for every predictive saccade that landed target location within ± 80–160 ms of its onset (± 20% of the stimulus onset asynchrony; SOA). Because the stimulus interval varied from trial to trial, the initial few saccades in each trial were reactive with latencies of approximately 200 ms. However, saccades in the middle of the sequence became predictive and synchronized with the stimulus (Figs. 9B and C). When reward was given for every reactive saccade (> 150 ms) in the other block of trials, the animals were able to switch their behavioral mode to generate only reactive saccades to the same stimulus sequence. A recent study has also shown that monkeys generate predictive tapping when such movements are properly reinforced by immediate rewards (Gamez et al., 2018). Thus, like humans, monkeys are capable of performing predictive synchronization, while unlike humans, synchronized movements are never spontaneously triggered and need to be motivated by external rewards.

During synchronized saccades, neurons in the cerebellar dentate nucleus exhibit strong periodic activity (Fig. 9D). Many neurons exhibit preparatory activity that peaks shortly before saccades or the onset of visual stimulus. Previous functional imaging studies in humans reported increased activity in the cerebellum and basal ganglia during synchronized movements (Bijsterbosch et al., 2011; Kung et al., 2013; Lee et al., 2016). Using the synchronized saccade paradigm developed so far, the underlying neuronal

mechanisms can be explored in experimental animals in future studies.

Summary and future directions

In this article, we reviewed recent studies on the role of the cerebellum in motor preparation and prediction of timing. Studies using the anti-saccade task have shown that the cerebellum plays a role in addition to the cortico-basal ganglia pathways. In humans, the volume of the posterolateral cerebellum correlates with the magnitude of error-related potentials recorded from the frontal cortex during anti-saccades (Peterburs et al., 2015). In monkeys, neurons in the cerebellar dentate nucleus exhibit strong preparatory activity and a transient activity for erroneous pro-saccades in the anti-saccade trials (Kunimatsu et al., 2016). During inactivation of these neurons, the rate of error trials slightly increased and the anti-saccades in successful trials became less accurate and had shorter reaction times. These results suggest that the cerebellum is important for deliberate control of saccades and might play a role in proactive inhibition and behavioral adjustment. Recent functional imaging studies using the stop-signal reaction time task also suggest that the cerebello-thalamo-cortical pathways are essential for error detection and subsequent behavioral adjustment (Ide and Li, 2011; Zhang and Li, 2012). In future studies, it will be important to examine the origin of the error-related scalp potentials during anti-saccades and the impacts of cerebellar neuronal activity on eye movements in both current and subsequent trials.

Recent studies using the self-timing task have shown that the time course of preparatory activity differs between neurons recorded from the cerebellar dentate nucleus and the striatal caudate nucleus. Neurons in the cerebellum start their activity about half a second before self-initiated movements regardless of the length of the mandatory delay period, while neurons in the striatum exhibit preparatory activity throughout the delay period (Kunimatsu et al., 2018). In contrast, neuronal correlates of trial-by-trial variation of self-timing first appear in the cerebellum and are later found in the striatum. Results of inactivation experiments suggest that the striatum controls movement timing in any delay condition, whereas the cerebellum may play a role in fine adjustment of self-timing in the range of several hundred milliseconds (Kunimatsu et al., 2018). Based on the time course of neuronal activity, it has been hypothesized that there are at least two distinct preparatory signals, each being relevant to the intended time interval and the stochastic variation in self-timing. This hypothesis has also been supported by other indicators, including pupil diameter (Suzuki et al., 2016) and low-frequency oscillations in the striatum (Suzuki and Tanaka, 2019). Future

studies need to elucidate how these different signals for self-timing are processed within the global cortico-subcortical network representing preparatory activity, which involves the dorsomedial frontal cortex (Merchant et al., 2011; Wang et al., 2018), the posterior parietal cortex (Maimon and Assad, 2006; Jazayeri and Shadlen, 2015) and the motor thalamus (van Donkelaar et al., 1999; Tanaka, 2007). Furthermore, because neuromodulators such as dopamine (Coull et al., 2011; Kunimatsu and Tanaka, 2016; Yc et al., 2019), acetylcholine (Kunimatsu and Tanaka, 2016) and noradrenaline (Suzuki and Tanaka, 2017) have been shown to play a role in self-timing, investigation of how these substances modulate the signals within the network is necessary. Finally, the roles of the overlying cerebellar cortex in the generation of ramping activity in the cerebellar nucleus need to be clarified. The increased activity in the cerebellar nucleus likely reflects pausing activity in the Purkinje cells in the cerebellar cortex (Ishikawa et al., 2014a; Heiney et al., 2014a; Chabrol et al., 2019). The direct inputs from the mossy fibers may also contribute to the activity in the deep cerebellar nuclei because the preparatory activity already exists in the mossy fibers (Ishikawa et al., 2014b) and the granule cells (Wagner et al., 2019). A recent study successfully identified different types of neurons in the primate cerebellar cortex during hand movements (Tomatsu et al., 2016). In future studies, comparison of signals within the local circuitry may reveal the way of signal processing in the cerebellar cortex and nucleus.

The cerebellum is also involved in predicting the timing of periodic events in the absence of movements. Studies using the oddball detection task in monkeys have reported periodic neuronal activity in the cerebellar dentate nucleus and the caudate nucleus in the striatum that increases gradually with stimulus repetition (Ohmae et al., 2013; Uematsu et al., 2017; Kameda et al., 2019). The peak of the neuronal firing rate in the cerebellum occurs around the time of stimulus onset regardless of the frequency of periodic stimuli, and the prediction of stimulus timing based on the time course of neuronal activity is more accurate in the cerebellum than the striatum. Although some neurons in the cerebellar nucleus exhibit a strong rebound activity in response to stimulus omission in trials with short interstimulus intervals, the effects of inactivation are more pronounced for longer interstimulus intervals (Ohmae et al., 2013). Given that detection of stimulus omission in humans relies on temporal prediction only when stimulus frequency is less than 4 Hz (Ohmae and Tanaka, 2016), the predictive signals in the cerebellum may be used in trials with longer interstimulus intervals. However, the transient activity found in trials with a short interstimulus interval can be viewed as the prediction error signal for stimulus omission, and this signal is possibly to be

used in other behavioral conditions. Because some neurons involved in the oddball detection task show no or only weak preparatory activity in the self-timing task, there might be multiple functional modules in the cerebellar nucleus for different timing tasks.

Synchronized movements to periodic stimuli such as tapping are useful for examining cerebellar functions (Spencer et al., 2003; Matsuda et al., 2015). Although it has been thought that vocal non-learners lack the ability of predictive synchronization (Patel et al., 2009), recent studies have successfully trained monkeys to generate synchronized eye or hand movements through reinforcement learning (Takeya et al., 2017; Gamez et al., 2018). Previous functional imaging studies in humans have shown that the activity of the cerebellum and striatum increases during synchronized movements compared with reactive movements (Lee et al., 2016). It is expected that a detailed neuronal mechanism can be clarified by using non-human primates.

Recent studies in monkeys have shown that neurons in the motor cortices exhibit an early excitation and subsequent inhibition in response to electrical stimulation applied to the superior cerebellar peduncles, and that the later inhibitory response predominates the earlier excitatory response in duration and amplitude (Nashef et al., 2018). In addition, the prolonged low-frequency stimulation applied to the superior cerebellar peduncles reduces the input from the cerebellum to the motor cortex (Nashef et al., 2019), possibly due to the high-pass property of the thalamic relay neurons (Gornati et al., 2018). These facts indicate that the output node of the cerebellum does not simply send excitatory signals to the cerebral cortex via the thalamus, and that the information might be modified by the ascending pathways. Future research should take this point into consideration.

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Figure legends

Figure 1. Diagram of the motor system. Modified from Allen and Tsukahara (1974).

Figure 2. Role of the cerebellum in anti-saccades. (A) Trial type was indicated by the color of the fixation point (FP). A white target spot appeared 16° eccentrically at the time of the FP offset. Animals were required to make a saccade toward (pro-saccade) or away from (anti-saccade) the target. (B) Neuronal activity in the cerebellar dentate nucleus in the anti-saccades task. The yellow symbol on each raster line indicates the time of saccade. (C) Time courses of the population activity for correct anti-saccade, erroneous anti-saccade, and correct pro-saccade trials. (D) Traces of eye position before and during inactivation of the left dentate nucleus. Data are aligned with the right target onset. Red traces indicate error trials. The open triangles indicate the time of target relocation (to the left) in the anti-saccade task. Note that in most error trials, the animal redirected the eyes to the correct location (left) before the relocation of the target. (E) Correlation between the changes in reaction time and accuracy. Numbers on each panel indicate Pearson's correlation coefficient (r) and critical p-value. Adapted from Kunimatsu et al. (2016).

Figure 3. Neuronal activity in the striatum and the cerebellar nucleus during a self-timed saccade task. (A) Sequence of events in the self-timed saccade task (upper panel). During central fixation, a cue flashed briefly in the peripheral visual field. Monkeys were required to remember the cue location and maintain fixation until the end of the predetermined mandatory delay interval that was indicated by the color of the fixation point. Animals received a reward if they correctly made a self-timed memory-guided saccade to the cue location after the mandatory delay period. (B) Timing of trial-by-trial variation of ramping activity. For each condition, trials were divided into three groups according to saccade latency. Inverted triangles indicate the time when the traces of the normalized neuronal firing rate started to diverge. Note that the trial-by-trial variation started earlier in the cerebellum than the striatum for medium and long intervals. Modified from Kunimatsu et al. (2018).

Figure 4. (A) Time courses of pupil diameter during the self-timed task. Trials were divided into three equally sized groups according to saccade latency. Red and blue traces represent the mean (± SE) pupil size for the earliest and latest saccade groups, respectively. The top bracket represents the time window used for quantitative measurement. Right, The same data aligned with saccade initiation (black triangle). (B) Relationship between pupil size and saccade latencies in two different interval conditions. Red and blue dots indicate short and

long interval conditions, respectively. Data points indicate the means (±95% CIs) of pupil size and saccade latency across 10 sessions. (C) Color-coded power spectra of LFPs in the caudate nucleus in the self-timed saccade trials. Zero in the abscissa indicates cue onset. (D) Mean power spectra during the pre-cue period for the same monkey as in C. (E) Pre-cue spectral modulation within and across interval conditions. For each interval condition, the data were divided into two groups according to saccade latency Blue and red represent short and long groups, respectively. The dots indicate the means (± 95% confidence intervals) for trials with contraversive saccades. The spectral power of the two groups were similar in all three conditions for ipsiversive saccades (not shown). Modified from Suzuki et al. (2016) and Suzuki and Tanaka (2019).

Figure 5. Neurons in the cerebellar dentate nucleus and the striatum during the oddball detection task. (A) Sequence of events in the task. During central fixation, a saccade target appeared horizontally, and then a brief stimulus surrounding the FP was presented repeatedly at a fixed inter-stimulus interval. Animals were trained to make a saccade in response to the stimulus omission (missing condition) or the changes in stimulus color (deviant condition). Different FP color indicated the different oddball conditions. (B, C) Example neurons in the dentate nucleus and caudate nucleus that exhibited periodic activity during fixation. Data were aligned with either the first stimulus (left) or the oddball (right). Panels A and C reproduced from Kameda et al. (2019).

Figure 6. Time courses of neuronal activity. (A, B) The population activities in the cerebellum (A) and the striatum (B) for different inter-stimulus intervals are aligned with the stimulus just before the oddball. Dashed portion of the traces indicates the data during 100 ms following the stimulus omission. (C) Prediction error of stimulus timing for each interval. Note that temporal prediction was better in the cerebellum than the striatum for all three intervals. Adapted from Ohmae et al. (2013) and Kameda et al. (2019).

Figure 7. Transient activity in the cerebellar dentate nucleus in the missing oddball trials, with only a minimal role in omission detection. (A) Time courses of neuronal activity in the two oddball conditions. Note that the firing rate following the occurrence of oddball was greater in the missing (red) than the deviant (blue) conditions. (B) Data for the neuron in A are realigned with saccades. Eye position traces are shown only for ipsiversive saccades. (C) Comparison of presaccade activity between conditions (missing divided by deviant) for different inter-stimulus intervals. Error bars indicate 95% confidence intervals. (D) Changes

in saccade latency during inactivation of the dentate nucleus in different conditions. Note that the inactivation effects were greater for longer stimulus intervals and for the missing oddball condition. Modified from Ohmae et al. (2013).

Figure 8. Activity of a single neuron recorded from the cerebellar dentate nucleus during the two different timing tasks. This neuron exhibited a significant periodic activity in the oddball detection task but showed virtually no firing modulation in the self-timed saccade task.

Figure 9. Neuronal correlates of synchronized movements. (A) Sequence of events in the synchronized saccade task. Two unfilled white square landmarks were presented horizontally throughout the trial. After a random fixation period (blue rectangle), the saccade target (red) alternated at the landmark locations (white square contours) with stimulus onset asynchrony (SOA) that was constant within each trial but varied from trial to trial. (B) Circular histogram of saccade latency for the 1st–2nd (white) and 7–8th (red) target steps in the sequence. 0° and 180° indicate the timing of right and left target onset, respectively. (C) Mean saccade latency as a function of target sequence. Error bar indicates ± 1SD. (D) A cerebellar dentate nuclear neuron exhibiting periodic activity during the task. Data are aligned with target onset (vertical blue and red lines). Green symbol on each raster line indicates saccade timing. A–C, modified from Takeya et al. (2017).

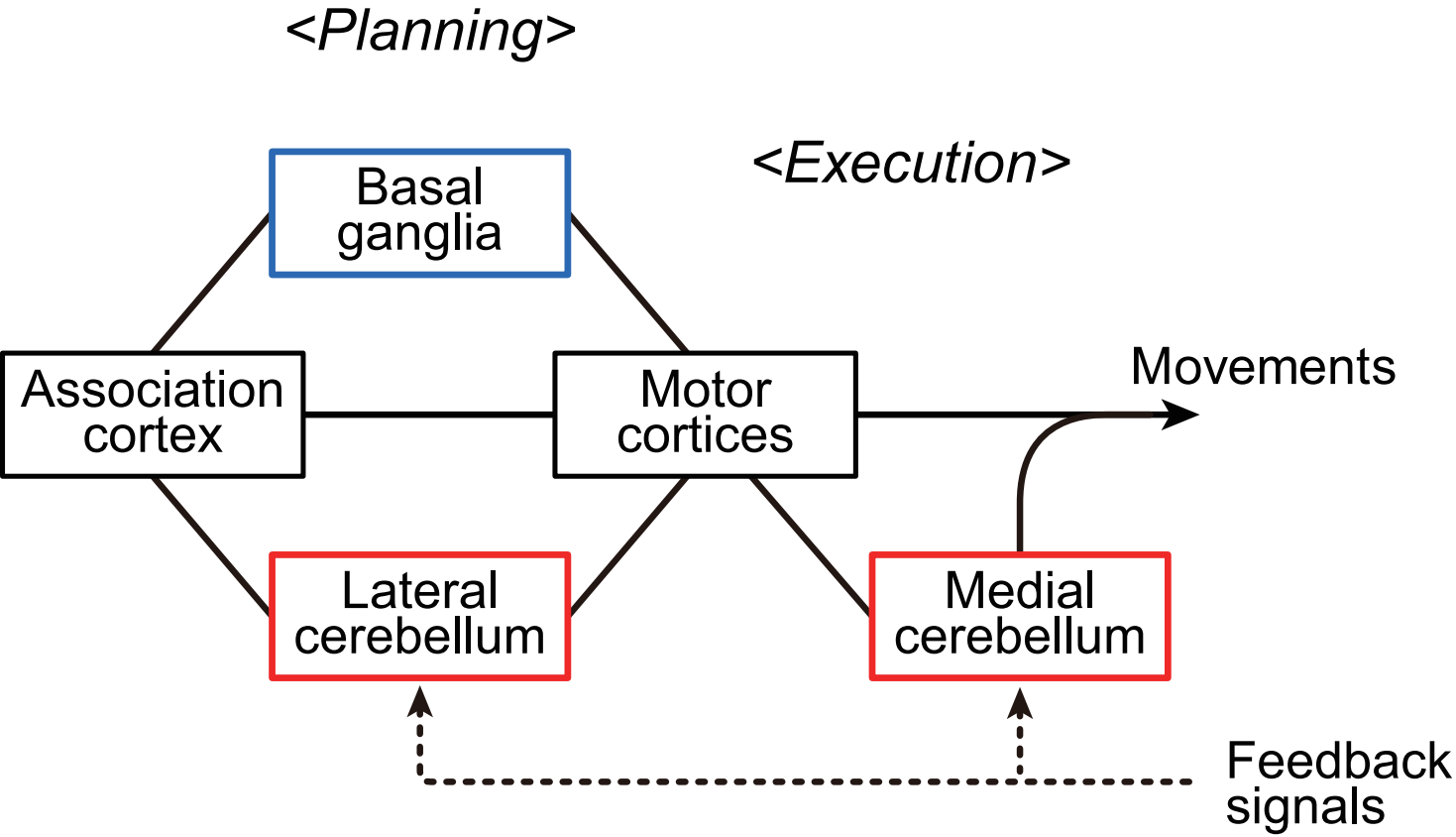
<Planning>
<Execution>
Basal ganglia
Association cortex
Motor cortices
Movements
Lateral cerebellum
Medial cerebellum
Feedback signals

Figure 1

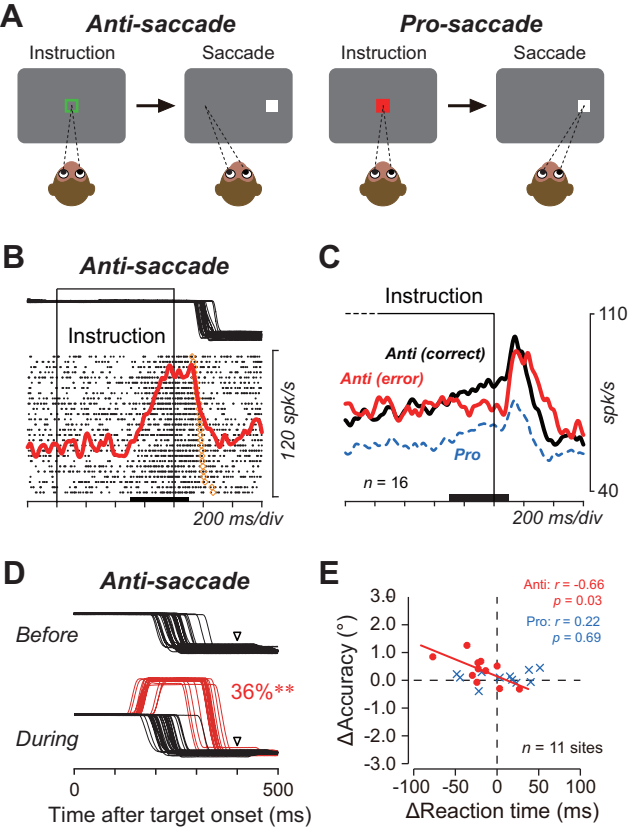
A
Anti-saccade
Instruction
Saccade
Pro-saccade
Instruction
Saccade
B
Anti-saccade
Instruction
120 spk/s
200 ms/div
C
Instruction
110
Anti (correct)
Anti (error)
spk/s
Pro
n = 16
40
200 ms/div
D
Anti-saccade
Before
36%**
During
0
500
Time after target onset (ms)
E
Anti: r = -0.66
p = 0.03
Pro: r = 0.22
p = 0.69
3.0
2.0
1.0
0.0
-1.0
-2.0
-3.0
ΔAccuracy (°)
n = 11 sites
-100
-50
0
50
100
ΔReaction time (ms)

Figure 2

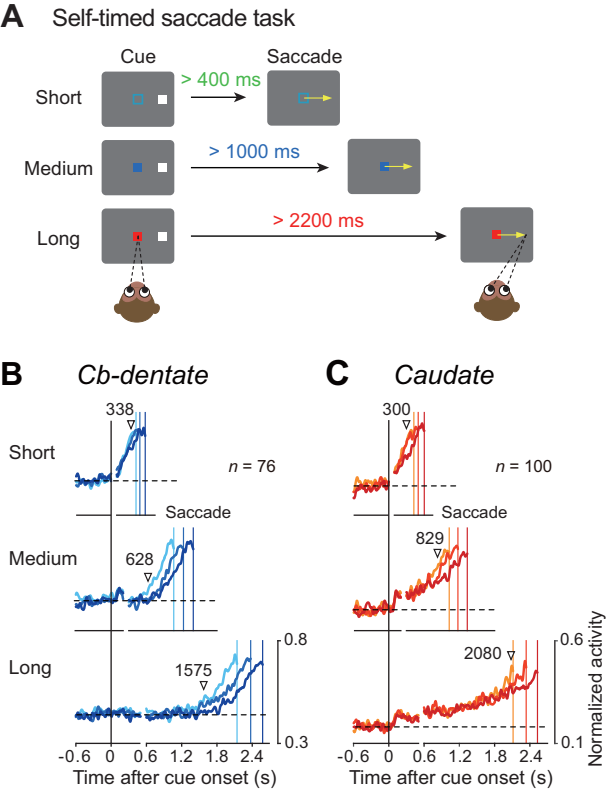
A
Self-timed saccade task
Cue
Saccade
Short
> 400 ms
Medium
> 1000 ms
Long
> 2200 ms
B
Cb-dentate
338
Short
n = 76
Saccade
Medium
628
1575
Long
0.8
0.3
-0.6 0 0.6 1.2 1.8 2.4
Time after cue onset (s)
C
Caudate
300
n = 100
Saccade
829
2080
0.6
0.1
-0.6 0 0.6 1.2 1.8 2.4
Time after cue onset (s)
Normalized activity

Figure 3

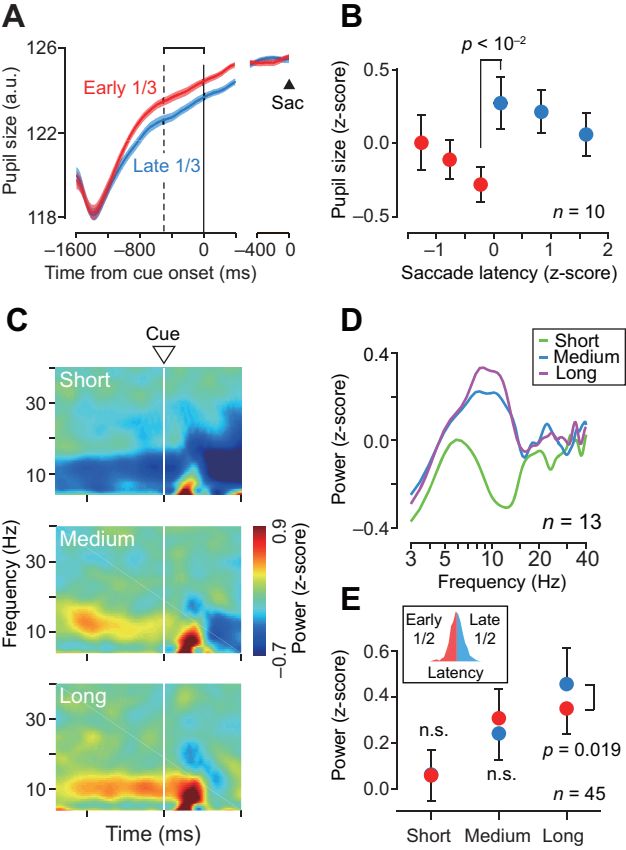
A
126
122
118
Pupil size (a.u.)
Early 1/3
Late 1/3
Sac
−1600
−800
0
−400
0
Time from cue onset (ms)
B
p < 10−2
0.5
0.0
−0.5
Pupil size (z-score)
n = 10
−1
0
1
2
Saccade latency (z-score)
C
Cue
Short
Medium
Long
30
10
Frequency (Hz)
0.9
−0.7
Power (z-score)
Time (ms)
D
Short
Medium
Long
0.4
0.0
−0.4
Power (z-score)
n = 13
3
5
10
20
40
Frequency (Hz)
E
Early 1/2
Late 1/2
Latency
0.6
0.4
0.2
0.0
Power (z-score)
n.s.
n.s.
p = 0.019
n = 45
Short
Medium
Long

Figure 4

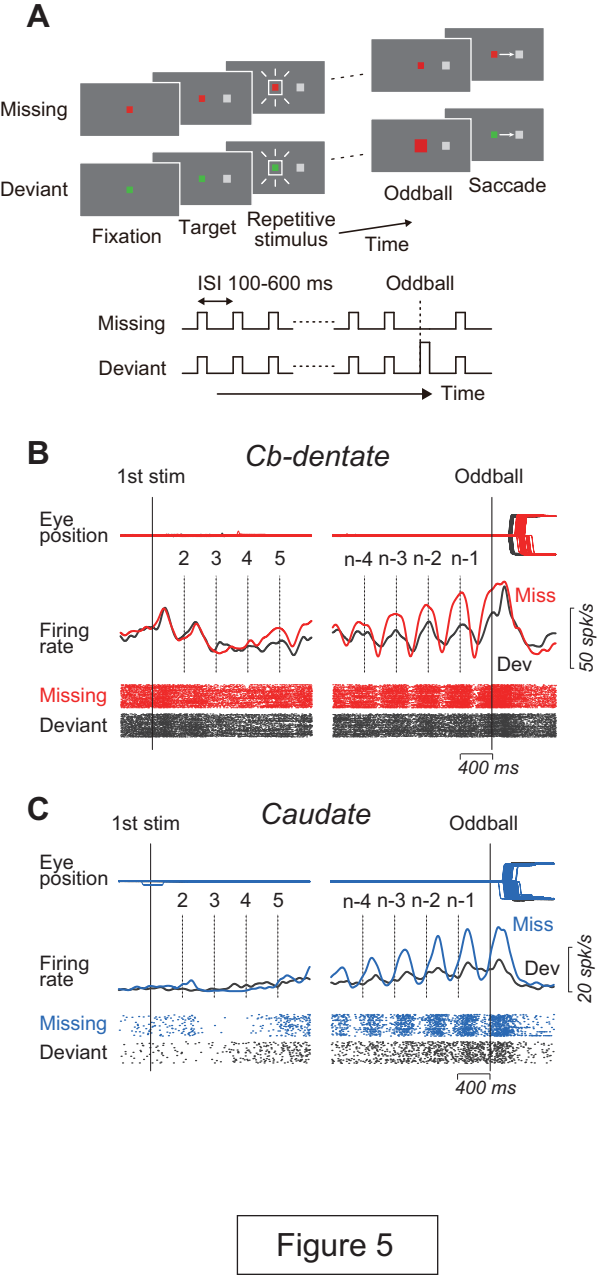
A
Missing
Deviant
Fixation
Target
Repetitive stimulus
Time
Oddball
Saccade
ISI 100-600 ms
Oddball
Missing
Deviant
Time
B
Cb-dentate
1st stim
Oddball
Eye position
2 3 4 5
n-4 n-3 n-2 n-1
Miss
Dev
Firing rate
50 spk/s
Missing
Deviant
400 ms
C
Caudate
1st stim
Oddball
Eye position
2 3 4 5
n-4 n-3 n-2 n-1
Miss
Dev
Firing rate
20 spk/s
Missing
Deviant
400 ms

Figure 5

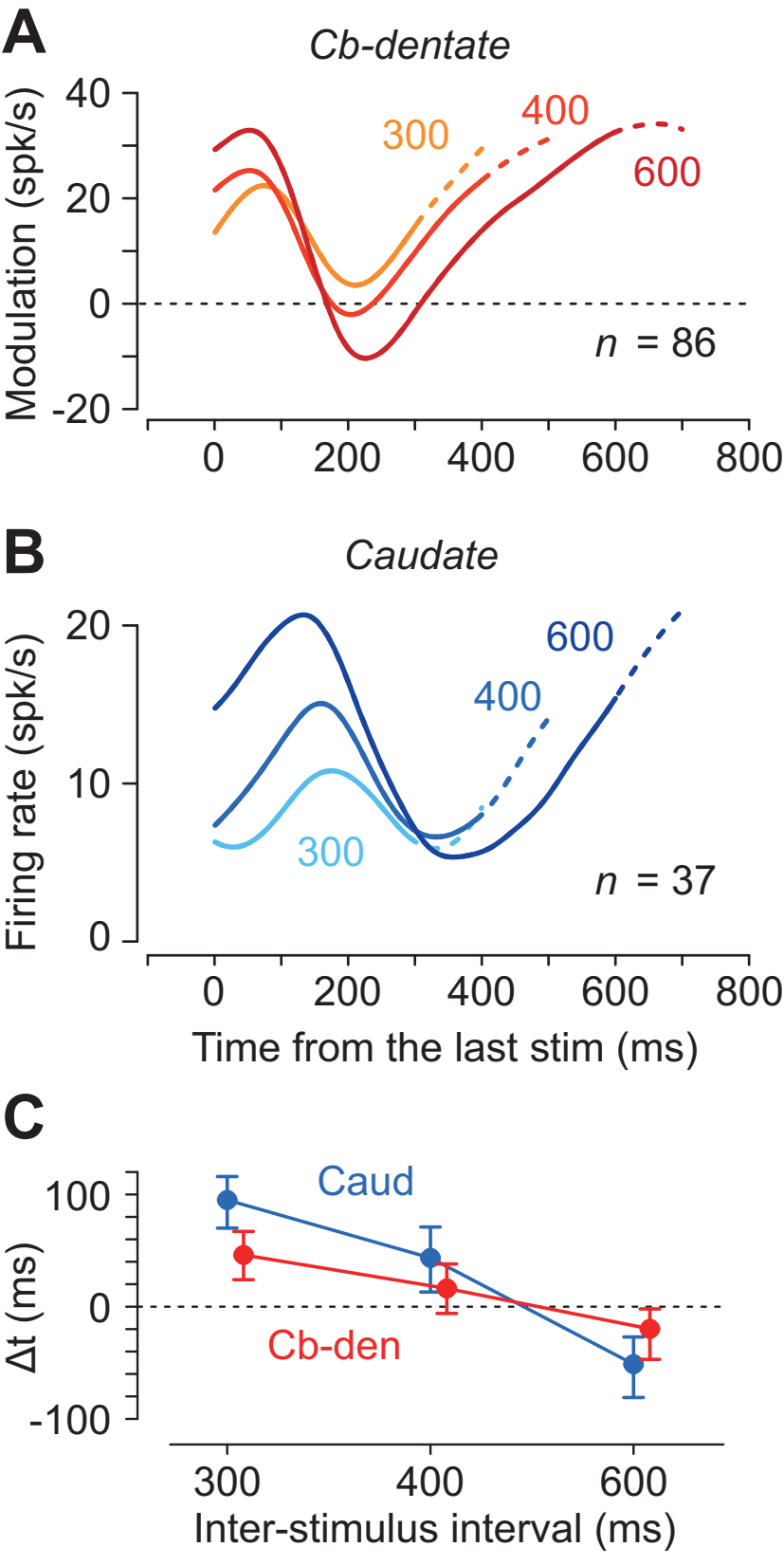
A
Cb-dentate
Modulation (spk/s)
40
20
0
-20
300
400
600
n = 86
0
200
400
600
800
B
Caudate
Firing rate (spk/s)
20
10
0
600
400
300
n = 37
0
200
400
600
800
Time from the last stim (ms)
C
Δt (ms)
100
0
-100
Caud
Cb-den
300
400
600
Inter-stimulus interval (ms)

Figure 6

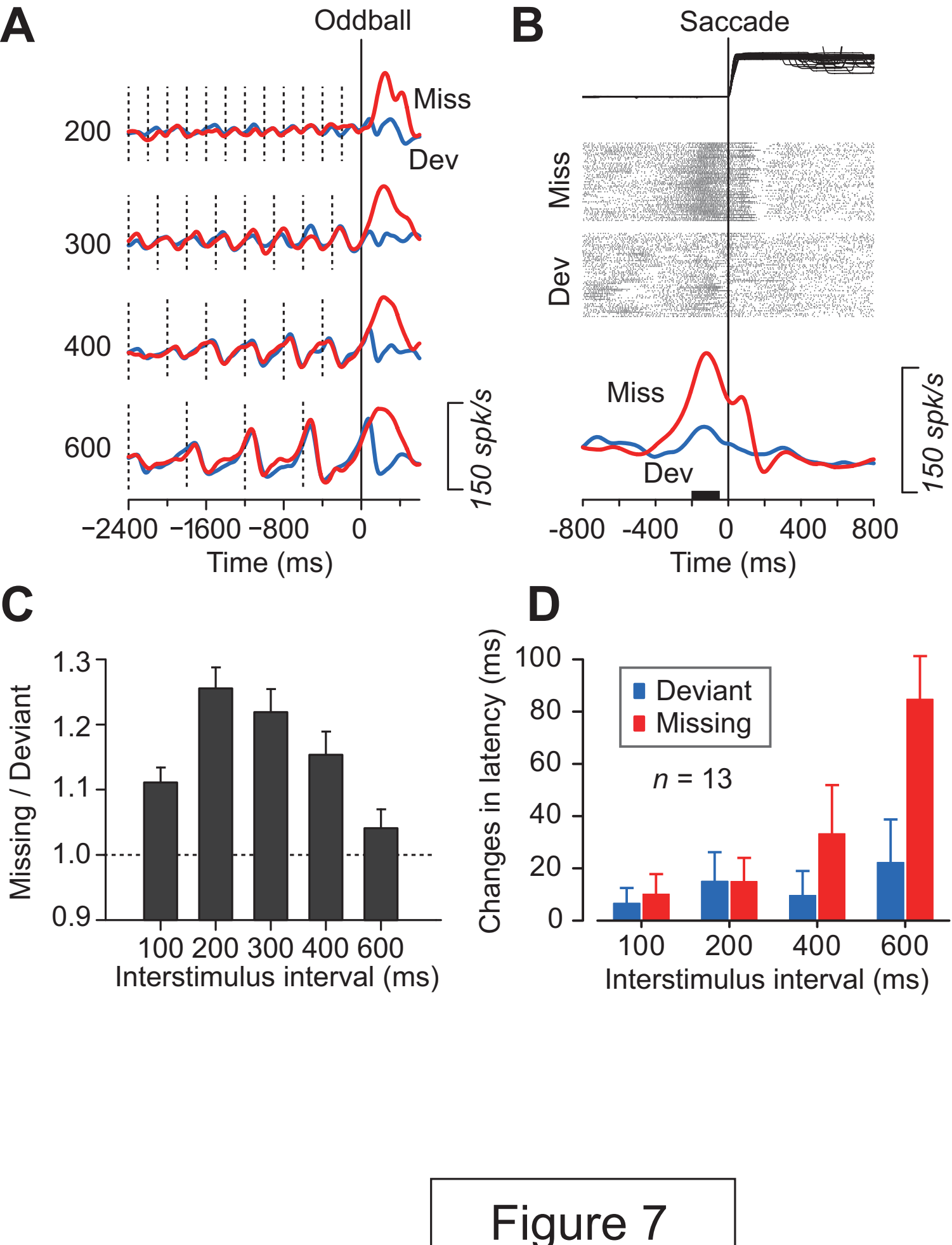
A
Oddball
Miss
Dev
200
300
400
600
150 spk/s
−2400 −1600 −800 0
Time (ms)
B
Saccade
Miss
Dev
Miss
Dev
150 spk/s
-800 -400 0 400 800
Time (ms)
C
Missing / Deviant
1.3
1.2
1.1
1.0
0.9
100 200 300 400 600
Interstimulus interval (ms)
D
Changes in latency (ms)
100
80
60
40
20
0
Deviant
Missing
n = 13
100 200 400 600
Interstimulus interval (ms)

Figure 7

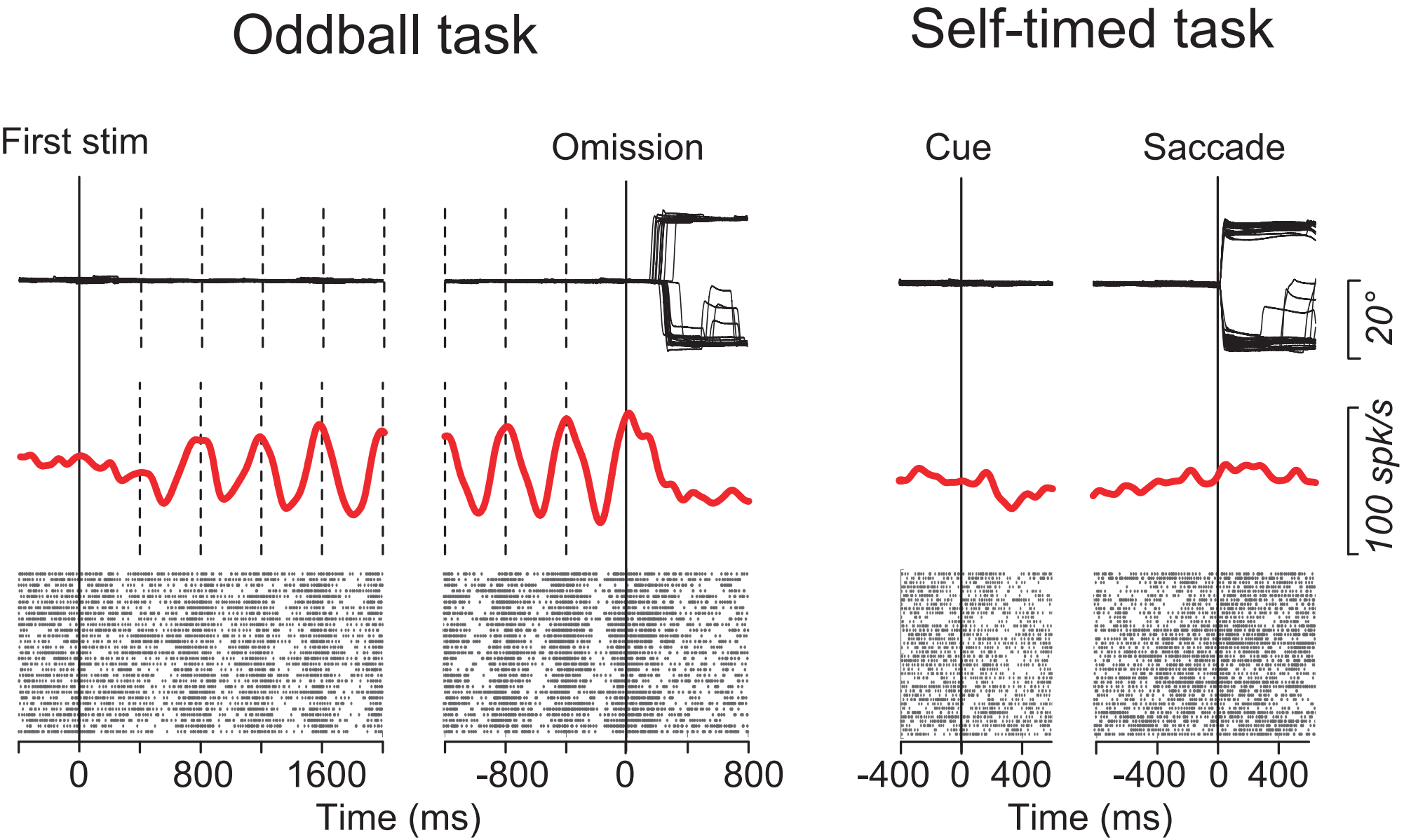
Oddball task
Self-timed task
First stim
Omission
Cue
Saccade
20°
100 spk/s
0
800
1600
-800
0
800
-400
0
400
-400
0
400
Time (ms)
Time (ms)

Figure 8

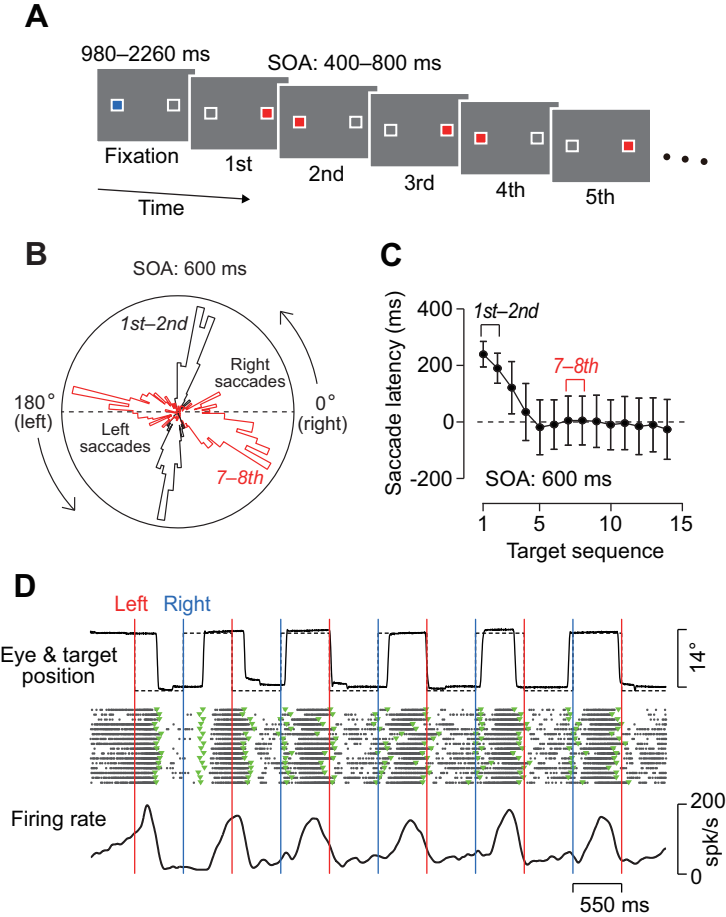
A
980–2260 ms
SOA: 400–800 ms
Fixation
1st
2nd
3rd
4th
5th
Time
B
SOA: 600 ms
1st–2nd
Right saccades
180°
(left)
0°
(right)
Left saccades
7–8th
C
Saccade latency (ms)
400
200
0
-200
1st–2nd
7–8th
SOA: 600 ms
1
5
10
15
Target sequence
D
Left
Right
Eye & target position
14°
Firing rate
200
spk/s
0
550 ms

Figure 9