- Title:

Novel behavioral tasks to explore cerebellar temporal processing in milliseconds in rats

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- ABSTRACT:

Temporal processing in milliseconds has been reported to rely on the cerebellum; however no detailed neuronal mechanisms have been published yet. This is because there are too few studies on the relationship between temporal processing in milliseconds and cerebellar neuronal spikes that organize behavioral timing. To demonstrate this relationship, it is necessary to record the spike activity while the animal is performing a behavioral task that requires specific temporal processing in milliseconds. In this study, we describe two novel timing tasks. These behavioral tasks comprise the following schedules: fixed ratio (FR) and differential reinforcement of low rate (DRL). This paper describes the behavioral differences between the absolute timing of individual intervals (duration-based timing) and the relative timing of rhythmic sequences (beat-based timing) in these novel tasks.

- Keywords:

Temporal processing, motor timing, rat behavior, DRL schedule, cerebellum

It is important for organisms to precisely predict when and where an event arises and to adequately act in a timely manner. Previous studies reported that temporal processing has been categorized into 4 timescales: microseconds, milliseconds, seconds, and circadian rhythms. Moreover, these are governed by different neuronal mechanisms [1, 2]. For instance, temporal processing in milliseconds has been reported to rely on the cerebellum; however, detailed neuronal mechanisms remain largely unclear [1].

To explore the relationship between cerebellar neural activity and temporal processing, some studies have shown a relationship between the response time of conditioned reflexes and neuronal activity in the cerebellar cortex [3, 4]. However, fewer studies have been reported on the relationship between the cerebellar neuronal spikes that organize voluntary-movement timing and temporal processing in milliseconds. Although previous studies have suggested that the cerebellar cortex is associated with the execution of well-timed voluntary movements [5, 6, 7], they observed only the voluntary movements of which timing was animals' autochthonous pace and did not control temporal properties by experimenter. Therefore, it is necessary to analyze spike activity when an animal is working voluntarily with sub-second timing information.

Besides the above problem, the question regarding which temporal coordination during continuous or discrete events precedes cerebellar timing functions remains controversial. Grube and colleagues (2010) [8] used the continuous transcranial magnetic theta-burst stimulation (cTBS) to investigate which cerebellar timing functions occurs between duration-based and beat-based timing. Duration-based timing is a function that counts absolute time between discrete events. Alternatively, beat-based timing measures the continuous inter-event intervals that have a rhythmic sequence. The above authors concluded that the cerebellar obligatory function of time perception lies in the absolute timing of single intervals (duration-based timing) rather than in the relative timing of rhythmic sequences (beat-based timing). In contrast, Ohmae and colleagues (2013) [9] demonstrated that the cerebellar dentate nucleus plays a major role in the prediction of repetitive-event timing. Therefore, to detect cerebellar spike activity that contributes to such temporal processing, it is necessary to record the cerebellar spike activity during the timing behavior that requires both duration-based and beat-based timings. Thus far, no study has reported the behavioral characteristics of duration-based and beat-based timings in experimental animals.

To resolve this, we devised 2 behavioral timing tasks. Both behavioral tasks include the fixed ratio (FR) and differential reinforcement of low rate (DRL) reinforcement schedules. These novel tasks enable rats to represent the information regarding duration-based or beat-based timings with almost identical movements. We trained the rats in these tasks and identified their behavioral characteristics that are crucial in comparing the cerebellar activities related to duration-based timing with those related to beat-based timing.

To identify the cerebellar spike patterns for temporal processing, the spikes during temporal processing in milliseconds should be compared with those during supra-second processing. Therefore, we assessed a supra-second temporal processing task. Because sudden shifts in the DRL value can disrupt behavioral performance [10], we provided a DRL criterion for naive rats and evaluated the influence of the shift effect.

10 male Wistar albino rats (Shimizu Laboratory Supplies, Kyoto, Japan) were used in the experiments. All rats were provided lab chow (1–3 h after each daily training session) in amounts sufficient to maintain approximately 80%–85% of their *ad libitum* weight. They were allowed free access to water along with daily light exposure between 08:00 and 21:00. All experiments were conducted between 10:00 and 20:00 h as per the *Guidelines for Care and Use of Laboratory Animals at Kyoto University* (2007), with approval from the Animal Research Committee of Kyoto University.

The rats were trained in the behavioral tasks in an operant chamber 22 × 32 × 45 cm (Ohara Ika, Tokyo, Japan). One chamber wall had a capacitance touch switch (14 ×15 mm) near the center of the wall and 55 mm above the floor to detect behavioral touch responses of the rats. On the opposite chamber wall, a food dispenser behind the wall delivered 25-mg food pellets to a food magazine located at the center of the wall, 10 mm above the floor. A brief tone sounded every time the dispenser delivered a pellet. A personal computer (NEC, Tokyo, Japan) and the Arduino Mega 2560 (Arduino Software, Italy) controlled the apparatuses.

The behavioral tasks require that a rat reach out 1 of its paws and touch a switch at regular fixed intervals of 500 or 1500 ms. When the rats failed to wait during the fixed intervals, the current trial was canceled by sounding an error buzzer tone and was started again (DRL schedule). Therefore, to succeed in each trial, the rats had to perceive the interval times between the touch responses. When fixed numbers of successive touch responses were successful, the rats were rewarded with a food pellet in that trial. We call that a "tandem FR *x* DRL *y* ms schedule."

If the required number of responses (FR criterion) is 2, then the rats must generate only 1 inter-response time (IRT). When the rats have sufficiently learned the task, they can precisely predict the shortest IRT that passes the criterion (DRL criterion value). Consequently, the behavioral response is based on absolute, duration-based timing. In contrast, when the FR criterion is > 2, the rats have to generate multiple IRTs. For example, when the FR criterion is 3, the rats have to generate IRT 2 times. Therefore, the rats touch the switch continuously with regular intervals, and the touches begin to yield some rhythms. We postulate that such behavior corresponds to beat-based timing.

Because it is possible that the rats learned absolute time by repetition even when the FR criterion is >2, it can be said that the duration-based and beat-based timings are interdependent. However, there must be an effect of succession of responses (i.e., relative timing) under the FR ≥ 3 schedules. While successive responses are generated, the existence of preceding response(s) affects the timing of next one(s). The effect of succession for temporal processing has been demonstrated in several former studies [8, 11]. Therefore, we could infer that the duration-based and beat-based timings are not identical temporal processing events.

At the initial step of training, the rats were required to touch the switch to get a pellet. The rats knew that they actually touched the switch through LED, which lit up when the switch was touched. At this stage, all rats touched the switch using their noses. At the next step, an acrylic plate was inserted between the rats and the switch (Fig 1A, left). This design prevented the rats from using their noses to touch the switch. The center of the plate had a slit (width 10 mm), and the rats could touch the switch through the slit (Fig 1A, right). Thereafter, the plate location was set so that the rats could touch the switch using either the right or left paw but not with their noses, and consequently, all rats begin to touch the switch using their paws.

Subsequently, the rats were randomly divided into Group I and Group II and the tandem FR-DRL schedule was introduced into the tasks. In Group I, the rats received a tandem FR 2 DRL 500 ms schedule first. The rats were rewarded when they touched the switch after 500 ms following the preceding response (Fig. 1B). When they responded during the 500 ms, a buzzer tone was presented, and the switch was covered by a guillotine door for 3 s. A session was ended when either the rats had earned 200 food pellets or 1 h had passed.

Every experimental condition was continued for 5 sessions, and we defined these 5 sessions as 1 block. Group I rats received the tandem FR 2 DRL 500 ms schedule first. After a block of the tandem FR 2 DRL 500 ms schedule, a procedure of limited hold (LH) was applied, allowing the rats to further attend the fixed interval. LH comprised a fixed available time period for response following the DRL interval. For example, in the tandem FR 2 DRL 500 ms schedule with LH at 1500 ms, the rats had to respond in 1500 ms after 500 ms following the preceding response. When the rats did not respond in LH, a brief buzzer tone was presented, and the switch was covered by the guillotine door for 3 s. After 1 block of the tandem FR 2 DRL 500 ms schedule with LH at 1500 ms, the tandem FR 3 DRL 500 ms block was performed. Next, LH was added, similar to FR 2 sessions. The same procedure was repeated until a block of a tandem FR 4 DRL 500 ms schedule with LH at 1500 ms was over [Fig. 1C (i)]. A tandem FR 2 DRL 1500 ms schedule was conducted following the tandem FR 4 DRL 500 ms schedule with LH at 1500 ms. The subsequent sequence was conducted as described in Fig. 1C (i). The maximum FR value was 3 in the 1500 ms DRL [Fig. 1C (ii)].

The Group II rats received a tandem FR 2 DRL 1500 ms schedule first. Like Group I, LH introduction and increase in the FR criterion were alternately applied to every block [Fig. 1C (ii)]. Following a block of the tandem FR 3 DRL 1500 ms with LH at 1500 ms, a block of the tandem FR 2 DRL 500 ms schedule was conducted. Thereafter, LH introduction and increase in the FR criterion were applied similar to that in Group I. The test session was concluded when a block of the tandem FR 4 DRL 500 ms schedule with LH at 1500 ms block was finished [Fig. 1C (ii)].

IRTs of each tandem FR–DRL schedule were recorded and analyzed for each session. IRTs of 0–100 ms were excluded from analysis because these responses may reflect the rats' involuntary quick multiple responses or a response burst. Moreover, to avoid the warm up effect, the initial 3 trials in each session were eliminated from analysis. We analyzed the initial 2 and last 2 sessions of every block and referred to these sessions as "early stage" and "late stage" of learning, respectively. We defined the former as the training session of the block condition and the latter as the test session.

Under the Group I tandem FR 2 DRL 500 ms schedule, incorrect IRTs notably decreased from the early to late stage of learning (blue and red dotted lines in Fig. 2A). In addition, the peak IRTs of relative frequency shifted from around 150 ms to around 500 ms, wherein the effectiveness of getting rewards was the highest. Moreover, IRTs of the late stage were more concentrated around 500 ms compared with those of the early stage (Fig. 2B). The median of IRTs was longer than 500 ms at the late stage. The Mood test revealed that the IRT distribution at the late stage significantly differed from that of the early stage ($Z = 14.81$, $p < 0.001$). The average number of generated IRTs of the early stage was 379.0 and the corresponding number for the late stage was 457.2. Therefore, every rat finally generated IRTs around or more than 400 times during 2 sessions of the early stage and a successive third session before the last stage of learning. These results are comparable to the previous studies using eye movements [12]. It is probably sufficient to induce motor or cognitive learning in the cerebellum. These results suggest that the rats learned the requirements of the tandem FR 2 DRL 500 ms schedule and accurately predicted 500 ms intervals. This means that the task of the tandem FR 2 DRL 500 ms schedule can let the rats represent duration-based timing, i. e., temporal processing based on absolute timing.

At the early stage of learning under the tandem FR ≥ 3 DRL 500 ms schedules, the IRT distribution of the intervals between the first and second responses of a trial (first IRTs) was significantly more scattered than that at the late stage of learning under the tandem FR 2 DRL 500 ms schedule (Mood test, $Z = 2.50$, $p < 0.05$), although the numbers of responses were same. In contrast, the IRT distribution of the intervals between the second and third responses of a trial (second IRTs) did not significantly differ (Mood test, $Z = 0.44$). These results suggest that the rats changed the strategy for temporal representation from duration-based to beat-based timing after the change in FR value.

Under the tandem FR ≥ 3 DRL 500 ms schedules, IRT distribution revealed an order effect (Fig. 3): The later the responses were generated in each trial, the more accurately the rats predicted the fixed interval under the tandem FR ≥ 3 DRL 500 ms schedules (Fig. 3A, C). In fact, interquartile ranges gradually narrowed closer to the reward (Fig.3B, D). The Mood test revealed that the IRT distribution for the first IRTs significantly differed from that for the second IRTs under the tandem FR 3 DRL 500ms schedule ($Z = 3.48$, $p < 0.001$). The Fligner–Killeen test revealed a significant difference between the distributions of the 1st, 2nd and 3rd IRT under the tandem FR 4 DRL 500ms schedule ($\chi^2 = 195.57$, df = 2, $p < 0.001$). Further, *Post-hoc* analysis revealed significant differences between all combinations (1st–2nd: $Z = 10.54$, $p < 0.001$; 1st–3rd: $Z = 12.57$, $p < 0.001$; 2nd–3rd: $Z = 2.99$, $p < 0.01$). Moreover, on comparing the tandem FR 3 DRL 500 ms schedule with FR 4 DRL 500 ms, we determined that the order effect was enhanced after the learning progression from FR 3 to FR 4. With the 3rd IRTs of the tandem FR 4 DRL 500ms schedule, 75% IRTs were longer than 500 ms, which was a fixed interval. Besides, testing the rats under the tandem FR 4 DRL 500 ms schedule individually, we identified the same effect in all rats. These results indicate that the order effect was robust. As described above, the accuracy of temporal prediction differed in the trials under the FR $\geq$ 3 schedules. Therefore, on comparing the neural activity related to duration-based timing with that of beat-based timing, it may be adequate to use only the activity during IRTs closest to reward delivery.

To compare temporal processing in milliseconds with supra-second processing, we analyzed the behavior in the tandem FR 2 DRL 1500 ms schedule. Under the Group II tandem FR 2 DRL 1500 ms schedule, the learning effect (increase of IRTs around the fixed interval and decrease of incorrect and overly long IRTs) was observed, similar to that under the Group I tandem FR 2 DRL 500 ms schedule (Fig. 4A). In addition, the IRT distribution shifted to the fixed interval from the early to late stage of learning (Fig. 4B). The Mood test revealed that the IRT distribution at the late stage significantly differed from that of the early stage ($Z = 2.72$, $p < 0.01$). Consequently, this task can let the rats represent information for supra-second processing. As a result, we are able to use this task to compare the neural activity between the millisecond and supra-second processing modes.

To verify the DRL value shift effect, we analyzed the behavior under the Group I tandem FR 2 DRL 1500 ms schedule. The results indicated that under the tandem FR 2 DRL 1500 ms schedule, the responses were more accurate rather than disrupted (Fig. 4).

This implies that the negative DRL shift effect was not involved in this task, contrary to a previous study [10]. It may be because the previous study used longer DRL values (15–60 s) than the present study.

In this work, we show that rats are able to represent information for temporal processing in milliseconds in a tandem FR–DRL schedule task. Under the tandem FR 2 DRL 500 ms schedule, the rats only need 2 training sessions to accurately represent information for the 500 ms interval. This task can be called a "duration-based timing task." Under the tandem FR ≥ 3 DRL 500 ms schedules, i. e. beat-based timing task, we revealed the order effect of the IRT distribution. Because the most accurate IRT seems to be the one closest to the reward, only IRTs closest to the reward should probably be used for comparison with duration-based timing. Furthermore, we suggest that these tasks could be used for comparing cerebellar neuronal activity between the millisecond and supra-second processing modes.

We referred to a study by Kitazawa et al. (1998) [7], which demonstrated that the "spatial" gap between actually touched positions and target positions induced error encoding by Purkinje cellular complex spikes. In our tasks, the "temporal" gap between the required time intervals and observed IRTs could induce error signals from the Purkinje cells.

According to Albus, Marr, and Ito's theory, the cerebellar function includes supervised learning based on a hypothesis of long–term depression (LTD) [13]. Experimental [3] and theoretical [14, 15, 16] studies indicated that learning-dependent timing is mediated by the parallel fiber–Purkinje cell synaptic LTD. Therefore, we speculate that climbing fiber inputs encode the generated reaching timing and can induce LTD by sending signals to Purkinje cell synapses in synchronization with parallel fiber inputs. As a result, the onset latency or duration of later reaching timing becomes more adequately tuned.

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FIGURE LEGENDS

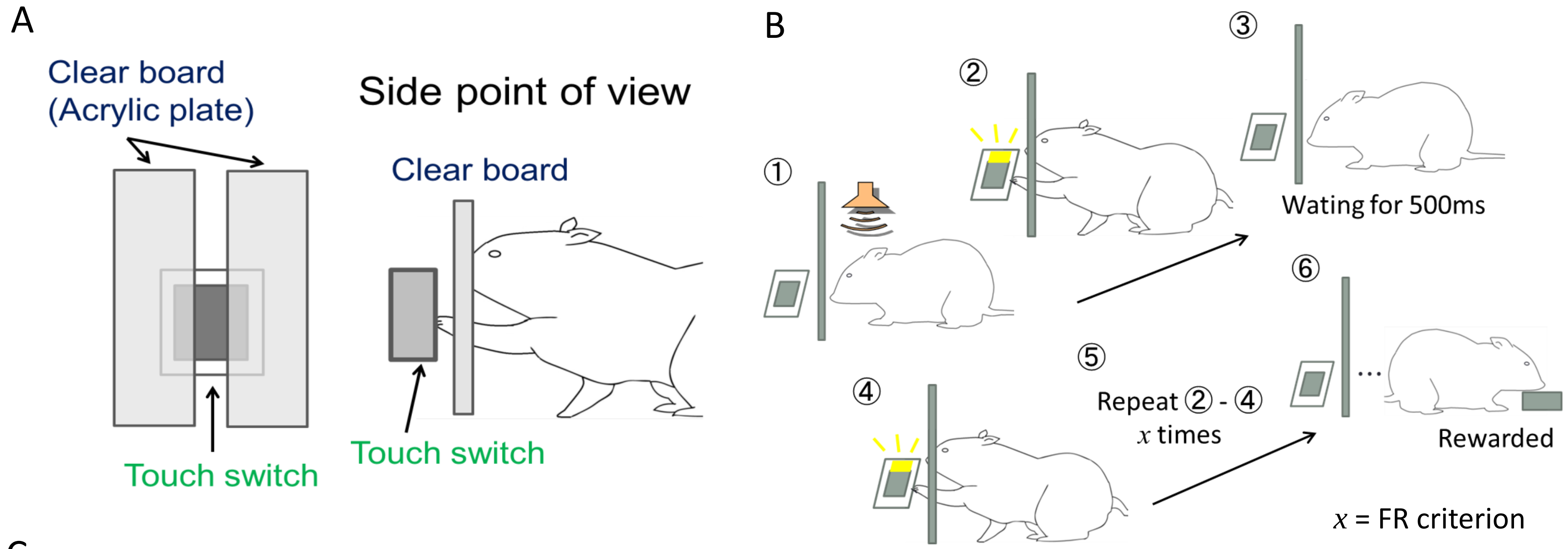
Fig. 1. Schematic illustrations of the behavioral timing tasks and the experimental procedures. **(A)** The touch switch and the acrylic plate in the operant chamber. **(B)** The behavioral sequence for the timing tasks. **(C, D)** The experimental conditions. The Group I rats received sequence ***i*** in Fig. C first, followed by sequence ***ii***. The Group II rats received sequence ***ii*** first, followed by sequence ***i***.

Fig. 2. Learning of the tandem FR 2 DRL 500ms schedule in the Group I rats. **(A)** The IRT distribution under the tandem FR 2 DRL 500ms schedule at the early stage (blue solid and dotted lines) and the late stage (red solid and dotted lines) of learning. The IRT frequencies longer than 3000 ms are presented together. **(B)** Box plots of the IRT distribution for the tandem FR 2 DRL 500ms schedule at the early and late stages of learning. The dotted line indicates the fixed interval. Asterisks indicate statistical significance ($p < 0.001$).

Fig. 3. The order effect of the tandem FR ≥ 3 DRL 500 ms schedules in the Group I rats. **(A, C)** The IRT distribution under the tandem FR 3 DRL 500ms (A) and tandem FR 4 DRL 500ms schedules (C). The 1st, 2nd and 3rd IRTs are intervals between the first and second, the second and third, and between the third and fourth responses respectively. The IRT frequencies longer than 3000 ms are presented together. **(B, D)** Box plots of distribution for each sequential IRT under the tandem FR 3 DRL 500ms (B) and tandem FR 4 DRL 500ms schedules (D). The dotted lines indicate the fixed interval. Asterisks indicate statistical significance (*** $p < 0.001$, ** $p < 0.01$).

Fig. 4. Behavioral performance under the tandem FR 2 DRL 1500ms schedule. **(A, C)** The IRT distribution under the tandem FR 2 DRL 1500 ms schedule in Groups II (A) and I (C). The IRT frequencies longer than 4500 ms are presented together. In Fig. A, incorrect responses at the early stage of learning (blue dotted line) are plotted along the right vertical axis and the others along the left axis. **(B, D)** Box plots of the IRT distributions at the early and late stages of learning of the tandem FR 2 DRL 1500 ms

schedule in Groups II (B) and I (D). Maximum values (upper error bars) are not shown because overly high values were observed. The dotted lines indicate the fixed interval. Asterisks indicate statistical significance ($p < 0.01$); n.s. no statistical significance.



C

i	tandem FR 2 DRL 500ms	→	tandem FR 2 DRL 500ms with LH 1500ms	→	tandem FR 3 DRL 500ms	→	tandem FR 3 DRL 500ms with LH 1500ms	→	tandem FR 4 DRL 500ms	→	tandem FR 4 DRL 500ms with LH 1500ms
	5 sessions		5 sessions		5 sessions		5 sessions		5 sessions		5 sessions
ii	tandem FR 2 DRL 1500ms	→	tandem FR 2 DRL 1500ms with LH 1500ms	→	tandem FR 3 DRL 1500ms	→	tandem FR 3 DRL 1500ms with LH 1500ms				

1 block

D

	First	Second
Group I	i	ii
Group II	ii	i

Fig. 1

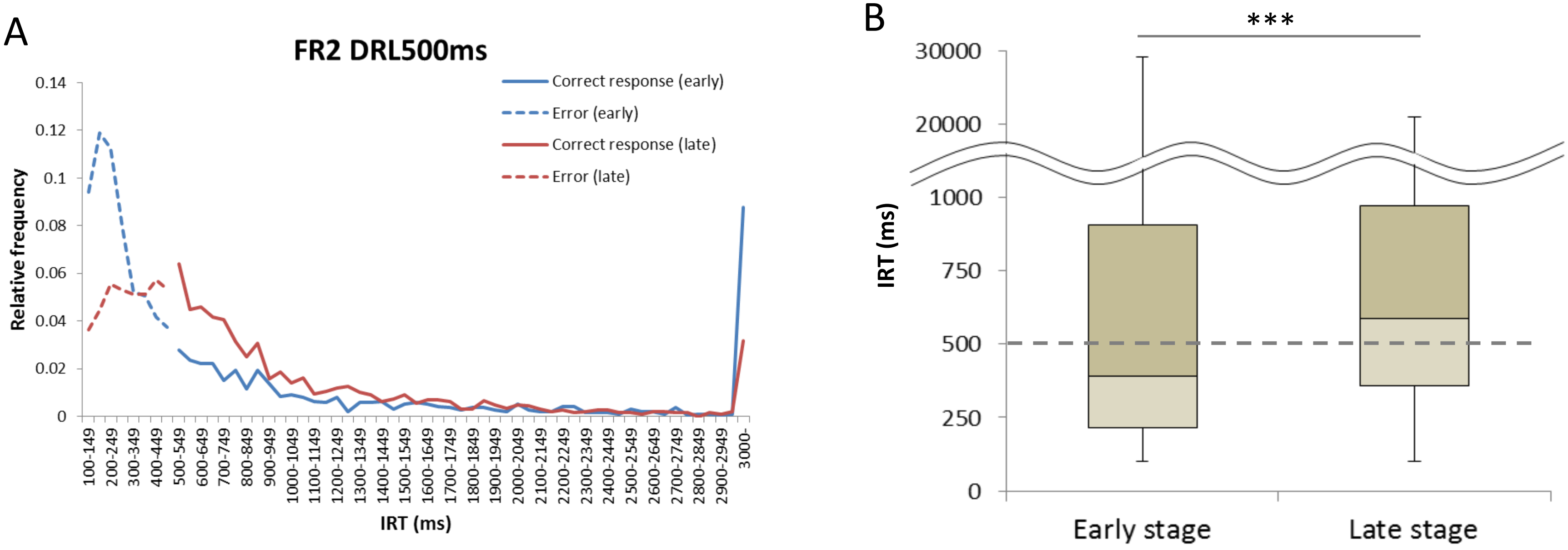

A
FR2 DRL500ms
Correct response (early)
Error (early)
Correct response (late)
Error (late)
Relative frequency
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
100-149
200-249
300-349
400-449
500-549
600-649
700-749
800-849
900-949
1000-1049
1100-1149
1200-1249
1300-1349
1400-1449
1500-1549
1600-1649
1700-1749
1800-1849
1900-1949
2000-2049
2100-2149
2200-2249
2300-2349
2400-2449
2500-2549
2600-2649
2700-2749
2800-2849
2900-2949
3000-
IRT (ms)
B
***
IRT (ms)
30000
20000
1000
750
500
250
0
Early stage
Late stage

Fig. 2

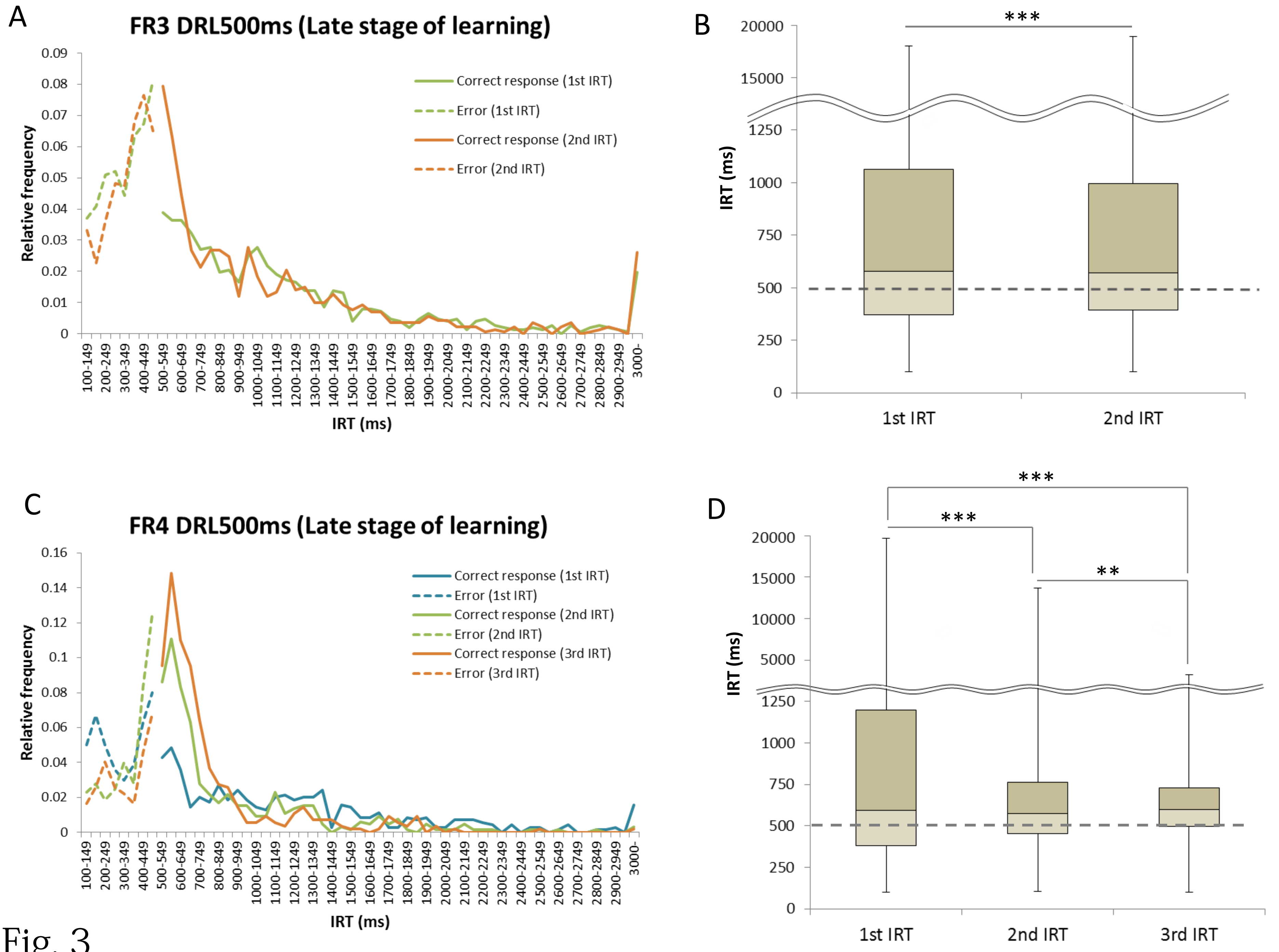

A
FR3 DRL500ms (Late stage of learning)
Relative frequency
IRT (ms)
Correct response (1st IRT)
Error (1st IRT)
Correct response (2nd IRT)
Error (2nd IRT)
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
100-149
200-249
300-349
400-449
500-549
600-649
700-749
800-849
900-949
1000-1049
1100-1149
1200-1249
1300-1349
1400-1449
1500-1549
1600-1649
1700-1749
1800-1849
1900-1949
2000-2049
2100-2149
2200-2249
2300-2349
2400-2449
2500-2549
2600-2649
2700-2749
2800-2849
2900-2949
3000-
B
***
IRT (ms)
20000
15000
1250
1000
750
500
250
0
1st IRT
2nd IRT
C
FR4 DRL500ms (Late stage of learning)
Relative frequency
IRT (ms)
Correct response (1st IRT)
Error (1st IRT)
Correct response (2nd IRT)
Error (2nd IRT)
Correct response (3rd IRT)
Error (3rd IRT)
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
D
***
***
**
IRT (ms)
20000
15000
10000
5000
1250
1000
750
500
250
0
1st IRT
2nd IRT
3rd IRT

Fig. 3

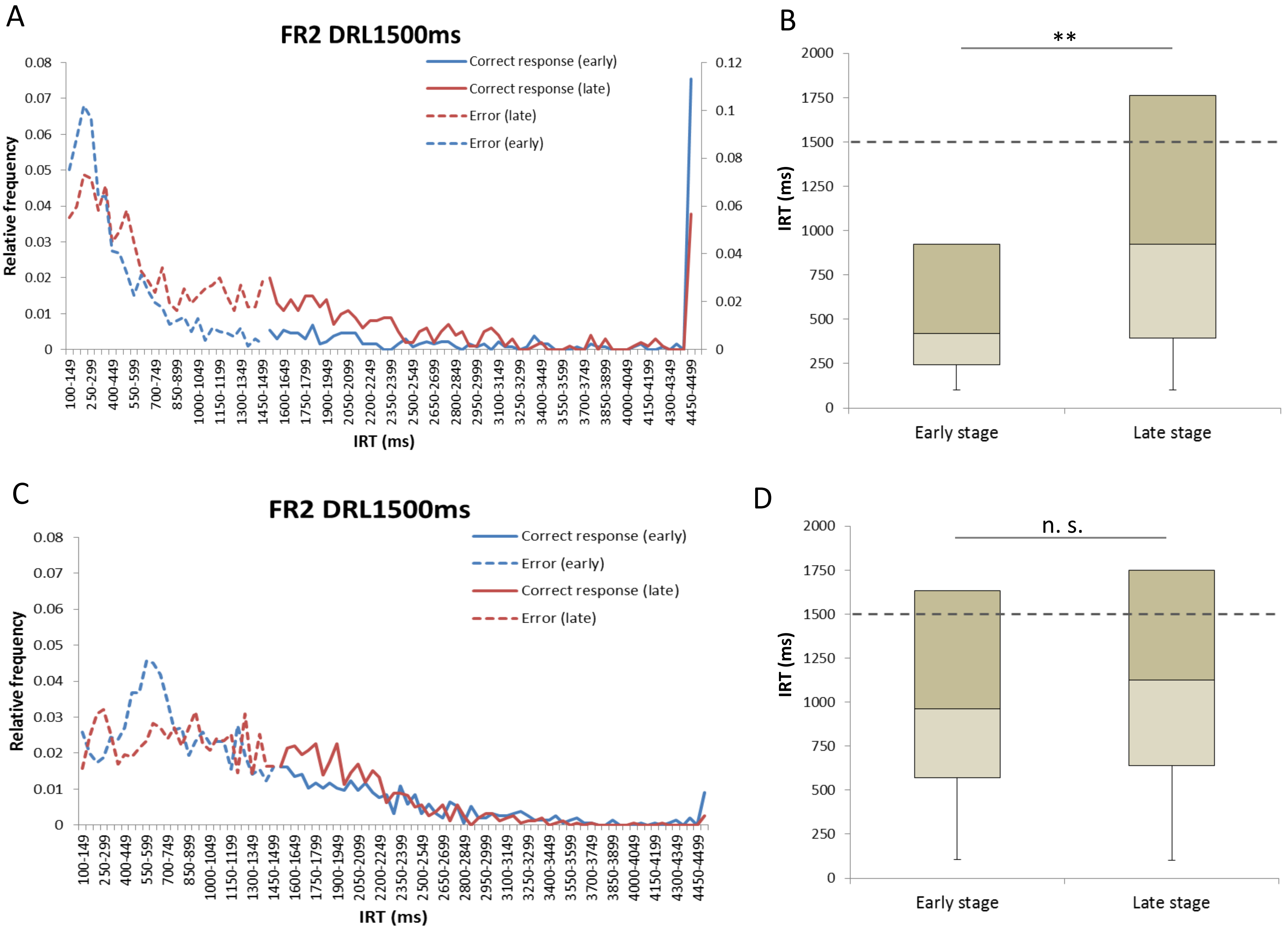

A
FR2 DRL1500ms
Correct response (early)
Correct response (late)
Error (late)
Error (early)
Relative frequency
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0.12
0.1
0.08
0.06
0.04
0.02
0
100-149
250-299
400-449
550-599
700-749
850-899
1000-1049
1150-1199
1300-1349
1450-1499
1600-1649
1750-1799
1900-1949
2050-2099
2200-2249
2350-2399
2500-2549
2650-2699
2800-2849
2950-2999
3100-3149
3250-3299
3400-3449
3550-3599
3700-3749
3850-3899
4000-4049
4150-4199
4300-4349
4450-4499
IRT (ms)
B
**
IRT (ms)
2000
1750
1500
1250
1000
750
500
250
0
Early stage
Late stage
C
FR2 DRL1500ms
Correct response (early)
Error (early)
Correct response (late)
Error (late)
Relative frequency
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
IRT (ms)
D
n. s.
IRT (ms)
2000
1750
1500
1250
1000
750
500
250
0
Early stage
Late stage

Fig. 4