

Asymmetry in updating long-term memory for time

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The present study evaluates the updating of long-term memory for duration. After learning a temporal discrimination associating one lever with a standard duration (4 sec) and another lever with both a shorter (1-sec) and a longer (16-sec) duration, rats underwent a single session for learning a new standard duration. The temporal generalization gradient obtained 24 h later showed a modification in long-term memory for durations longer than the standard but only when the new duration was longer than the one initially learned. The effect was confirmed for another set of durations (0.5–2–8 sec). Our study demonstrates asymmetry in updating long-term memory for time.

[Supplemental material is available for this article.]

Learning and memory updating are based on error detection, so that learning/updating occurs when something new happens. Time-based error detection supposes a comparison between current tracked time and stored/memorized time of the expected event. This is what is at work when on your usual way back home you are judging that the traffic light is broken because it has stayed red for too long, based on your memory of that traffic light duration.

Memory of time has been invoked in early treatments of timing (Pavlov 1927; Treisman 1963; Gibbon 1977). Animal research has shown that long-term memory for time is formed in a single session, or even in a single trial (Balsam et al. 2010; Diaz-Mataix et al. 2013; Tallot et al. 2020), while human research has recently shown that it follows biological rules, such as a consolidation time course during the hours following encoding (Cocenas-Silva et al. 2014), which are different from those underlying temporary storage of duration. An in-depth investigation of the neural bases of long-term memory for time requires research in animals, in protocols that isolate the learning of duration from any other aspects of the task (e.g., contingencies and rules).

One protocol is to shift temporal contingencies after the initial learning of the task has been stabilized in performance, and observe how updating occurs at the behavioral level. With this approach, human research has mainly concentrated on temporal reference memory created and manipulated within a single session, and thus has not studied its long-term form. For example, Ogden et al. (2008) reported interference in memory, as the temporal generalization gradient for a recently encoded duration was altered by the introduction of another generalization task, whether the new standard was of a shorter or longer duration. Also showing effects in both directions, Simen et al. (2011) found rapid adaptation to successive new, longer or shorter, time targets. Animal research has analyzed the dynamics of behavioral adaptation to new fixed interval (FI) values (e.g., Meck et al. 1984; Lejeune et al. 1997) or CS-US interval in a Pavlovian paradigm (Dallérac et al. 2017), changes in the duration–action association in temporal discrimination tasks (Church and Deluty 1977), or through the demonstration of averaging of time (FI) memories (e.g., Swanton et al. 2009; De Corte and Matell 2016). The difficulty with all these approaches is that they often necessitate several sessions to extract/

analyze the behavioral outcome, while memory for the new time is presumably updated and consolidated within hours after the first session. In addition, the behavioral adaptation may differ depending on the magnitude and direction of the difference between the new relevant temporal values and those (shorter or longer) stored in long-term memory (Higa 1997; Lejeune et al. 1997). Importantly also is the fact that these approaches mix two factors: the learning of the new temporal rule and the behavioral adaptation to it, which likely depends on the behavioral protocol used, thus rendering interpretation of effects difficult to link with a specific factor. This may also explain in part why the results are conflicting with sometimes fast adaptation, or in contrast slow adaptation, or even no adaptation to new temporal rules.

The aim of the present study was to assess in rats the ability to update in long-term memory a duration memorized in a single session. We developed a temporal generalization procedure, akin to human studies of memory for time (Cocenas-Silva et al. 2014; Derouet et al. 2019), enabling the use of both shorter or longer durations while isolating the formation of a new temporal memory through the investigation of the extent to which it interferes with an already formed stabilized memory. Rats were trained (temporal discrimination training) (see the Supplemental Material) to press one lever (left or right) after a 4-sec tone stimulus duration and the other lever after a shorter (1-sec) or longer (16-sec) tone duration, as an equivalent to the “same” versus “different” task in the training phase for temporal generalization assessment in humans (Wearden 1992). Reward (food pellet) was given if the correct lever was pressed. All the animals showed a good general level of acquisition and discrimination between the durations (see the Supplemental Material). Animals were then assigned to four groups, equilibrated according to their acquisition performance (Supplemental Fig. S1). For three groups, animals were submitted to a single session (called shift session) with 20 trials in which only one lever, the lever associated with the standard 4-sec duration, was presented at the end of the tone, but the tone duration was shorter than (2.5 sec), longer than (6.3 sec), or the same as

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(4.0 sec, no shift) the standard duration. Animals in the fourth group (control) remained in the colony room. Generalization tests were performed on the following 2 d, with six intermediate durations (2, 2.5, 3.2, 5, 6.3, 8 sec; 10 trials each) not reinforced, in addition to the standard duration (4 sec for 30 trials) and the two “extreme” durations (1 sec and 16 sec for 15 trials each) for which correct responding was reinforced.

The generalization gradients obtained on the first day of tests, 24 h after the shift session, differed between groups, and more so for the durations longer than the standard (Fig. 1A). An analysis of variance (ANOVA) performed on the proportion of responses to the lever associated with the 4-sec standard duration, $p(4 \text{ sec})$, with one between-subjects factor (four groups) and one within-subject factor (seven stimulus durations, excluding the reinforced extreme durations) showed a significant main effect of stimulus duration, $F_{(6,408)} = 46.88$, $P < 0.001$, confirming that rats did effectively discriminate between durations. However, there was a significant stimulus duration \times group interaction, $F_{(18,408)} = 1.892$, $P = 0.046$, while the main effect of group was not significant $F_{(3,68)} < 1$. This indicated that rats responded differently among groups de-

pending on the durations. Parsing the interaction, separate analyses, with stimulus durations shorter (2, 2.5, 3.2 sec) and longer (5, 6.3, 8 sec) than the standard (4-sec) duration, revealed a significant stimulus duration \times group interaction for long stimulus durations, $F_{(6,136)} = 4.050$, $P = 0.001$, but not for short-stimulus durations, $F_{(6,136)} = 1.494$, $P = 0.188$. Thus, the impact of the Shift session was specifically on stimulus durations longer than the standard duration. To characterize the effect, further comparisons were made restricted to these long stimulus durations. First, the 4-sec group did not differ significantly from the control group (no significant interaction or group differences, both $F_s < 1$). This demonstrated that the procedure itself (i.e., a forced-choice session with a single “standard” duration) did not produce a change in temporal generalization gradient. Second, compared with the 4-sec group, only the group of animals that experienced a shift session with a new standard > 4 sec showed a significantly modified generalization gradient (6.3-sec group: interaction, $F_{(2,68)} = 5.236$, $P = 0.010$, group effect, $F_{(1,34)} < 1$); 2.5-sec group: interaction, $F_{(2,68)} = 1.501$, $P = 0.232$, group effect, $F_{(1,34)} = 1.662$, $P = 0.206$). Analysis of individual slopes of regression confirmed that the decay

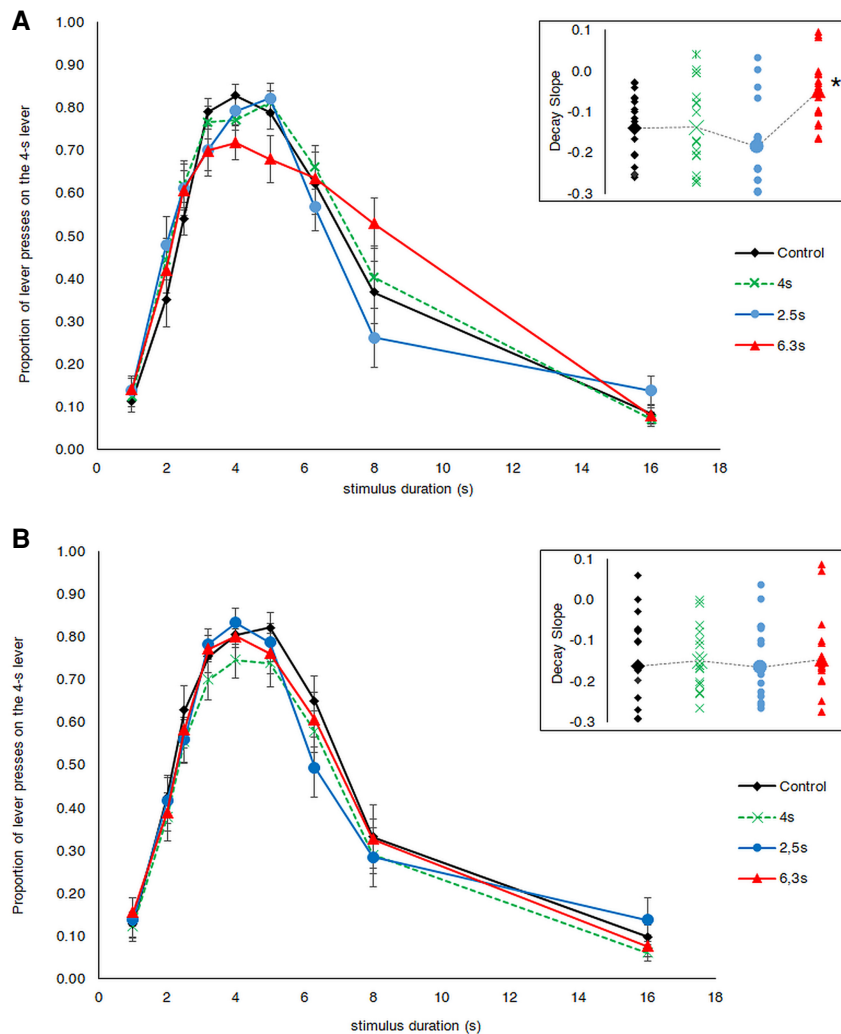


Figure 1. Proportion of lever presses on the 4-sec lever $-p(4 \text{ sec})$ - plotted against stimulus duration for the control, 4-, 2.5-, and 6.3-sec groups for the first (A) and the second (B) day of the generalization task. Error bars: \pm SEM. (Insets) Slope of the regression fitted on $p(4 \text{ sec})$ for 5-, 6.3-, and 8-sec test durations for each rat for the four groups, with a dotted line linking the group mean values. (*) Bonferroni $P \leq 0.05$, significant difference between the 6.3-sec group and each of the other groups.

magnitude of the generalization gradient differed among groups, $F_{(3,68)} = 6.38$, $P < 0.001$, and that only the 6.3-sec group differed from all the other groups, that is, the control group (Bonferroni, $P = 0.035$), the 4-sec group ($P = 0.05$), and the 2.5-sec group ($P < 0.001$) (Fig. 1A, inset). None of the other comparison pairs was significant ($P_s \geq 0.738$) (see Supplemental Fig. S2 for individual curves and slopes of regression for the rising and decay parts of the generalization gradient). Thus, the shift session with a new temporal reference had a significant impact only when it was to a longer duration than the initially learned standard duration, and the impact was asymmetrical with a flattening of the generalization gradient only for the stimulus durations longer than the standard duration.

As the original discrimination rules were in effect during the generalization test (i.e., retraining with the standard [4-sec] and extreme durations reinforced), the impact of the shift session should diminish with retraining. As expected, apart from the main effect of stimulus duration, $F_{(6,408)} = 84.261$, $P < 0.001$, showing that the rats still discriminated among durations, there were no other significant effects during the second day of the generalization test (effect of group and stimulus duration \times group interaction, both $F_s < 1$, ns) (Fig. 1B). Thus, the disruption of temporal judgment observed in the generalization test originated from the interference effects of the new temporal rule in the shift session, and reflected a rapid update in memory of the duration/action association rather than a general irreversible disturbance of behavior.

The asymmetry in the temporal generalization gradient suggesting interference effects only on the judgment of stimulus durations longer than the

standard duration raises the question of whether it reflects an effect specific to the range of durations used in our study, with judgment of durations <4 sec being immune to interference. It is also possible that memory updating requires a minimum temporal difference from the standard duration (2.3 sec vs. 1.5 sec, for shifts to longer and shorter durations, respectively). To address this issue, a new set of animals was trained on a discrimination between a 2-sec tone standard duration associated with a given lever, and either a 500-msec or 8-sec tone duration associated with the second lever (see the Supplemental Material). A shift session with a 3.15-sec tone duration (i.e., 1.15-sec difference from the standard) was given for one group compared with another group for which the 2-sec standard duration was not changed. The performance criterion was reached by both groups for the standard and long duration, but not for the 500-msec tone (see the Supplemental Material; Supplemental Fig. S3). Performance during the first day of the generalization test (1.25, 1.60, 2.5, 3.15 intermediate durations) run 24 h after the shift session showed an impact of the shift session when the new 3.15-sec duration was associated with the lever corresponding to the 2-sec standard duration, compared with when there was no change in duration (Fig. 2A). The mixed ANOVA performed on $p(2\text{ sec})$ confirmed that rats discriminated between durations (main effect of stimulus duration, $F_{(6,210)} = 12.212$, $P < 0.001$), with no significant main effect of group, $F_{(1,35)} < 1$, but a sig-

nificant stimulus duration \times group interaction, $F_{(6,210)} = 3.483$, $P = 0.008$), indicating that rats responded differently between groups depending on the stimulus durations. As in the previous experiment, a significant stimulus duration \times group interaction appeared for stimulus durations longer (2.5, 3.15, 4 sec), $F_{(2,70)} = 7.612$, $P = 0.001$, but not for those shorter (1, 1.25, 1.60 sec) than the standard duration ($F < 1$). Analysis of individual slopes of regression confirmed a significant difference between the two groups for the decay part of the generalization gradient ($F_{(1,35)} = 9.65$, $P = 0.004$) (Fig. 2A, inset; see Supplemental Fig. S4 for individual curves and slopes of regression for the rising and decay parts of the generalization gradient). Also as before, the effect was no longer visible on the second day of generalization test ($F < 1$ for group effect and stimulus duration \times group interaction) (Fig. 2B) while the main effect of stimulus duration remained significant, $F_{(6,210)} = 14.580$, $P < 0.001$). Thus, a 1.15-sec shift in the duration/action association within a range of durations <4 sec triggered an update in memory with an impact restricted specifically to durations longer than the standard duration. This effect was comparable with the one observed when the standard duration was 4 sec in duration and the memory update was to a longer duration with the same magnitude on a geometric scale (factor 1.575).

In all, the results show that a single session pairing a new duration with a learned response interferes with an already formed long-

term memory of a duration–action association. This result first provides further support for rapid learning of duration, extending the previous findings in Pavlovian settings in which a single trial was shown to suffice for learning an interval between conditioned and unconditioned stimuli (Balsam et al. 2010; Diaz-Mataix et al. 2013). In instrumental tasks, only few studies have examined the time course of behavioral adaptation, and the majority of them used paradigms in which the animals were repeatedly exposed to shifts in fixed interval values, and therefore may have learned to adapt. Nevertheless, when analyzed, the behavioral shifts were rapid, if not in a single trial (e.g., Higa et al. 2002).

The procedure we implemented here enabled us to highlight two, possibly independent, sources of asymmetry: (1) Memory updating was produced when the new standard duration was longer (upshift), but not shorter (downshift), than the initially trained standard duration. (2) The impact of the interference on the generalization gradient (i.e., flattening of the curve) was restricted to durations longer than the standard. The asymmetry cannot be due to a differential detection of temporal changes, as their sizes were equivalent on a geometric scale (in all upshift and downshift conditions), or even opposite to the effect predicted when comparing the two experiments on an arithmetic/absolute scale (significant impact of a 1.15-sec upshift in experiment 2 vs. no impact of a bigger 1.5-sec downshift in experiment 1). These asymmetrical effects resonate with previous reports showing asymmetries in the adaptation to new fixed interval values

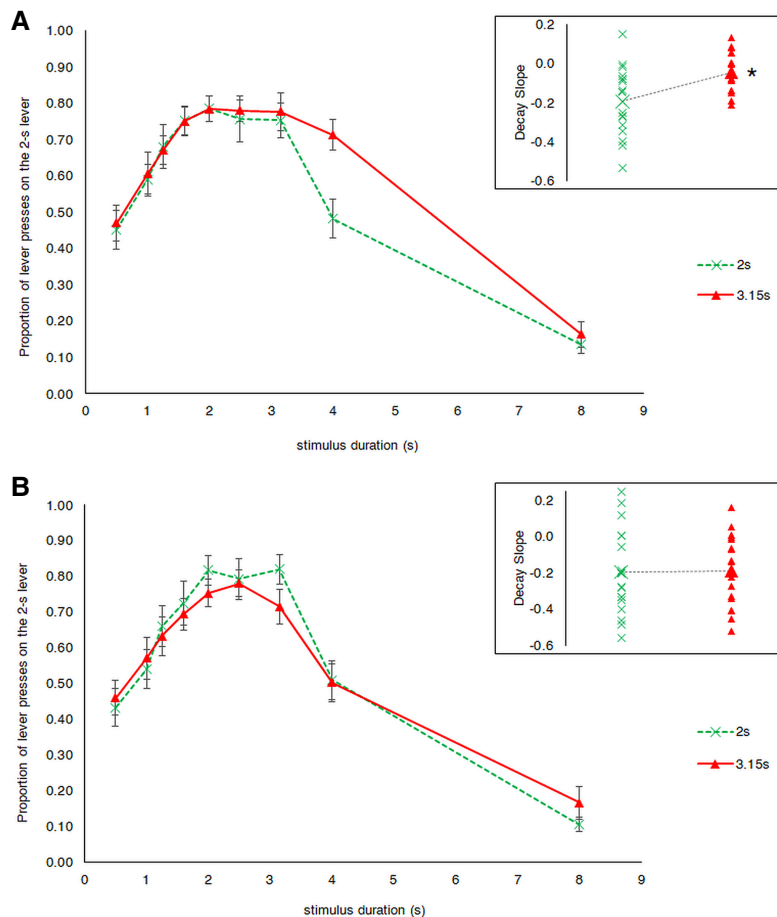


Figure 2. Proportion of lever presses on the 2-sec lever $-p(2\text{ sec})$ - plotted against stimulus duration for the 2-sec and 3.15-sec groups for the first (A) and the second (B) day of generalization task. Error bars: \pm SEM. (Insets) Slope of the regression fitted on $p(2\text{ sec})$ for 2.5-, 3.15-, and 4-sec test durations for each rat for the two groups, with a dotted line linking the group mean values. (*) Bonferroni $P < .05$, significant difference between the 3.15-sec group and the 2-sec group.

or to new duration/action association, albeit not always in the same direction. Shifts in fixed or peak interval schedules in rodents have produced mixed results, with reports of either symmetry or a tendency for faster adaptation to longer durations (e.g., Meck et al. 1984; Lejeune et al. 1997) or, in contrast, slower, or in some instances, no adaptation to the new schedule when the shift was to a longer duration, but faster adaptation when the shift was to a shorter duration (e.g., Higa 1996; 1997; Higa and Tillou 2001). Furthermore, readaptation to a short duration after a shift to longer duration is very rapid (Higa and Tillou 2001), which stands in contrast to our results, which could be interpreted as a fast learning of a longer duration and/or slow readaptation to a shorter duration. Previously reported asymmetries in adaptation to changing FI schedules may be partly explained through the learned anticipation of upcoming shifts, due to the repetition of shifts (Sanabria and Oldenburg 2014).

Our results may be better compared with tasks involving choice rather than anticipatory responding. In the temporal bisection task, no asymmetry has been reported in rats after shift to new duration/action pairings, whether to shorter or longer ranges (Church and Deluty 1977), but some asymmetry has been reported in pigeons with a noticeable change in behavior mainly when the long anchor duration was lengthened (Machado and Keen 2003), whose magnitude may depend on the initial training condition (Araiba and Brown 2017). In this type of task, categorization processes may be at play in addition to temporal generalization, possibly rendering the behavior less sensitive to changes in duration. However, the present observed asymmetry would suggest that the short and standard durations may have belonged to the same category, which is opposite to findings in the literature (Russell and Kirkpatrick 2007). Although our paradigm involved a discrimination task similar to the same/different task and temporal generalization gradient test used in humans, it can also be regarded as a discrimination with three—short versus standard versus long—durations, and a “dual”-bisection task during tests with intermediate duration values. The standard duration in our paradigm could be considered as a “long” anchor for the short-standard discrimination, but as a “short” anchor for the standard-long discrimination. In the first case, larger changes in behavior would be expected in the upshift condition than in the downshift condition (Araiba and Brown 2017), whereas in the second case no change would be expected (Machado and Keen 2003). Our results seem congruent with the reported asymmetry in the first case, and may also explain the lack of modification in the temporal generalization for the range of durations shorter than the standard duration.

By restricting the change in duration/action association to a single session of interference, rather than looking at repetitive or stable adaptation of behavior to new temporal contingencies, our experiment reveals new information about how a duration is learned and memorized in long-term memory, to serve as a reference for later comparison when choices are made. We show that memory updating happens rapidly and the new temporal reference is memorized for long-term storage for at least 24 h. Our results, however, clearly point to an asymmetry in updating the memory, an asymmetry that was also suggested in our recent experiment in humans (Derouet et al. 2019). Whether the asymmetry originates from an asymmetrical detection of changes, that is, shorter versus longer than the standard duration, or from differential speed of learning and/or adaptation to temporal contingencies will need to be addressed in future investigations. The present novel paradigm will enable answering these questions and provide grounds for fruitful assessments of the neurobiological basis of memory for time, critical for time-based error monitoring and adaptation of behavior to novel contingencies.

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References

- Araiba S, Brown BL. 2017. The effect of the long anchor duration on performance in the temporal bisection procedure. *Behav Processes* **135**: 76–86. doi:10.1016/j.beproc.2016.12.007
- Balsam PD, Drew MR, Gallistel CR. 2010. Time and associative learning. *Comp Cogn Behav Rev* **5**: 1–22. doi:10.3819/ccbr.2010.50001
- Church RM, Deluty MZ. 1977. Bisection of temporal intervals. *J Exp Psychol Anim Behav Process* **3**: 216–228. doi:10.1037/0097-7403.3.3.216
- Cocenas-Silva R, Oliveira Bueno JL, Doyère V, Droit-Volet S. 2014. Memory consolidation for duration. *Q J Exp Psychol* **67**: 1401–1414. doi:10.1080/17470218.2013.863375
- Dallérac G, Graupner M, Knippenberg J, Ruiz Martinez RCR, Ferreira Tavares T, Tallot L, El Massioui N, Verschuere A, Höhn S, Boulanger-Bertolus J, et al. 2017. Updating temporal expectancy of an aversive event engages striatal plasticity under amygdala control. *Nat Commun* **8**: 13920. doi:10.1038/ncomms13920
- De Corte BJ, Matell MS. 2016. Temporal averaging across multiple response options: insight into the mechanisms underlying integration. *Anim Cogn* **19**: 329–342. doi:10.1007/s10071-015-0935-4
- Derouet J, Doyère V, Droit-Volet S. 2019. The disruption of memory consolidation of duration introduces noise while lengthening the long-term memory representation of time in Humans. *Front Psychol* **10**: 745. doi:10.3389/fpsyg.2019.00745
- Diaz-Mataix L, Ruiz Martinez RC, Schafe GE, LeDoux JE, Doyère V. 2013. Detection of temporal error triggers reconsolidation of amygdala-dependent memories. *Curr Biol* **23**: 467–472. doi:10.1016/j.cub.2013.01.053
- Gibbon J. 1977. Scalar expectancy theory and Weber's law in animal timing. *Psychol Rev* **84**: 279–325. doi:10.1037/0033-295X.84.3.279
- Higa JJ. 1996. Dynamics of time discrimination: II. The effects of multiple impulses. *J Exp Anal Behav* **66**: 117–134. doi:10.1901/jeab.1996.66-117
- Higa JJ. 1997. Dynamics of temporal control in rats: the effects of a brief transition in interval duration. *Behav Processes* **40**: 223–229. doi:10.1016/S0376-6357(97)00021-1
- Higa JJ, Tillou P. 2001. Effects of increasing the time to reinforcement on interval timing in rats. *Int J Comp Psychol* **14**: 64–75.
- Higa JJ, Moreno S, Sparkman N. 2002. Interval timing in rats: tracking unsignaled changes in the fixed interval schedule requirement. *Behav Processes* **58**: 167–176. doi:10.1016/S0376-6357(02)00029-3
- Lejeune H, Ferrara A, Simons F, Wearden JH. 1997. Adjusting to changes in the time of reinforcement: peak-interval transitions in rats. *J Exp Psychol Anim Behav Process* **23**: 211–231. doi:10.1037/0097-7403.23.2.211
- Machado A, Keen R. 2003. Temporal discrimination in a long operant chamber. *Behav Processes* **62**: 157–182. doi:10.1016/S0376-6357(03)00023-8
- Meck WH, Komeily-Zadeh FN, Church RM. 1984. Two-step acquisition: modification of an internal clock's criterion. *J Exp Psychol Anim Behav Process* **10**: 297–306. doi:10.1037/0097-7403.10.3.297
- Ogden RS, Wearden JH, Jones LA. 2008. The remembrance of times past: interference in temporal reference memory. *J Exp Psychol Hum Percept Perform* **34**: 1524–1544. doi:10.1037/a0010347
- Pavlov IP. 1927. *Conditioned reflexes: an investigation of the physiological activity of the cerebral cortex*. Dover Publications, Mineola, NY.
- Russell R, Kirkpatrick K. 2007. The role of temporal generalization in a temporal discrimination task. *Behav Processes* **74**: 115–125. doi:10.1016/j.beproc.2006.08.004
- Sanabria F, Oldenburg L. 2014. Adaptation of timing behavior to a regular change in criterion. *Behav Processes* **101**: 58–71. doi:10.1016/j.beproc.2013.07.018
- Simen P, Balci F, deSouza L, Cohen JD, Holmes P. 2011. A model of interval timing by neural integration. *J Neurosci* **31**: 9238–9253. doi:10.1523/JNEUROSCI.3121-10.2011
- Swanton DN, Gooch CM, Matell MS. 2009. Averaging of temporal memories by rats. *J Exp Psychol Anim Behav Process* **35**: 434–439. doi:10.1037/a0014021
- Tallot L, Graupner M, Diaz-Mataix L, Doyère V. 2020. Beyond freezing: temporal expectancy of an aversive event engages the amygdalo-prefronto-dorsostriatal network. *Cereb Cortex* **30**: 5257–5269. doi:10.1093/cercor/bhaa100
- Treisman M. 1963. Temporal discrimination and the indifference interval: implications for a model of the 'internal clock'. *Psychol Monographs* **77**: 1–31. doi:10.1037/h0093864
- Wearden JH. 1992. Temporal generalization in humans. *J Exp Psychol Anim Behav Process* **18**: 134–144. doi:10.1037/0097-7403.18.2.134

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