Recall of sequences based on the position of the first cue stimulus in rats

Seiya Ishino · Yoshio Sakurai

Received: 28 October 2013 / Revised: 1 February 2014 / Accepted: 26 February 2014 / Published online: 22 March 2014
© Springer Science+Business Media Dordrecht 2014

Abstract We investigated the ability of rats to recall sequences of nose-poke holes with a modified serial reaction time task. In each trial, a sequence was randomly selected and the position of the first illuminated hole, which functioned as a cue stimulus, informed the rats whether the following sequence was a predictable one or not, based on prior training. The rats responded predictively only when the cues of the predictable sequences were presented. They did not show predictive responses when the cues of unpredictable sequences were presented, even though the unpredictable sequences partially had the same order of holes as the predictable sequences. These results indicate that the rats can recall sequences on the basis of presentation of the first cue stimulus informing predictable or unpredictable sequences. Recording neuronal activity while rats perform this behavioral task would be useful to elucidate neuronal mechanisms that mediate sequence recall.

Keywords Sequence recall · Rat · Reaction time distribution · ex-Gaussian distribution

Electronic supplementary material The online version of this article (doi:10.1007/s11571-014-9284-2) contains supplementary material, which is available to authorized users.

S. Ishino (✉) · Y. Sakurai
Department of Psychology, Graduate School of Letters, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan
e-mail: seiya.ishino@gmail.com

S. Ishino
Japan Society for the Promotion of Science, Tokyo 102-0083, Japan

Introduction

Sequence learning is critical for our ability to modulate our daily behavior in an efficient and adaptive manner. It is also important that we are able to recall a specific sequence in its entirety when we come across a part of it. In this case, the part functions as a cue to the rest of the sequence. Such recall of sequences on the basis of cues can manifest in predictive behaviors.

Sequence learning can be broadly classified into learning sequences of stimuli and learning motor sequences. Tasks requiring subjects to learn sequences of stimuli have been used to study the role of the hippocampal memory system in sequence learning in humans (Ross et al. 2009), rats (Fortin et al. 2002; Kesner et al. 2002; Manns et al. 2007) and mice, (Devito and Eichenbaum 2011) and in sequence discrimination in humans (Kumaran and Maguire 2006) and rats (Agster et al. 2002; Ginther et al. 2011). Meanwhile, the serial reaction time task (SRTT) was developed to study motor sequence learning (Nissen and Bullemer 1987) and studies using SRTT suggest a role for the striatum-based memory system in the sequence learning and predictive behaviors observed in this task in humans (Grafton et al. 1995; Rauch et al. 1997) and rats (Christie and Dalrymple-Alford 2004). Moreover, the serial implicit learning task (SILT) (Jay and Dunnett 2007) and extended sequence learning task (ESLeT) (Dunnett et al. 2012) also suggest striatum contribution to motor sequence learning. Some studies using SRT tasks, however, have also shown hippocampal contribution to the learning of higher order sequences, wherein successive stimuli could be predicted only from multiple preceding stimuli, in humans (Schendan et al. 2003) and rats (Ergorul and Eichenbaum 2006).

However, these previous studies mainly focused on sequence learning including discrimination learning of

sequences rather than recall of learned sequences. Furthermore, though the tasks with sequences of olfactory stimuli are suitable to study episodic memory in rats and mice because subjects can learn a sequence of odors in one or a few trials (Fortin et al. 2002; Kesner et al. 2002; Manns et al. 2007), these tasks cannot be used to investigate the neuronal mechanisms that regulate sequence recall and predictive behaviors as they require subjects to choose stimuli presented earlier in sampling phases but do not require them to employ predictive behaviors based on sequence recall. Therefore, it is not clear yet whether rats can perform predictive behaviors that are contingent on their recall of sequences when they come across a part of them. Human fMRI studies have reported increased activity in the hippocampus during the recall of learned sequences (Lehn et al. 2009; Ross et al. 2009). However, it is necessary to test the ability of rats to recall a sequence upon being presented with a part of the sequence in order to investigate the neuronal mechanisms of information processing of sequences.

In the present study, we investigate whether rats can anticipate future events and respond with predictive behaviors when they come across a part of a learned sequence of events but not when they are presented with a part of an unlearned sequence. For that, we used a behavioral task, a cued serial reaction time task (cSRTT), which was modified SRTT or ESLeT (Dunnett et al. 2012), to investigate memory recall of sequences of holes based on cue presentation and analyzed the reaction times of the rats' behavior in response to sequences of holes.

Materials and methods

A total of five male Wistar albino rats (Shimizu laboratory supplies, Kyoto, Japan) were used in this study. These rats were approximately 12 months of age and weighed between 520 and 560 g at the beginning of the experiment. They were individually housed with a 13-h/11-h light/dark cycle. Cage dimensions were 250 (long) $\times$ 150 (wide) $\times$ 240 (high) mm. Lights were kept on from 8:00 a.m. to 9:00 p.m. All behavioral training was conducted during the light phase of the cycle. All rats were fed lab chow between 1 and 3 h after their daily sessions to maintain their body weight at $>80\%$ of their free-feeding weight. Water was freely available in their home cages. All procedures were in accordance with the Kyoto University Animal Research Committee guidelines.

Behavioral training took place in an operant chamber [330 (long) $\times$ 300 (wide) $\times$ 455 (high) mm] placed in a shield box (Japan Shield Enclosure, Osaka). Five nose-poke holes (15 mm in diameter) were horizontally arranged (40 mm from center to center), 55 mm above the floor on a side wall. Each hole was equipped with an infrared

sensor to detect nose-pokes and also contained a light-emitting diode (LED). Another LED and a speaker for the buzzer were located on the upper wall. An automatic dispenser installed outside the chamber delivered a 25 mg food pellet to a magazine that was located 20 mm above the floor and 25 mm below the center hole. The behavioral task was controlled using a PC-9821 (NEC, Tokyo).

In cSRTT, the rats were required to produce three successive nose-poke responses, each of which required them to hold their nose in an illuminated hole for 2 s before moving to the next illuminated hole in the sequence, to get a reward (Fig. 1). The five holes were numbered 1–5 from left to right. The illumination sequences of 2–4–1 and 4–2–5 were fixed and defined as predictable sequences because the rats could predict the exact position of the next illuminated hole when either hole 2 or hole 4 was presented as the first illuminated hole by training in the repetition session. In the repetition session, these 2 predictable sequences of holes were repeatedly presented every ten trials. For example, the predictable sequence 2–4–1 was repeated for ten trials, then the predictable sequence 4–2–5 was repeated for ten trials, then the predictable sequence 2–4–1 was repeated for ten trials again, and so forth. The rats were trained by repetition session using a criterion of $\geq 80\%$ correct trials in a session. All rats but rat 16 reached the criterion in only one session (rat 16 needed four sessions). Then, the rats were tested on their ability to recall the learned sequences in the mixed session. In the mixed session, one predictable or one unpredictable sequence was presented pseudo-randomly in each trial, without repetition. Ten sequences beginning from hole 3 (3–1–2, 3–1–4, 3–2–1, 3–2–4, 3–2–5, 3–4–1, 3–4–2, 3–4–5, 3–5–2, 3–5–4) were defined as unpredictable sequences because the rats could not predict the exact position of the next illuminated hole when hole 3 was presented as the first illuminated hole. Subsequently, the repetition and mixed sessions were alternately conducted. The total numbers of repetition and mixed sessions for each rat were as follows (repetition/mixed), rat 1: 55 sessions/54 sessions, rat 3: 58 sessions/57 sessions, rat 16: 57 sessions/54 sessions, rat 23: 26 sessions/25 sessions, rat 24: 16 sessions/15 sessions. Learning curves were shown in Supplemental material. The intertrial interval was 5 s in both repetition and mixed sessions. The number of trials in a session used in the analysis was 80–160 and differed for each rat.

The reaction times (RTs) were defined as RT1, the elapsed time between the end of the first response and the beginning of the second response, and RT2, the elapsed time between the end of the second response and the beginning of the third response. If a nose-poke response was made to one of the non-illuminated holes, it was considered an error (ER). Cases when the rat did not respond to the next illuminated hole within the 2 s time limit or when it removed its nose

Fig. 1 Schematic of the cSRTT. An example of a sequence of holes (predictable sequence 2-4-1) is shown. First, one of the five holes and the LED on the wall were illuminated. The rat made a nose-poke response to the illuminated hole, which switched off both the illumination in the hole and the LED on the wall, and held its nose in the hole for 2 s (the first response). After nose-poking for 2 s, both the LEDs of the hole and on the wall were illuminated again. When the rat removed its nose from the hole, the illuminated hole was switched off and the other hole was illuminated. The rat again responded to the

illuminated hole within 2 s and held its nose in the hole for 2 s (the second response). After the rat removed its nose from the hole, the illuminated hole was switched off and a third hole, different from the already illuminated holes, was illuminated. The rat then responded to the illuminated hole within 2 s and held its nose in the hole for 2 s (the third response) as before and was rewarded. A trial would end when the rat was either rewarded or when it made an incorrect response

from the illuminated hole before 2 s had elapsed were defined as time error (TER) and hold error (HER), respectively. These errors led to the switching off of both the illuminated hole and the LED on the wall, and a 1 s buzzer noise was generated, following which no reward was given and the same trial was repeated (a correction trial).

We analyzed data that had both ≥ 80 trials and ≥ 80 % correct ratios in each session. We combined the RTs from the last three or five repetition sessions (five sessions were combined for rats 1, 3, and 16 because their mean trial numbers were not as high as those of rats 23 and 24; see Supplemental methods) and from the last ten mixed sessions. We analyzed the RTs using ex-Gaussian distribution, which is known to provide a good fit for the RT distribution (Dawson 1988; Heathcote et al. 1991). The ex-Gaussian distribution is defined by the following equation—probability density function:

$$f(x|\mu, \sigma, \tau) = \frac{1}{\tau\sqrt{2\pi}} \exp\left(-\frac{\sigma^2}{2\tau^2} - \frac{x-\mu}{\tau}\right) \cdot \int_{-\infty}^{\frac{x-\mu}{\sigma} - \frac{\sigma}{\tau}} \exp\left(-\frac{y^2}{2}\right) dy \quad (1)$$

where μ and σ correspond to the mean and the standard deviation (SD) of the Gaussian component, respectively, and τ corresponds to both the mean and the SD of the exponential component (Heathcote et al. 1991). The best-fitting ex-Gaussian parameters were estimated using maximum likelihood estimation.

In addition, we averaged RT1 and RT2 using the Vincent averaging method (Ratcliff 1979). The predictable sequences in the repetition session (Rep), the predictable sequences in the mixed session (Mix-P), and the unpredictable

sequences in the mixed session (Mix-U) were defined as sequence conditions. Note that we analyzed RTs in the Mix-U that were the same distances between holes as predictable sequences. For each rat, the Vincent histograms of RT1 (Rep: 2-4/4-2, Mix-P: 2-4/4-2, Mix-U: 3-1/3-5; note that RTs for only 3-5 of Mix-U was used in three rats because the animals exhibited a position bias (see Supplemental methods), and RT2 (Rep: 4-1/2-5, Mix-P: 4-1/2-5, Mix-U: 1-4/2-5/4-1/5-2) for each sequence condition were constructed (see Supplemental methods). The ex-Gaussian distribution was fitted to the Vincent histograms for estimating the ex-Gaussian parameters. In addition, means and SDs of the RTs that were used to construct Vincent histograms were calculated.

Sequences 2-4, 4-2, 2-5, and 4-1 of the latter half of the unpredictable sequences (3-2-4, 3-4-2, 3-2-5, and 3-4-1) were defined as Overlap-U because they had partially the same holes as the predictable sequences. RTs in the Overlap-U were averaged over subjects by Vincent averaging because the number of RTs in the Overlap-U was not adequate to analyze the distributions for each rat. In addition, we analyzed the percents of errors, TER and HER in the predictable and unpredictable sequences of holes in the mixed sessions. For example, the percent of errors on predictable sequences for each rat was obtained by dividing the total number of errors on predictable trials across sessions by the total number of predictable trials across sessions.

Results

The ex-Gaussian parameters for the RTs in each sequence condition (Rep, Mix-P, and Mix-U) were compared to

Fig. 2 Predictive responses on the basis of the recall of predictable sequences of holes. Estimated μ , σ , τ parameters, means and SDs averaged over subjects in each sequence condition in RT1 (a) and RT2 (b). Error bars represent $\pm$ SD. Asterisks indicate significant differences ($*p < 0.05$, $**p < 0.01$) as assessed by multiple comparisons (Ryan's method). Rep: the repetition session, Mix-P: the

predictable sequence in the mixed session, Mix-U: the unpredictable sequence in the mixed session. c Percent error (ER), time error (TER) and hold error (HER) for the predictable (P) and unpredictable (U) sequences in the mixed sessions. Error bars represent $\pm$ SD. Asterisks indicate significant differences ($***p < 0.001$), as assessed by simple main effect test of sequence condition

determine whether the rats responded with predictive behaviors based on their recall of the predictable sequences of holes. In addition, the mean RTs and their SDs in each sequence condition were analyzed and compared with the results of the ex-Gaussian analysis. A one-way repeated-measures ANOVA followed by Ryan's method for multiple comparisons was used for each estimated ex-Gaussian parameter, mean and SD. Figure 2a, b shows the averaged values of the estimated parameters, means and SDs in RT1 and RT2.

For μ and σ in RT1, there was no significant difference between sequence conditions. For τ in RT1, the main effect of sequence condition was significant ($F_{(2,8)} = 6.37$, $p < 0.05$) and the value of τ for Mix-U significantly increased compared with that for Rep (Ryan's method: $p < 0.05$) (Fig. 2a). However, in contrast with μ and σ in RT1, the use of means and SDs in RT1 yielded a significant main effect of sequence condition (mean: $F_{(2,8)} = 17.27$, $p < 0.01$; SD: $F_{(2,8)} = 9.41$, $p < 0.01$). The means for Mix-U were significantly increased compared with those for Rep and Mix-P (Ryan's method: Rep vs. Mix-U, $p < 0.01$; Mix-P vs. Mix-U, $p < 0.05$), and the SDs for Mix-U were significantly increased compared with those for Rep (Ryan's method: $p < 0.01$) (Fig. 2a).

For μ and σ in RT2, the main effect of sequence condition was significant (μ : $F_{(2,8)} = 40.05$, $p < 0.001$; σ :

$F_{(2,8)} = 64.01$, $p < 0.001$) and the values of μ and σ for Mix-U were significantly increased compared with those for Rep (Rep vs. Mix-U, μ : $p < 0.01$, σ : $p < 0.01$) and Mix-P (Mix-P vs. Mix-U, μ : $p < 0.01$, σ : $p < 0.01$), respectively (Fig. 2b). For τ in RT2, the main effect of sequence condition was significant ($F_{(2,8)} = 7.92$, $p < 0.05$), and the value of τ for Rep were significantly decreased compared with those for Mix-P (Ryan's method: Rep vs. Mix-P, $p < 0.05$) and Mix-U (Ryan's method: Rep vs. Mix-U, $p < 0.05$), respectively (Fig. 2b). Similarly to μ and σ in RT2, the use of means and SDs in RT2 yielded a significant main effect of sequence condition (mean: $F_{(2,8)} = 68.53$, $p < 0.001$; SD: $F_{(2,8)} = 89.02$, $p < 0.001$). The means and SDs for Mix-U were significantly increased compared with those for Rep (Ryan's method: mean: Rep vs. Mix-U, $p < 0.01$; SD: Rep vs. Mix-U, $p < 0.01$) and Mix-P (Ryan's method: mean: Mix-P vs. Mix-U, $p < 0.01$; SD: Mix-P vs. Mix-U, $p < 0.01$) (Fig. 2b). However, in contrast with μ and σ in RT2, the means and SDs for Mix-P were significantly increased compared with those for Rep (Ryan's method: mean: $p < 0.05$; SD: $p < 0.01$) (Fig. 2b).

Figure 2c shows the percents of errors (ER), TER and HER for Mix-P and Mix-U in the mixed sessions. A two-way ANOVA followed by Ryan's method for multiple comparisons was used for the analysis of errors. The main effect of sequence condition was significant ($F_{(1,8)} = 14.81$, $p < 0.05$),

Fig. 3 Discrimination between Mix-P and Overlap-U. Cumulative distributions of RTs and the best fitting ex-Gaussian curves for the first half (a) and second half (b) of the predictable sequences in the mixed sessions (Mix-P) and unpredictable sequences that have partially the same holes as the predictable sequences [Overlap-U: 2-4 and 4-2 of 3-2-4 and 3-4-2 (a), 4-1 and 2-5 of 3-4-1 and 3-2-5 (b)]. Note that these RTs were averaged by Vincent averaging over subjects. Estimated μ , σ , and τ parameters of the best fitting ex-Gaussian curves for the cumulative distributions of 2-4/4-2 (c) and 4-1/2-5 (d) in the Mix-P and Overlap-U

and was qualified by a significant interaction between sequence condition and error condition ($F_{(2,8)} = 13.21$, $p < 0.01$). The simple main effect of sequence condition for ER were significant ($F_{(1,12)} = 39.60$, $p < 0.001$). The simple main effect of error condition for the Mix-U was significant ($F_{(2,16)} = 9.95$, $p < 0.01$). Multiple comparisons indicated significant differences between ER and TER and between ER and HER (ER vs. TER: $p < 0.01$, ER vs. HER: $p < 0.01$).

Next, we examined whether the rats responded predictively to the Overlap-U sequence of holes. The second half of 3-2-4/3-4-2 (i.e., 2-4/4-2) in Overlap-U was compared with the first half of Mix-P, and the second half of 3-4-1/3-2-5 (i.e., 4-1/2-5) in Overlap-U was compared with the second half of Mix-P. Figure 3a, b shows the cumulative distribution curves, which consist of data averaged by Vincent averaging over subjects and the best fitting ex-Gaussian curves. Both 2-4/4-2 and 4-1/2-5 distributions showed significant differences between Overlap-U and Mix-P (Fig. 3a, b, Kolmogorov–Smirnov test, 2-4/4-2: $p < 0.05$, 4-1/2-5: $p < 0.001$). Figure 3c, d shows the estimated parameters of the ex-Gaussian curves shown in Fig. 3a, b. Similar to the results in Fig. 2b, the μ and σ values for Mix-P were decreased compared with those for Overlap-U, and the τ value was almost the same for Mix-P and Overlap-U in both 2-4/4-2 (c) and 4-1/2-5 (d) distributions.

Discussion

We found no significant difference in μ and σ between Rep and Mix-P in RT1 and RT2. This result indicates that the rats responded predictively to Mix-P because the Gaussian part of the RT distributions of Rep and Mix-P in RT1 and RT2 were similar. In addition, we found no significant difference in μ and σ between Mix-U and the other two sequence conditions in RT1. This result can be attributed mainly to a position bias in the second responses to Mix-U in three rats (rats 3, 16, and 23), and does not mean predictive responses to unpredictable sequences. Although there were significant differences in mean and SD between Rep and Mix-U in RT1, and between Rep and Mix-P in RT2, the exponential part of RT distributions may have misled these significant differences. In fact, we found a significant difference in τ between Rep and Mix-U in RT1, and between Rep and Mix-P in RT2. Moreover, the finding that the μ and σ values for Mix-U in RT2 were significantly increased compared with those for Rep and Mix-P indicates that the rats did not respond predictively to Mix-U in RT2. In addition, the finding that the rats responded more accurately to Mix-P than they responded to Mix-U indicates that the rats responded predictively to Mix-P. Furthermore, the RT distribution of Overlap-U was significantly different from that of Mix-P, and the RTs of

Overlap-U were distributed to the slower side compared with those of Mix-P. Therefore, the rats did not predict the exact positions of the next illuminated holes for Overlap-U and discriminated Mix-P from Overlap-U.

There was no significant difference in τ between Mix-P and Mix-U, whereas there were significant differences in this parameter between Rep and the other two sequence conditions in RT2. Therefore, the τ value may reflect the effect of changing the sequence of holes presented at each trial, rather than that of predictability. In humans, task-switch costs (performance deterioration) are observed when one of two tasks is presented at random on each trial as compared with when a task is repeatedly presented (Souza et al. 2012; Steinhauser and Hübner 2009). Similarly, a list-switch cost is produced when a to-be-remembered list of digits is changed on each trial (Oberauer 2005). The list-switch cost is also produced when the subjects are required to retrieve one of three well-learned lists presented at random (Souza et al. 2012). Both task- and the list-switch costs are caused by a proactive effect; it is assumed that after a switch, responses are influenced by the trial immediately preceding the switch (Souza et al. 2012; Steinhauser and Hübner 2009). A previous study reported that task-switch cost is reflected in the τ parameter of the ex-Gaussian distribution (Steinhauser and Hübner 2009). Thus, it is possible that the significant differences in τ between Rep and Mix-P in RT2 (Fig. 2b) reflect the list-switch cost in humans as reported by Souza et al. (2012). This list-switch cost may be interpreted as the time cost for the retrieval of learned sequences from long-term memory (Oberauer 2005; Souza et al. 2012). Thus, the RT distribution analysis using an ex-Gaussian function enabled us to determine the relation between the ex-Gaussian parameters and cognitive functions. Moreover, analysis performed using mean RTs could be misleading.

In summary, the present study not only showed that the rats recalled predictable sequences of holes when they came across the first stimulus of those sequences but also that they discriminated between predictable and unpredictable sequences upon sequence recall. These means that predictive responses were triggered by the position of the first illuminated hole rather than only the position of illuminated holes, i.e., by integrating the position of the sequence with the position of the illuminated holes.

The present behavioral task was very similar to the ESLeT reported by Dunnett et al. (2012). In the ESLeT, rats were required to perform five successive nose-poking periods, and the position of the first illuminated hole informed the rats on whether the following sequence was a predictable or unpredictable one, as in our task. However, the ESLeT was an implicit learning task for rats, similar to the human SRTT, to learn a predictable sequence. In contrast, the rats in our task learned two predictable

sequences in the repetition session, and the repetition and mixed sessions were interleaved. Therefore, our task may not be an implicit learning task. Moreover, predictability could be reflected to a greater extent in the RTs in our task compared with the ESLeT because the rats were able to prepare to respond to the next illuminated holes during the nose-poking periods for 2 s during each trial. In fact, the differences in speed (especially in RT2) and accuracy between predictable and unpredictable sequences were apparent in the present task. Therefore, the RTs observed in our behavioral task may reflect a more habitual behavior or more explicit recall of sequences than those observed in the ESLeT. In addition, our previous study reported episode-dependent neuronal activity in the hippocampus during the nose-poking period for 1 s in the delayed spatial alternation task (Takahashi et al. 2009). Therefore, the nose-poking periods in our behavioral task may be useful to investigate neuronal activity related to information processing of internal and external events, including sequences.

Using this behavioral task, we can now investigate the neuronal mechanism that mediate the recall of sequences by recording neuronal activity from the hippocampus of rats performing the task because the hippocampus is believed to be critical for integrating information and for associative learning (Rawlins 1985; Wallenstein et al. 1998). However, the present behavioral task may be striatum-dependent rather than hippocampus-dependent because overtraining has been shown to decrease the hippocampal contribution and instead increase the striatal contribution (Schendan et al. 2003; Packard and Knowlton 2002; Poldrack et al. 2001). Nevertheless, a previous study reported hippocampal activity in an early sequence acquisition stage as well as during a later stage with stabilized learning effect (Gheysen et al. 2010) and another study reported that hippocampal activity increased more during the period of recall of learned sequences than during the period of sequence learning (Ross et al. 2009). Moreover, a study with rats reported a role for the hippocampus in the discrimination of overlapping sequences of odors even after extensive training (Agster et al. 2002). These studies suggest that the hippocampus may play a role for the recall of learned sequences and the discrimination of overlapping sequences even after sufficient learning. In future work, it will be necessary to investigate whether behavior in this task is hippocampal or striatum dependent using pharmacological and/or lesion experiments, and to investigate the neuronal mechanisms of the hippocampal and striatum memory systems that are used for the recall of learned sequences.

Various brain regions, for example, prefrontal cortex, parietal cortex, premotor cortex, cerebellum and the supplementary motor area (Rauch et al. 1997; Willingham et al. 2002) as well as the hippocampus and striatum have

been implicated in sequence learning. Thus, these regions as well as the hippocampus could be involved in the recall of learned sequences when part of the sequence is presented (Ross et al. 2009). Therefore, this behavioral task could also be useful to study neuronal networks for the recall of learned sequences by simultaneously recording neuronal activity from several regions.

Acknowledgments This study was supported by JSPS KAKENHI Grant Nos. 245242 (S.I.), 24243069, and 24223004 (Y.S.). We thank all the members of the laboratory for their advice.

References

- Agster KL, Fortin NJ, Eichenbaum H (2002) The hippocampus and disambiguation of overlapping sequences. *J Neurosci* 22:5760–5768
- Christie MA, Dalrymple-Alford JC (2004) A new rat model of the human serial reaction time task: contrasting effects of caudate and hippocampal lesions. *J Neurosci* 24:1034–1039
- Dawson MRW (1988) Fitting the ex-Gaussian equation to reaction time distributions. *Behav Res Meth Instrum Comput* 20:54–57
- Devito LM, Eichenbaum H (2011) Memory for the order of events in specific sequences: contributions of the hippocampus and medial prefrontal cortex. *J Neurosci* 31:3169–3175
- Dunnett SB, Fuller A, Rosser AE, Brooks SP (2012) A novel extended sequence learning task (ESLeT) for rodents: validation and the effects of amphetamine, scopolamine and striatal lesions. *Brain Res Bull* 88:237–250
- Ergorul C, Eichenbaum H (2006) Essential role of the hippocampal formation in rapid learning of higher-order sequential associations. *J Neurosci* 26:4111–4117
- Fortin NJ, Agster KL, Eichenbaum HB (2002) Critical role of the hippocampus in memory for sequences of events. *Nat Neurosci* 5:458–462
- Gheysen F, Van Opstal F, Roggeman C, Van Waelvelde H, Fias W (2010) Hippocampal contribution to early and later stages of implicit motor sequence learning. *Exp Brain Res* 202:795–807
- Ginther MR, Walsh DF, Ramus SJ (2011) Hippocampal neurons encode different episodes in an overlapping sequence of odors task. *J Neurosci* 31:2706–2711
- Grafton ST, Hazeltine E, Ivry R (1995) Functional mapping of sequence learning in normal humans. *J Cogn Neurosci* 7:497–510
- Heathcote A, Popiel SJ, Mewhort MDJ (1991) Analysis of response time distributions: an example using the stroop task. *Psychol Bull* 109:340–347
- Jay JR, Dunnett SB (2007) An operant serial implicit learning task (SILT) in rats: task acquisition, performance and the effects of striatal lesions. *J Neurosci Meth* 163:235–244
- Kesner RP, Gilbert PE, Barua LA (2002) The role of the hippocampus in memory for the temporal order of a sequence of odors. *Behav Neurosci* 116:286–290
- Kumaran D, Maguire EA (2006) The dynamics of hippocampal activation during encoding of overlapping sequences. *Neuron* 49:617–629
- Lehn H, Steffenach HA, van Strien NM, Veltman DJ, Witter MP, Håberg AK (2009) A specific role of the human hippocampus in recall of temporal sequences. *J Neurosci* 29:3475–3484
- Manns JR, Howard MW, Eichenbaum H (2007) Gradual changes in hippocampal activity support remembering the order of events. *Neuron* 56:530–540
- Nissen MJ, Bullemer P (1987) Attentional requirements of learning: evidence from performance measures. *Cogn Psychol* 19:1–32
- Oberauer K (2005) Control of the contents of working memory—a comparison of two paradigms and two age groups. *J Exp Psychol Learn Mem Cogn* 31:714–728
- Packard MG, Knowlton BJ (2002) Learning and memory functions of the basal ganglia. *Annu Rev Neurosci* 25:563–593
- Poldrack RA, Clark J, Paré-Blagoev EJ, Shohamy D, Crespo Moyano J, Myers C, Gluck MA (2001) Interactive memory systems in the human brain. *Nature* 414:546–550
- Ratcliff R (1979) Group reaction time distributions and an analysis of distribution statistics. *Psychol Bull* 86:446–461
- Rauch SL, Whalen PJ, Savage CR, Curran T, Kendrick A, Brown HD, Bush G, Breiter HC, Rosen BR (1997) Striatal recruitment during an implicit sequence learning task as measured by functional magnetic resonance imaging. *Hum Brain Mapp* 5:124–132
- Rawlins JN (1985) Associations across time: the hippocampus as a temporary memory store. *Behav Brain Sci* 8:479–528
- Ross RS, Brown TI, Stern CE (2009) The retrieval of learned sequences engages the hippocampus: evidence from fMRI. *Hippocampus* 19:790–799
- Schendan HE, Searl MM, Melrose RJ, Stern CE (2003) An fMRI study of the role of the medial temporal lobe in implicit and explicit sequence learning. *Neuron* 37:1013–1025
- Souza AS, Oberauer K, Gade M, Druey MD (2012) Processing of representations in declarative and procedural working memory. *Q J Exp Psychol (Hove)* 65:1006–1033
- Steinhauser M, Hübner R (2009) Distinguishing response conflict and task conflict in the Stroop task: evidence from ex-Gaussian distribution analysis. *J Exp Psychol Hum Percept Perform* 35:1398–1412
- Takahashi M, Lauwereyns J, Sakurai Y, Tsukada M (2009) Behavioral state-dependent episodic representations in rat CA1 neuronal activity during spatial alternation. *Cogn Neurodyn* 3:165–175
- Wallenstein GV, Eichenbaum H, Hasselmo ME (1998) The hippocampus as an associator of discontiguous events. *Trends Neurosci* 21:317–323
- Willingham DB, Salidis J, Gabrieli JD (2002) Direct comparison of neural systems mediating conscious and unconscious skill learning. *J Neurophysiol* 88:1451–1460