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# Dynamic of spatio-temporal binding in rats

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23 **Abstract**

24 Time and space are commonly approached as two distinct dimensions, and rarely combined  
25 together in a single task, preventing to compare their interaction. In this project, using a version of a  
26 timing task with a spatial component, we investigate the learning of a spatio-temporal rule in  
27 animals. To do so, rats were placed in front of a 5-hole nose-poke wall in a Peak Interval (PI)  
28 procedure to obtain a reward, with two spatio-temporal combination rules associated with different  
29 to-be-timed cues and lighting contexts. We report that, after successful learning of the  
30 discriminative task, a single Pavlovian session was sufficient for the animals to learn a new spatio-  
31 temporal association. This was evidenced as a beneficial transfer to the new spatio-temporal rule, as  
32 compared to control animals that did not experience the new spatio-temporal association during the  
33 Pavlovian session. The benefit was observed until 9 days after. The results are discussed within the  
34 framework of adaptation to a change of a complex associative rule involving interval timing  
35 processes.

36

37 **Introduction**

38 Can we access time without having another dimension associated to it, such as an action, or  
39 space, or a sequential event? Aristotle proposed that the spatial and temporal contingencies are  
40 intrinsically linked together, and cannot be dissociable. Since the 19<sup>th</sup> century, with the emergence  
41 of behavioral experiments, several scientists studied the interaction of these two dimensions; for  
42 example, Piaget found that children base their judgements of time and duration on their experience  
43 of distance (Piaget, 1927/1969). Fairly recent data confirm that representation of duration is  
44 expressed through distance notions, but not the reverse, showing that space and time are  
45 asymmetrically dependent on each other (Casasanto and Boroditsky, 2008). To what extent these  
46 are bound together, in terms of learning and adaptation to spatio-temporal changes is not yet clear.

47 Skinner pointed out the difficulty to experimentally dissociate between where and when an  
48 event occurred, as the memory of the event itself is built on this very association (Skinner 1956;  
49 Meck et al, 1984; Crystal, 2009; Meck et al, 2013; Church, 2013 for a more recent review see  
50 Church 2014). Many studies have focused on the animal's abilities to learn, consolidate and retrieve  
51 spatial or temporal information, although to a lesser extent for the latter, disregarding the potential  
52 involvement of the other (space or time) parameter. Spatial memory in animals has been extensively  
53 studied through the use of arena exploration, in radial maze (Olton et al, 1977) and the Morris water  
54 maze (Morris et al, 1986) in rodents, and many other more complex and ethological experimental  
55 setups, such as arena with food cached for monkeys (Lavanex and Lavanex, 2006), rodents (Jacobs  
56 and Limans, 1991; Jacobs 1992; Davenport et al, 2000; Gould et al 2010), and even pigs (Mendl et  
57 Al, 1997). In comparison, learning of the temporal dimension has been less investigated. Mainly,  
58 time processing has been assessed either through the sequential order of events (Fortin et al, 2002;  
59 Kesner et al, 2002), or through the time interval (the duration of a segment of time) (Church et al,  
60 1976; Holders and Roberts, 1985; for a review see Buhusi and Meck, 2005). In a Pavlovian task  
61 combining reinforcement time with locations and reinforcement probabilities, a recent study  
62 indicates that mice could learn to associate time intervals and locations in order to optimize their  
63 behavior (Tosun et al, 2016). However, it is not known to what extent this behavior is flexible when  
64 new spatio-temporal rules are learned, and to what extent time and location are bound in memory.

65 Considering their ecological occurrence, time and space are two dimensions that cannot be  
66 dissociated. Indeed, the ability to learn the spatio-temporal variability of important events can  
67 confer considerable advantages to animals in the context of both resources seeking as well as  
68 predators' avoidance (Crystal 2009). The associative learning of space and time is also referred to  
69 as place-time learning, and it has been demonstrated possible with classical conditioning in animals  
70 (Wilkie et al, 1997; Thorpe and Wilkie, 2002). Gallistel (1990) proposed that whenever a  
71 biologically significant event occurs, a memory code is created that contains the nature of the event,

72 as well as the time and place in which it occurred, constituting a tripartite memory. However, still,  
73 very little is known regarding the learning of a spatio-temporal (-event or -reward) memory.

74 Animals can learn time fast (Davis et al, 1989; Bevins and Ayres, 1995; Balsam et al, 2002;  
75 Diaz-Mataix et al, 2013), and adapt rapidly (i.e. within a few sessions) to changes in temporal rules  
76 in a peak interval protocol (Lejeune et al, 1997; Guilhardi et al, 2005; Sanabria et al, 2014; Dallérac  
77 et al, 2017). Similarly, animals can also adapt quickly to changes in a spatial rule from session to  
78 session (Morris et al, 1986; Blanco et al, 2006). Tosun et al. (2016) demonstrated that animals can  
79 make Bayesian inferences based on spatio-temporal knowledge they previously learned to optimize  
80 their time-switching behavior to get the food reward. How the animal learns these two dimensions,  
81 and to what extent they are independent of each other, remains unclear.

82 The aim of the present study was to investigate the dynamics of learning location and time  
83 when associated together. For this purpose, learning of spatio-temporal rules was manipulated in a  
84 memory paradigm including 3 phases (See Figure 1 for the experimental design): **(phase 1)**  
85 **Instrumental training phase of specific spatio-temporal rules associated to different contexts:**  
86 a Peak Interval (PI) task combining the learning of contextual (different house lights and tone  
87 frequencies), spatial (nose poke) and temporal (peak interval) information; **(phase 2) Spatio-**  
88 **temporal shift in a single Pavlovian session to control the amount of exposure to stimuli and**  
89 **reinforcement during the learning of a new spatio-temporal rule:** some rats were shifted to a  
90 new spatio-temporal association (new location and new time) specific to one context using a  
91 Pavlovian paradigm, while the others were kept to the trained spatio-temporal rule; **(phase 3)**  
92 **Instrumental training following the new spatio-temporal rule to assess the impact of the**  
93 **preceding session and the dynamic of learning a spatio-temporal association:** during nine days,  
94 the new spatio-temporal rule was enforced for all animals under the PI procedure. We expected that  
95 the rat exposed to the shift in phase 2 will benefit from this training, and show a better learning of  
96 the new spatio-temporal rule in phase 3 than the control group. Our analysis aimed at determining

97 whether the benefit is observed for either location or time, or both, and at deciphering to what  
98 extent the learning of new location and new time are linked.

99

## 100 **Material and Method**

### 101 *Animals*

102 12 adult male Sprague-Dawley rats (Janvier, France; average weight 320g) were housed in pairs in  
103 Plexiglas cages, with food and water *ad libitum*. After one week of adaptation, food access was restricted to  
104 keep the animals at 85% of their normal weight. The experiment was performed in accordance with the  
105 recommendations of the European Economic Community (86/609/EEC) and the French National Committee  
106 (87/848) for care and use of laboratory animals.

107 *refaite*

### 108 **Figure 1: Experimental design**

109 (A) Phase 1: Training / Experimental paradigm for the learning of the spatio-temporal association: in context A (red light), the first nose-poke in the  
110 hole#2 lit (empty circle) after 15s after the onset of a 1kHz tone is rewarded (1 pellet), with a maximum tone duration of 45s (also duration of probe  
111 non-reinforcement trials/reinforcement trials), whereas in context B (green light) the spatio-temporal rule is hole#4 reinforced after 60s and a  
112 maximum tone duration of 120s. (B) Phase 2: Pavlovian spatio-temporal shift/ The experimental group is presented a Pavlovian session with a new  
113 spatio-temporal rule in context B (Hole#1 lit is reinforced with 3 pellets at 30s after tone onset), while the control group is presented the previous rule  
114 (hole#4, reinforced at 60s). Both groups are then presented the intact context A (hole#2 lit, reinforced at 15s) in a Pavlovian manner as well. (C)  
115 Phase 3: Dynamic of spatio-temporal learning (days 1 to 9 after phase 2). Both groups are presented the new rule (hole#1, 30s) in context B, while the  
116 paradigm associated to context A (hole#2, 15s) remains the same as in initial training. For these sessions, all the nose-poke holes are lit.

117

### 118 *Apparatus*

119 The experiment took place inside cages (Rat Test Cage, Coulbourn Instruments, USA; dimensions in  
120 cm: 30Lx25lx30h) with a 5-holes nose-poke wall on the left (each hole being 2.5 cm of diameter and spaced  
121 by 2 cm, « 5-holes nose poke », Coulbourn Instruments), a magazine (4x3x3cm) connected to a feeder on the  
122 opposite side to deliver the reward (45 mg pellets, Rodent Grain-Based Diet, Bioserv). The magazine was lit  
123 when the reward was delivered. Two house-lights were the only light source in the cage during the trials, one

124 green and one red placed at two distinct extremities of the cage, and served as contextual cues in addition to  
125 auditory cues- see below. A speaker was placed on the top of the chamber for delivery of sounds as timing  
126 cues. Each of the 5 holes and the magazine were equipped with photoelectric cells to register the activity  
127 (nose-poke, NP) of the animals. The cages were placed into a ventilated (background noise, 65dB)  
128 soundproof box. The experiment was monitored by the software Graphic State (Coulbourn instruments,  
129 USA).

130

### 131 *Protocol*

#### 132 *Phase 1: Training*

133 *Pre-training:* On the first day of the experiment, the rat was placed into the operant box for a 30 min  
134 session on Continuous Reinforcement (CRF). At the beginning of the session, two pellets were placed into  
135 each of the 5 lit holes of the nose-poke wall to encourage the animal to visit them. Each time the animal  
136 entered one of the holes, the magazine lit and a pellet was delivered. When the animal entered its nose in the  
137 magazine, the light switched off and a new trial began.

138 *Training:* The aim of this phase was to train the animals to learn a complex spatio-temporo-  
139 contextual rule. From day 2 for 41 sessions (8 weeks), the animals were submitted to a Peak-Interval (PI)  
140 procedure in which they were presented with two different spatio-temporal rules, each associated with a  
141 specific context, presented each day in a pseudo randomized order (A followed by B, or B followed by A).  
142 Those two contexts were made distinguishable by a house light, red for context A vs. green for context B,  
143 and two different timing cues (1kHz-80dB and 11kHz-80dB tones, for A and B respectively). Each context  
144 was associated with a spatial rule indicated by a light in one of the nose-poke holes (hole#2 in A and #4 in  
145 B). The reward was delivered according to a different Fixed-Interval (FI) in each context (15s after tone  
146 onset in A, and 60s after tone onset in B) : the first nose-poke after the time into the appropriate hole  
147 triggered the delivery of reinforcement and switched on the magazine light and turned off the tone. Probe  
148 trials, in which no reinforcement delivery was programmed, consisted of 45s for the tone associated with the

149 FI 15s, and 120s for the FI 60s. Thus, the animal learnt two spatio-temporal rules, each associated to a  
150 specific context (context A: hole#2-15s; context B: hole#4-60s, see figure 1A).

151 In order to keep the animal motivated at the beginning of training, we began with 8 Probe trials for 49  
152 reinforcement trials in each context (the first trial in each context was always reinforced), for 10 sessions.  
153 Then, we used a ratio of 24 Probe for 37 reinforcement trials until the 8 weeks of training were completed.  
154 The inter-trial-interval (ITI) randomly varied between 5 and 30 seconds (15 s on average) in the context A  
155 and between 10 and 30 seconds (20 s on average) in B.

156

### 157 *Phase 2: Shift of the spatio-temporal association*

158 In this part of the experiment (day 41), two groups (n=6) were formed, and equilibrated according to  
159 their performances. All rats were submitted to a single session during which 3 pellets were delivered in a  
160 Pavlovian manner at the end of the timing cue, independently of the animal's behavior. We began with 8  
161 trials in context B (figure 1B, right side) , during which the control group received the rewards according to  
162 the previously learnt association (hole#4 lit - 60s), whereas the experimental group was submitted to a shift  
163 of this associative rule, with the rewards delivered in another hole at another time (hole#1 lit - 30s).  
164 Immediately following this phase, 8 trials rewarded with 3 pellets in context A were also presented in a  
165 Pavlovian manner, while keeping its corresponding spatio-temporal rule (hole#2 lit-15s, figure 1B, left side).

166

### 167 *Phase 3: Dynamic of spatio-temporal learning*

168 The Phase 3 was designed to assess, in the 9 following days, the impact of the single Pavlovian  
169 session during which the spatio-temporal rule was shifted, through the measurement of the behavioral  
170 adaptation to this new rule in the instrumental task. Therefore, in the context B, only the new rule hole#1 –  
171 30s was reinforced (all holes were lit) while in the context A the rules remained unchanged (hole#2, 15s). A  
172 rapid learning of the spatio-temporal We hypothesized thatthe experimental group would benefit from the  
173 previous exposure to the new spatio-temporal rule, and will show better or faster adaptation in comparison to

174 the control group. The duration of the Probe trials remained as in phase 1. The first day after phase 2, the rats  
175 were submitted to context B first, and then to context A, but the order was pseudo-randomized for the  
176 following sessions.

177

178

179 *Statistical analyses*

180 Only the unreinforced probe trials were used to analyze the behavior of the animals. The spatial  
181 behavior was assessed by measuring for each rat the percentage of number of nose-pokes (NP) in each hole,  
182 then averaged per group. The temporal behavior associated to each hole was analyzed by plotting the  
183 function for rate of response (NP) against 1s time bins in context A and 2s time bins in context B. For  
184 comparison of temporal behavior between holes for the sessions after the shift, the temporal activity was  
185 normalized by the overall activity of the rats for the hole of interest.

186 The statistical analyses were performed by SPSS, JASP and Prism. Frequentist ANOVAs Student t-  
187 tests were used to assess the spatial and temporal learning. We used an alpha level of .05 for all statistical  
188 tests. Bayesian ANOVAs were further conducted to better characterize findings in the temporal behavior.

189

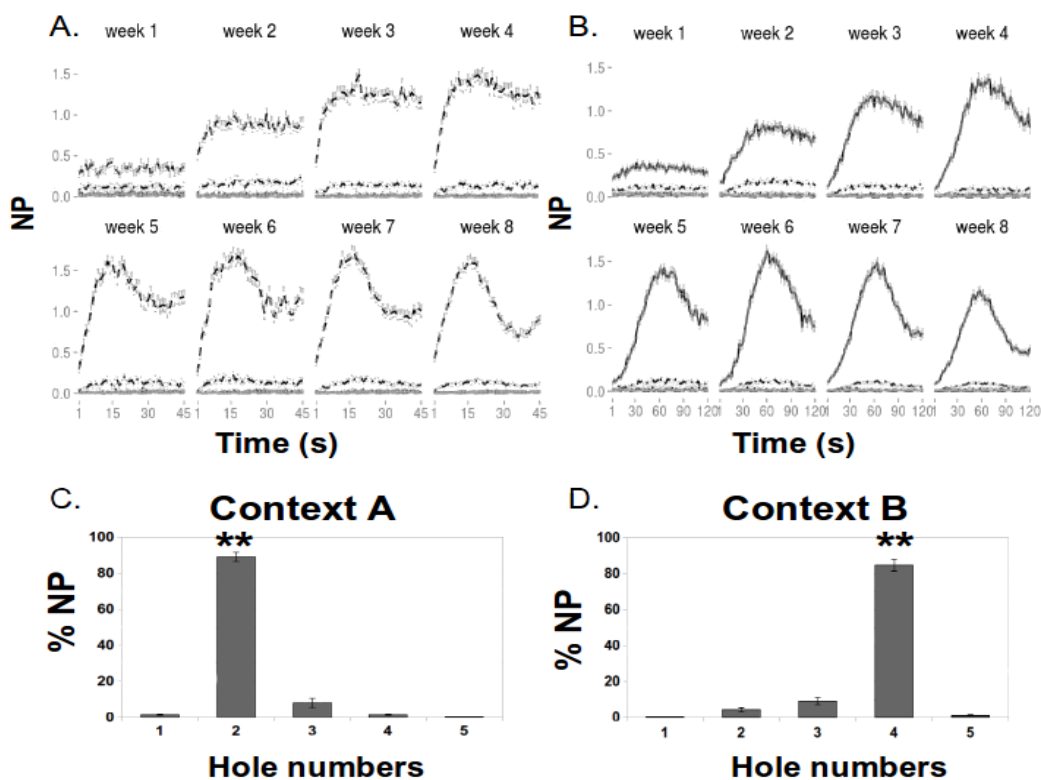
## 190 **Results**

191 *Training phase*

192 The temporal behavior associated to each hole in each context over the course of the 8 weeks  
193 of training of phase 1 is shown in figure 2A and B. A differential behavior associated to each  
194 spatio-temporal rule developed progressively with training up to a well segregated temporal  
195 behavior, with numbers of nose-poke peaking around 15s in Hole #2 in context A and around 60s in  
196 Hole #4 in context B. The spatial behavior was also well segregated, as shown in figure 2C and D.

197 In effect, during the last week of training (week 8), the number of visits for the holes of interest of  
 198 each context were significantly higher than for the other holes, as revealed by the Paired t-tests  
 199 analyses: the Hole #2 was more visited in context A (NP= 88%, SE=2.7) than in B (NP=3.8%,  
 200 SE=1.1) ( $t(10)=29.4, p<.001$ ), while the Hole#4 was more visited in context B (NP=86%, SE=2.6)  
 201 than in context A (NP=1.4%, SE=0.3) ( $t(10)=32.6, p<.001$ ).

202



203

204 **Figure 2: spatio-temporal training**

205 Temporal behavior over the 8 weeks of training in each hole in context A with nose-poke reinforced if in hole #2 after 15s after tone onset (A), and in  
 206 context B with nose-poke reinforced if in hole#4 after 60s after tone onset (B). Number of Nose-Poke (NP) (+/-SE in grey ribbon) in function of time  
 207 (s) for each of the holes. Spatial performance expressed as a percentage of number of Nose-Poke (+/-SE) in the 5 holes at the end of training (week 8)  
 208 in context A (C) and in context B (D). \*\*  $p<.001$  compared to all the other holes.

209

210 *Dynamic of spatio-temporal association*

211 In Phase 2, half of the animals (experimental group) were subjected to a change of the spatio-  
212 temporal rule in context B only, from 60s-Hole#4 to 30s-Hole#1, in a Pavlovian session. The other  
213 half (control group) were also submitted to a Pavlovian session, but keeping the initial spatio-  
214 temporal association. From day 1 to day 9 of Phase 3, the new spatio-temporal (30s-Hole#1) rule  
215 was enforced in context B for both groups. The impact of Phase 2 (Shift of the association) was  
216 expected to be observable during the next session (expecting a benefit for the experimental group),  
217 when both groups were returned to the peak interval procedure with the new spatio-temporal rule  
218 enforced in context B and all the holes lit. The analysis of behavior on day 9 aimed to determine  
219 whether the benefit might have weakened because both groups were further trained under the new  
220 FI schedule.

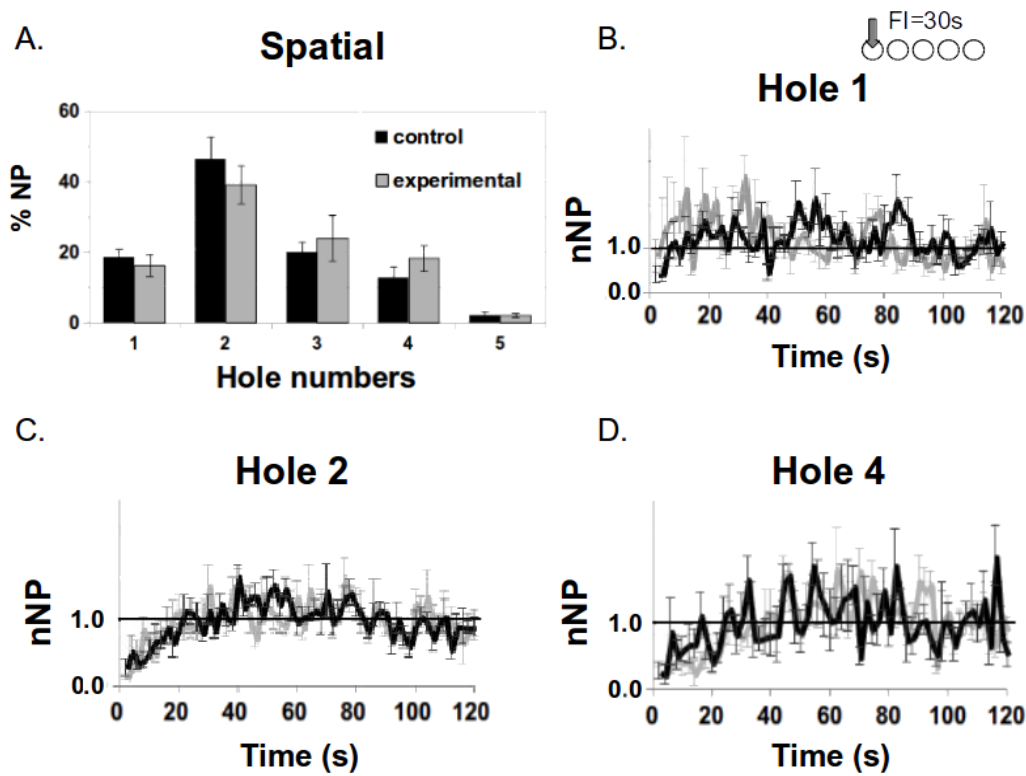
221

#### 222 *Day +1 after the Shift of the association– Context B*

223 From day 1 to day 9 of Phase 3, the new spatio-temporal (30s-Hole#1) rule was enforced in  
224 context B for both groups. The impact of Phase 2 (Shift of the association) was assessed during the  
225 first session of the instrumental task (day+1), expecting a benefit for the experimental group. As  
226 shown in figure 3A, the spatial behavior of the animals at Day+1 was distributed over several holes,  
227 and clearly differed from their behavior at the end of training during Phase 1 (see figure 2D). We  
228 focused our analyses on three of the holes, the new and old reinforced holes (#1, #4, respectively),  
229 as well as the hole reinforced in the other context (#2). There was no difference between groups for  
230 any of these holes ( $t(10) < 1.12$ , ns). Compared to their behavior in Phase 1, the animals decreased  
231 significantly their visits in the old hole #4 ( $t(10) = -17.84$ ,  $p < .001$ ), and increased their visits in the  
232 new hole #1 ( $t(10) = 9.56$ ,  $p < .001$ ). However, even if the hole #2 was not reinforced in this context,  
233 we also observed a significant increase of visits of this hole ( $t(10) = 8.74$ ,  $p < .001$ ). Surprisingly, the  
234 hole #3, which had never been reinforced, was more visited by the animals now than during the

235 phase 1 ( $t(10) = 4.11, p < .05$ ). In contrast, the number of visits in the hole #5 remained low, and not  
 236 significantly different from phase 1 ( $t(10)=1.65, ns$ ).

237



238

239 **Figure 3: Impact of the Shift session at Day+1 in context B**

240 (A) Spatial activity (%NP +/- SE) at day 1 after the shift session for all the holes in context B. Temporal behavior for the two groups in the newly  
 241 reinforced hole #1, now reinforced at 30s (B), the reinforced hole in the other context, hole #2 (C) and the previously reinforced hole #4 (D). The  
 242 temporal behavior is normalized by the mean activity in the corresponding hole. Control group in black and experimental group in grey.

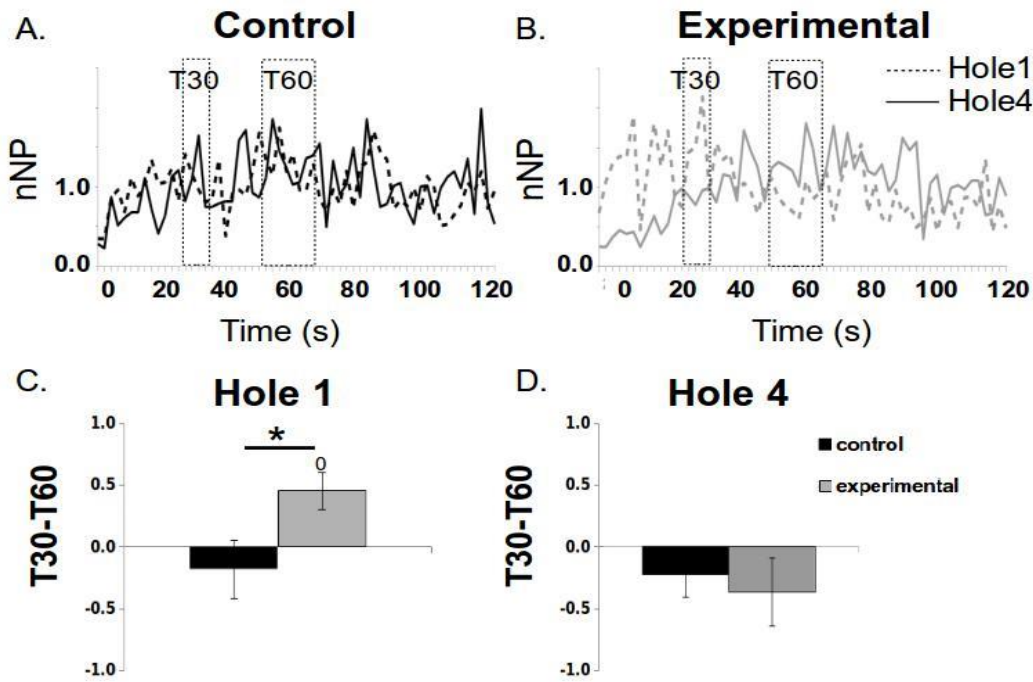
243

244 The temporal behavior of the animals is shown in the figure 3 (BCD) for the holes #1, #2 and  
 245 #4, respectively. For hole #2, hole #3 and hole #4, there was a discriminable temporal pattern  
 246 (significant effect of time,  $F(59,590)=3.61$ ,  $F(59,590) = 2.41$  and  $F(59,590)=2.82$ ,  $p < .001$  for  
 247 hole#2, #3 and #4, respectively), with no group x time interaction ( $F(59,590) < 1.02$  for all, ns).  
 248 Interestingly, the animals tended to visit these holes with a maximum activity centered at the old  
 249 60-s temporal rule. The temporal pattern in hole #3 was similar to hole #2 and #4 (data not shown),

250 confirming the spatial generalization . The lack of differential behavior between groups was  
251 confirmed with Bayesian analyses: a JZS Bayes factor ANOVA with default prior scales revealed  
252 that the main effect model was preferred to the group x time interaction model by a Bayes factor of  
253 30.82 for hole #2, 6.36 for the hole #3, and 22.74 for the hole #4.

254         Importantly however, the two groups showed a differential temporal behavior in the hole #1  
255 (significant group x time interaction,  $F(59,590)=1.44$ ,  $p=.021$ ), with the activity of experimental  
256 animals peaking earlier, according to the new 30-s temporal rule (figure 3B). Additionally, a more  
257 refined analysis of this Day+1 session revealed that only the animals exposed to the new rule in  
258 phase 2 presented an adjusted spatio-temporal binding to this new rule. As shown in figure 4A, the  
259 temporal behavior of the control animals did not differ significantly in the new (#1) and old (#4)  
260 reinforced holes (no hole x time interaction:  $F(59,590)=1.14$ ,  $p=.22$ ), suggesting that the animals  
261 did not adapt to the change of rule. Bayesian Repeated measure ANOVA confirmed that the main  
262 effect model was preferred to the hole x time interaction model by a Bayes factor of 7.81. In  
263 contrast, the behavior of experimental animals did differ temporally between those two holes  
264 (interaction hole x time:  $F(59, 590)=2.16$ ,  $p< .001$ ) (figure 4B). Bayesian statistics further  
265 confirmed this result, as the hole x time interaction model was preferred to the main effects by a  
266 Bayes factor of 9811.33. The animals visited the new hole (#1) at the new time (30s) and  
267 additionally kept the old spatio-temporal association, visiting the old hole more around the old time  
268 (hole #4, 60s). This pattern of results indicates that the behavior of the experimental animals was  
269 linked to the spatio-temporal associations.

270



271

272 **Figure 4: Spatio-temporal binding**

273 The temporal behavior in the new hole (#1) (dashed line) and old hole (#4) (solid line) is compared for the control (A) and experimental (B) groups  
 274 (normalized NP by the overall activity in function of time). For each animal, the mean activity during a temporal window centered at 60s (old time)  
 275 was subtracted to the mean activity during a temporal window centered at 30s (new time) for comparison between the two groups for the new (C) and  
 276 old (D) holes. Significant differences are displayed as: from zero =“0”and between groups = “\*” when  $p < .05$ .

277

278 In order to assess more specifically the learning of the spatio-temporal association, we  
 279 compared the mean level of activity in those two holes when restraining to temporal windows  
 280 centered at the new and old timing rules. For each animal and each hole, the mean activity for the  
 281 60-s window (from 52-68s) was subtracted to the mean activity for the 30-s window (from 26-34s)  
 282 and compared between the two groups for the new and old holes (figures 4C and D). Following this  
 283 calculation, a behavior linked to a spatio-temporal learning would thus be positive (more activity in  
 284 the new hole/new time and no differential or less activity in the other combinations new hole/old  
 285 time, old hole/new time or old hole/old time). For the hole #1 (new hole) this difference was  
 286 positive only for the experimental group, indicating that the animals visited more the hole #1 at 30s  
 287 (in concordance with the new rule) than at 60s (t-test to zero:  $t(5)=3.03$ ,  $p=.029$ ). However, no such

288 difference was observed for the control group ( $t(5)=-0.75, p=0.49$ ) confirming that the animals did  
289 not have a discernible temporal behavior in this hole. This analysis also revealed a difference  
290 between the two groups ( $t(10)=2.249, p=.048$ ) in this hole (figure 4C). The same analysis for the  
291 old hole (hole #4, figure 4D) showed no differential spatio-temporal behavior (difference from zero,  
292  $t(5)=-1.33, p=.24$  and  $t(5)=-1.33, p=.24$  for control and experimental groups), and no statistical  
293 differences between the two groups ( $t(10)=0.70, p=.50$ ).

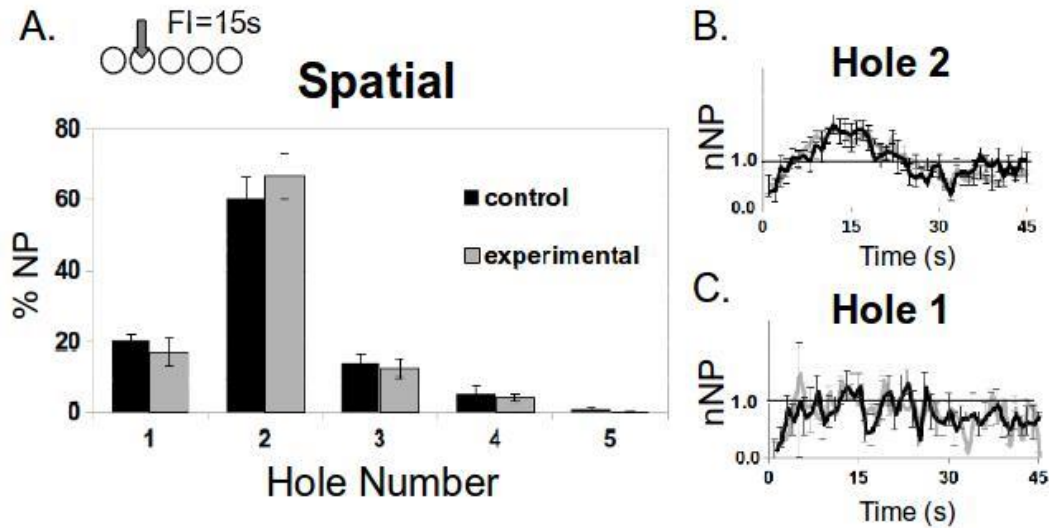
294

#### 295 *Day +1 after the Shift of the spatio-temporal association – Context A*

296 The context A was not associated to a change of the spatio-temporal rule. Therefore, no  
297 change was expected in the behavior of the animals, and no difference between the two groups  
298 either. Indeed, as shown in the figure 5, all the animals kept an adjusted spatio-temporal behavior.  
299 With regard to their spatial behavior, the animals visited mainly the hole #2, reinforced in this  
300 context, but showed also a slight increased activity in the hole newly reinforced in the other context  
301 B, hole #1 (figure 5A). We focused our analyses on these two holes (#2 and #1). There was no  
302 significant difference between the two groups in neither of these two holes ( $t(10)<1.31, ns$ ). Despite  
303 the fact that the spatial rule had not been changed in this context, the animals decreased  
304 significantly their visits in the hole #2 ( $t(10)=-5.45, p<.001$ ), and increased their visits in the hole  
305 #1 ( $t(10)=9.25, p<.001$ ), compared to their behavior before phase 2. The numbers of visits in the  
306 holes #3, #4 and #5 were not significantly different from before the phase 2 (respectively:  $t(10) =$   
307  $2.03, t(10) = 2.17, t(10) = .08; ps>.05$ ).

308 However, with regard to the temporal behavior in holes #1 and #2 (depicted in figure 5BC),  
309 all the animals showed an increased activity centered at the peak interval time for this context (15s)  
310 in both holes (significant effect of time,  $F(44,440)=1.75, p<.01$  for hole #1, and  $F(44,440)=8.31,$   
311  $p<.001$  for hole #2; and no hole x time interaction in either case  $F_s<1.14, ns$ ), with no difference

312 between groups (no group x time interaction,  $F_s < 1$ , ns confirmed by a Bayesian analysis, with the  
 313 main effect model preferred to the interaction model by a Bayesian factor of 148.77 for hole #1 and  
 314 75.83 for hole #2).



315

316 **Figure 5: Impact of the shift session at Day+1 in context A**

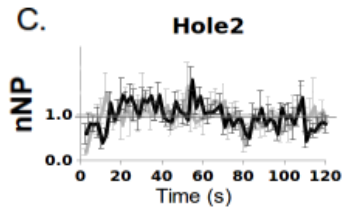
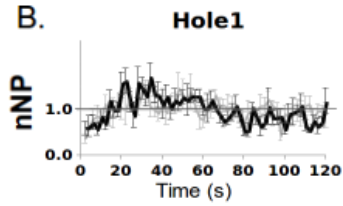
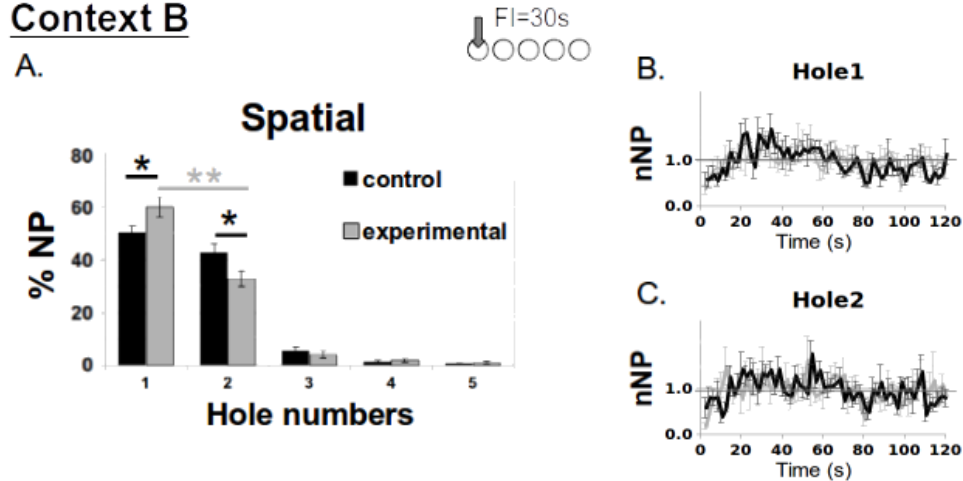
317 (A) Spatial activity (%NP +/- SE) at day 1 after phase 2 for all the holes in context A. Temporal behavior for the two groups in the hole of interest #2  
 318 (B), and the new hole #1 reinforced in context B (C). The temporal behavior was normalized by the overall activity of the animals in the  
 319 corresponding hole.

320

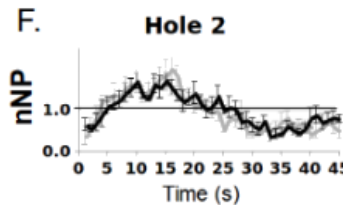
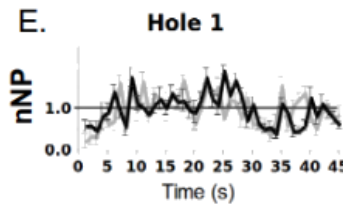
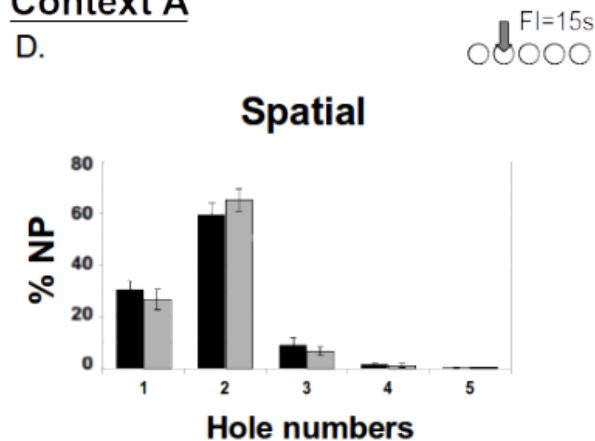
321 ***Day +9 after the Shift of the spatio-temporal association– All contexts (B&A)***

322 In order to assess the evolution of the impact of the shift of the spatio-temporal rule, the  
 323 animals were trained under the new context B spatio-temporal rule for 9 days. The results obtained  
 324 at Day+9 for the two contexts are shown in figure 6.

## Context B



## Context A



325

326 **Figure 6: Impact of the shift session at Day+9 in the two contexts**

327 (A) Percentages of Nose-Pokes (%NP +/- SE) for each of the holes in context B, for the control (black) and the experimental (grey) groups. Between  
 328 groups (black, \* $p < .05$ ) and within group (grey, \*\* $p < .001$ ) analyses focusing on holes #1 and #2, reinforced holes in context B and A, respectively.  
 329 Normalized temporal activity in context B (nNP +/-SE) in function of time) in holes #1 (B) and #2 (C) for control (black) and experimental (grey)  
 330 groups. (D) Percentages of Nose-Pokes (%NP +/- SE) for each of the holes in context A, for the control (black) and the experimental (grey) groups.  
 331 Temporal activity (NP +/-SE) in function of time in context A in holes #1 (E) and #2 (F) for control (black) and experimental (grey) groups.

332 First, in both contexts (figure 6A & D), there was still a spatial generalization to the hole  
 333 reinforced in the other context (around 20-40%), whereas the activity in hole #4 was extinguished.  
 334 Second, interestingly, the benefit of the shift session was visible on the spatial behavior in context B  
 335 (figure 6A), as the experimental group showed a higher level of activity in hole #1 compared to hole  
 336 #2 ( $t(5) = -4.48, p = .007$ ), whereas it was not the case for the control group ( $t(5) = -1.33, p = .24$ ). This  
 337 differential behavior was confirmed with between group differences with higher activity for the

338 experimental group in the reinforced hole #1 ( $t(10)=2.20$ ,  $p=.026$ ) and lower activity for the  
339 unreinforced hole #2 in this context ( $t(10)=2.19$ ,  $p=.027$ ), as compared to the control group. No  
340 differential spatial behavior was observed in context A (figure 6D), with a similar level of activity  
341 between groups for both hole #1 and #2 ( $t(10)<1.50$ , ns). These results indicate that the control  
342 animals did not differentiate the hole #1 from the hole #2 in context B, showing that they did not yet  
343 fully learn the new spatial component of the rule, contrarily to the experimental group who showed  
344 an adjusted spatial behavior in this task.

345         The temporal behavior did not differ between groups in neither hole #1 or #2 for both  
346 contexts (no significant group x time interaction,  $F_s(59,590)<1$ , ns with a Bayes factor of 33.37 for  
347 #1 and of 23.54 for #2 in favor of a main effect for context B ;  $F_s(44,440)\leq 1.0$ , ns for context A,  
348 also confirmed by a Bayes factor of 4.58 for hole #1 and 242.86 for hole #2). Both groups showed  
349 an activity peaking around 30s in context B, and around 15s in context A, with a sharper temporal  
350 function in the reinforced hole (hole#1 in context B, and hole #2 in context A) than in the non-  
351 reinforced holes. These results show a correct learning of the temporal rule for both groups that is  
352 well controlled by the context.

353

## 354 **Discussion**

355         The aim of the present study was to investigate the learning of space and time when both  
356 dimensions are associated and to assess whether the two dimensions are learnt independently of  
357 each other. For this purpose, we developed an experimental paradigm based on a nose-poke setup  
358 and peak-interval procedure to assess the learning of a new spatio-temporal association, once the  
359 rules have been acquired. The main results showed (1) a spatio-temporal binding, which is  
360 conserved when the rule is changed, and a fast and robust adaptation to the new associative rule; (2)

361 a faster learning of the timing rule which is not dissociable neither from a spatial nor a contextual  
362 dimension.

363 After learning the two spatio-temporal associations in each context during Phase 1, the  
364 animals were subjected once to a shift of this rule (Phase 2). They benefited from this single session  
365 (or shift of the spatio-temporal rule) in adapting faster to this new rule in Phase 3. Indeed, we  
366 observed that the experimental animals expressed a differential spatio-temporal binding according  
367 to both the old rule (hole #4, 60s) and the new rule (hole #1, 30s), indicating that the spatial and  
368 temporal components of the rule had been learned bound together, in a coherent association within  
369 the context. At the same time, the spatio-temporal association learned in context A (hole #2  
370 reinforced at 15s) was spared, which confirms that the animals were able to discriminate between  
371 the two contexts, despite a slight spatial generalization to the hole #1.

372 Interestingly, the impact of the shift session was still visible after 8 additional days of  
373 training, as only the experimental group presented the appropriate spatio-temporal behavior (hole  
374 #1, 30s, in context B). The spatial generalization observed for the control group suggests that the  
375 spatial component might be learned later in comparison to the timing rule, as we will discuss below.

376

### 377 *Spatio-temporal binding and adaptation to the change*

378 In this experiment, we submitted the animals to a shift of the spatio-temporal rule after the  
379 learning phase. As the initial rule had been learned, this paradigm permitted to isolate the learning  
380 of location and time, independently of the acquisition of the instrumental task. The main question  
381 was then: would one dimension shift before the other, or would the two dimensions be learned at  
382 the same rate?

383           The results showed a facilitated adaptation to a change in an associative rule combining place  
384 and interval time learning. The pattern of results indicates that a single session was sufficient for the  
385 animal to learn a new spatio-temporal association. First and foremost, this result supports the work  
386 of our colleagues (Molet and Miller, 2013; Buhusi, 2014; Tosun et al, 2016) by confirming that  
387 animals are able to encode the location and temporal attributes of a given situation. Secondly, this  
388 study shows that interval time can be learnt fast which echoes the findings of several studies  
389 showing that animals can learn time in one session. For example, Guilhardhi and Church (2005)  
390 showed that rats were able to adapt quickly to repeated shifts in a PI task. Similarly, Dallérac et al  
391 (2017) observed that rats can exhibit fast adaptation of temporal fear conditioned responses when  
392 changing the time between the CS and US in a conditioned suppression task. Other reports have  
393 shown that time is learned in a single trial (Diaz-Mataix et al, 2013; Davis et al, 1989).Recent  
394 research also reported that mice are able to adjust their temporal behavior quickly and abruptly  
395 (only one trial) to a change of reinforcement rule, by using probabilistic estimate of the rule  
396 (Kheifets and Gallistel 2012). In a comparable manner, it is well known that animals can rapidly  
397 adapt to changes in spatial representation. For example, animals are able to rapidly adapt to changes  
398 in spatial memory tasks, accompanied with a remapping of the hippocampal place cells (O'Keefe  
399 and Dostrovsky, 1976; Morris, 1986; Moser et al, 2008; for review see Eichenbaum et al, 1999;  
400 Hartley et al , 2013). In addition, a recent study in monkeys by Kowk and collaborators (2015)  
401 confirmed that animals can exhibit flexibility to rapidly adapt to spatio-temporal changes in a  
402 delayed matching-to-position task. Our results thus comfort the previous results of the literature,  
403 extending it further. In sum, our present findings confirm that rodents do have the capacity to  
404 perceive and adjust quickly their behavior to a complex change of a rule, supporting the view that  
405 animal may represent time and space in their memory, therefore offering a framework for decision  
406 making, as suggested in a recent review (Gur et al, 2108).

407 More importantly, our results show that when learned in association, there is a spatio-  
408 temporal binding formed that governs behavior in a selective manner according to each of the old  
409 and new rules. Surprisingly, though, the behavior of the control animals was not spatially adjusted 8  
410 days after the shift, while their temporal behavior was not significantly different from the  
411 experimental animals in the new reinforced location (hole #1). The imprecision in nose-poke choice  
412 might be due to the fact that, in phase 3, all nose-pokes were lit. In a similar situation, Tosun et al  
413 (2016) showed that when two previously reinforced locations are lit at the same time, the animals  
414 explore the two locations with a switching behavior between the two locations governed by the  
415 temporal rules associated with them. Furthermore, the behavior of experimental animals in the  
416 present experiment clearly shows that time and space were bound together (see figure 4). The fact  
417 that the temporal pattern of the visits to the hole #2 was not related to its specific association in the  
418 other context, nor to the old or new temporal rule in this context (see figure 6), suggests that the  
419 animal's behavior reflected some imprecision in spatial memory (as also suggested by the activity  
420 in hole #3). Nevertheless, the results may indicate that the spatial dimension needs more time to be  
421 learned than the temporal one. One may argue, however, that the situation was not symmetrical for  
422 both dimensions, as the long-to-short shift in the temporal dimension could be seen as without  
423 ambiguity for the animal (because reinforcement is available earlier than expected) contrary to the  
424 spatial situation where all possible locations were lit. Further experiments will be needed to  
425 question the hierarchical organization in memory of spatial and temporal representations. In the  
426 framework of working memory, an asymmetry of the representation of spatial and temporal  
427 information has been found regarding the type of task and/or the sensory modality engaged (Buhusi  
428 et al, 2013; Noyce et al, 2015; Michalka et al, 2015). Gallistel (2011) proposed that abstract  
429 dimensions such as time, space and numbers could be represented as magnitudes. But little is  
430 known about the link of this representation within a contextual event and the formation of a  
431 meaningful memory articulating those parameters together.

432 In sum, regarding the processing of spatial and temporal dimensions, it appears from these  
433 results that when the association is presented to the animals in an explicit manner (with a Pavlovian  
434 shift of the rule), time and space are learned together, exhibiting spatio-temporal binding. However,  
435 without precise indications, such as visual cues, time may be learnt before space.

436

437 *Binding of time and space within context*

438 In the present work, in addition to the spatio-temporal association, the animals had to learn  
439 the difference between two different contexts (A and B) which differed by the lighting of the  
440 experimental box and the frequency of the discriminative timing stimuli (tone). While this situation  
441 provides a control for the specificity of the obtained effects, it also gives some indication of whether  
442 there had been some tripartite (time-location-context) memory formed. The rats' ability to learn a  
443 complex association of space-event-context has been well documented in many behavioral  
444 paradigms assessing episodic-like memory in rodents, and is referred to as the what/where/which  
445 context association (for similar studies, see Eacott and Norman, 2004; Eacott et al, 2005; Easton  
446 and Eacott 2008; Eacott and Easton 2010). A recent work from Crystal and Smith (2014) also  
447 reported that rats can dissociate episodic events based on contextual cues in order to form a bound  
448 representation of multiple dimensions of the memory. But these studies focused on episodic-like  
449 memory, and used a very different time scale than the second-to-minute range. To our knowledge,  
450 no experiment has studied a contextual dimension in the framework of interval timing.

451 Our results show a clear time-location-context associated behavior, as shown by the fact that  
452 the animals were able to discriminate between the two contexts during the initial training (Phase 1).  
453 In addition, the representation of the context appeared to be conserved in Phase 3, as shown by an  
454 appropriate spatio-temporal behavior in context A (hole #2-15s) and the correct adaptation to the  
455 new rule of the context B (hole #1-30s) by the experimental animals. Nevertheless, two

456 observations can be made. First, while the spatio-temporal rule was not changed in context A, a  
457 slight increase in visits was observed in the hole #1 in this context (hole newly reinforced in context  
458 B). Second, the hole #2 (reinforced in context A) was still visited in context B even at the end of  
459 phase 3 (especially in control animals), although it had never been reinforced in that context. Thus,  
460 there was some generalization of the spatial learning between the two contexts despite their very  
461 different characteristics, especially the highly discriminable timing cues (1 kHz vs. 11 kHz). One  
462 may suspect that the fact that all the nose-poke holes were lit in Phase 3 may have played a role,  
463 although proximity between the holes could not be the sole factor, as no such increase in responding  
464 was found in the opposite side, equally distant to hole #2 (i.e., hole # 3). Importantly, this  
465 uncertainty was weakened by the Pavlovian shift session in the experimental animals. Furthermore,  
466 the temporal behavior was properly adjusted to the context from day one in the experimental  
467 animals, suggesting that a time-context association is learned faster than a space-context  
468 association. Further experiments will be necessary to clearly compare the speed of learning of each  
469 of the components of the space-time-context triplet, and the rules governing their binding.

470

#### 471 *Neuronal representation of the association*

472         Where could the binding between space and time be encoded in the brain? Are space and  
473 time represented in the same anatomical structures? Up to date, two brain areas have been reported  
474 to support spatial and interval timing processes.

475         Firstly, the basal ganglia, in particular the dorsal striatum, is known to be critical in interval  
476 timing and temporal processes (for a review see Buhusi and Meck, 2005). A rapid adaptation to a  
477 change of rule has been previously linked to a change in the firing rate of the task-modulated striatal  
478 neurons (Portugal et al, 2011). The author of this study suggested that rather than event times, the  
479 striatum might encode the timing of adaptive behavioral transitions between options based on the

480 environmental statistics. Similarly, Mello et al (2015) demonstrated in an electrophysiological  
481 experiment that striatal neuronal populations can quickly adapt to the immediate task demands by  
482 rescaling their temporal tuning to abrupt changes in delays to reinforcement, similar to our present  
483 task. Furthermore, the striatum has been reported to be involved in spatial memory; for example, it  
484 has been shown that lesions in the dorsal part of the striatum leads to deficits in spatial learning  
485 (Block et al, 1993; McDonald and White, 1994; Lee et al, 2014). A recent study in rats also  
486 confirmed that a unilateral lesion of this structure can lead to a disruption of spatio-temporal  
487 integration (Blankenship et al, 2017), which may lead to think that the dorsal striatum might be  
488 involved in our present task.

489         Secondly, the hippocampal formation has been extensively studied regarding spatial  
490 navigation (O'Keefe and Dostrovsky, 1971; Save et al, 1992; Maguire et al, 1997; Goodrich-  
491 Hunsaker et al, 2008). In addition, it is known that the hippocampal place cells are able to code for  
492 interval time as well (Pastalkova et al, 2008; MacDonald et al, 2011; Kraus et al, 2013) and that  
493 fornix lesions (initially found to impair spatial learning) impair the detection of temporal changes  
494 (Kwok et al, 2015). The involvement of hippocampus in interval timing has been highlighted in a  
495 recent study (Jacobs et al, 2013), although in a supra-minute time range. Another recent finding also  
496 suggests that hippocampus and memory-related mechanisms are involved in spatio-temporal  
497 integration bringing evidence that the hippocampi are critical components of internal clock  
498 mechanism (Buhusi et al (2013). All these results are clues pointing into the direction that the  
499 hippocampal formation might also be involved in the spatio-temporal binding that we report in our  
500 present study, and more research needs to be conducted to further clarify this question.

501

502         In conclusion, using a behavioral paradigm that enables the study of the interaction of space,  
503 interval time and context, and their overall binding, we have found differential dynamics of space

504 and interval time learning, and a tripartite space-time-context binding. The matters of probabilistic  
505 estimate of rules, animal cognitive representation and behavioral adaptation to a change of rule still  
506 demand more investigation. We believe that our experimental design can be a basis for further  
507 investigations related to the hierarchical learning of such a complex association. We hope that it  
508 will foster to a better understanding of the neural mechanisms supporting the integrated  
509 representation of space, interval time and context, and therefore contribute to the development of  
510 more refined therapeutic approaches for memory impairment and related diseases.

511

512

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