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3 **Neural encoding of time in the animal brain**

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13 **Abstract**

14

15 The processing of temporal intervals is essential to create causal maps and to predict
16 future events so as to best adapt one's behavior. In this review, we explore the different
17 brain activity patterns associated with processing durations and expressing temporally-
18 adapted behavior in animals. We begin by describing succinctly some of the current
19 models of the internal clock that can orient us in what to look for in brain activity. We
20 then outline how durations can be decoded by single cell activity and which activity
21 patterns could be associated with interval timing. We further point to similar patterns that
22 have been observed at a more global level within brain areas (e.g. local field potentials)
23 or, even, between these areas, that could represent another way of encoding duration or
24 could constitute a necessary part for more complex temporal processing. Finally, we
25 discuss to what extent neural data fit with internal clock models, and highlight
26 improvements for experiments to obtain a more in-depth understanding of the brain's
27 temporal encoding and processing.

28

29 *Keywords (3-12):* interval timing; electrophysiology; local field potentials; oscillations;
30 time cells; single unit recordings; multi-unit recordings; animal models

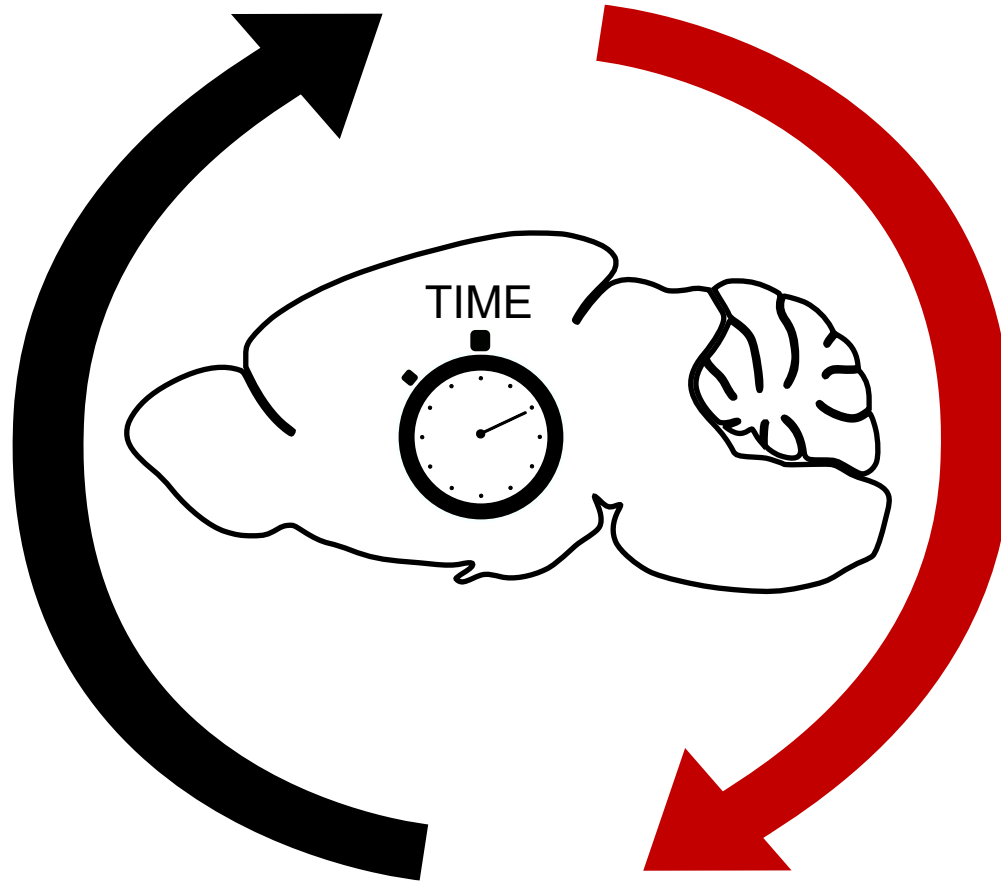
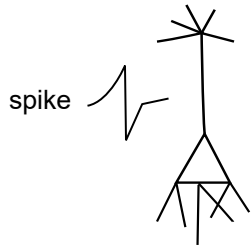
31 **Highlights**

- 32 • Durations can be encoded in various patterns of single unit activity
- 33 • Population activity and communication between brain areas can also encode
34 durations
- 35 • Combination of unit and population activity may be the basis of our internal
36 clock
- 37 • Experiments designed to study the neural basis of interval timing are needed

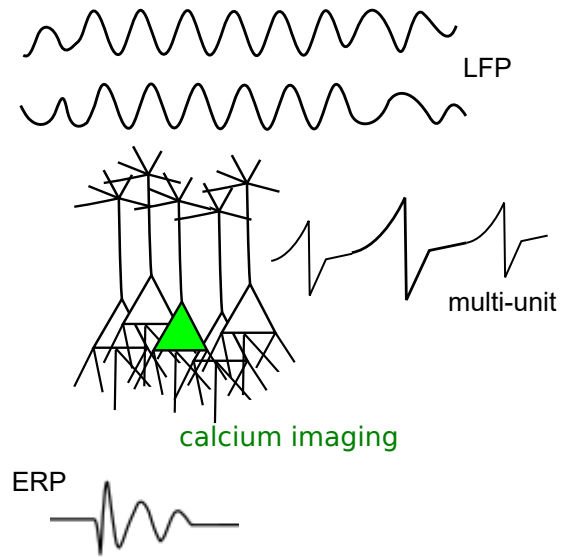
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39

Single cell coding



Population coding



40 **1. Introduction**

41 42 1.1 Time and the internal clock

43
44 A sense of time exists in most species, from drosophila to fish, pigeons, rats,
45 humans (for review, see Buhusi and Meck, 2005) and even honeybees (Craig et al., 2014).
46 It is essential for survival as it allows individuals to extract the predictability of events
47 and to adapt their behavior to respond at the appropriate time. We use our implicit sense
48 of time to be able to cross the street **while staying safe by estimating the speed and**
49 **time it takes for a car to reach us**, or to know when to give up on a presumed broken
50 traffic light. Although we may be aware of how much time is passing by, we may not pay
51 attention to the absolute duration of events. We can, however, be taught to explicitly pay
52 attention to how many seconds are passing between lightning and the associated thunder
53 clap to determine if we should hide or not. Both implicit and explicit timing are used in
54 our daily life. Although crucial for complex cognitive functions, understanding how the
55 brain encodes durations remains an unsolved problem, especially because brain
56 processing works at a millisecond range (e.g. one action potential lasts for around 5ms),
57 thus providing high precision in short timescales but creating a challenge to timing multi-
58 seconds to minutes long durations.

59 While circadian rhythm (involved in hunger and sleep) - built around a 24h cycle
60 - is poorly adjustable (as exemplified by jetlag), interval timing - in the seconds to minutes
61 range - is flexible, learned, and covers a larger range of durations to allow for a rapid
62 adaptation to changes in the environment. In contrast to the well-described dependence
63 of circadian rhythm on the suprachiasmatic nucleus, many brain structures have been
64 linked to interval timing. On the other end of the timescale (in the range of a few hundred
65 milliseconds), there is motor timing, which is involved in the automatic synchronization

66 and control of movements (Rammsayer, 1999). The cerebellum is often considered to be
67 the seat of motor timing because of its role in the processing and integration of multiple
68 sensory and somatosensory inputs, as well as the optimization of motor output (for a
69 review, see Spencer and Ivry, 2013). We will focus the present review on interval timing,
70 which enables organisms to create temporal maps and manage predictions about the
71 outcome of situations, and has therefore a strong cognitive component (Buhusi and Meck,
72 2005).

73 Most species, from insects to primates, process temporal information as if they
74 were using a stopwatch, suggesting the existence of a conserved function for an internal
75 clock across evolution (Buhusi and Meck, 2005; Church, 1984, 1978; Matell and Meck,
76 2000). Animals' internal clock seems to encode time in a linear fashion (Church, 1984;
77 Gibbon and Church, 1981) and can be used to time signals from different modalities in a
78 sequential or a simultaneous manner (Gibbon et al., 1984; Olton et al., 1988). The internal
79 clock can also be stopped and reset, as shown in gap paradigms (where the insertion of a
80 "pause" in the timed stimulus induces a shift of the temporal behavior dependent on the
81 duration of the "pause"), whether in an instrumental or Pavlovian, appetitive or aversive
82 condition (e.g. Aum et al., 2004; Church, 1984, 1978; Roberts and Church, 1978; Tallot
83 et al., 2016).

84 Treisman (1963) was one of the first to propose a model for this internal clock.
85 He described three components: a pacemaker, an accumulator, and a memory stage. The
86 beginning of a stimulus closes a switch between the pacemaker and accumulator which
87 starts the accumulation of 'ticks' (i.e. temporal units) for the duration of the stimulus. At
88 the end of the stimulus, the number of ticks accumulated is saved in the memory stage to
89 be retrieved and compared with future durations. In most cases, interval timing follows
90 the scalar property (i.e., Weber's law applied to time), that is, the precision with which a

91 given duration is estimated decreases in an inversely proportional manner to the length of
92 that duration. **However, not all temporal behaviors follow the scalar property**
93 **whether in humans (Wearden and Lejeune, 2008) or in animals (Lejeune and**
94 **Wearden, 2006).**

95 To account for the scalar property of time, storage and retrieval from memory are
96 assumed imperfect. The scalar expectancy theory - the most influential timing model up
97 to now - was developed by Gibbon in (1977), and further improved by Church in 1984.
98 It expands on the memory stage of Treisman's internal clock by incorporating: a working
99 memory component, a multiplicative factor for storage in a reference memory, and a
100 decision rule to determine if 'yes' or 'no' the duration being measured is similar to
101 previously encoded durations.

102 Our main question - "What are the potential neurobiological correlates of time?"
103 – is therefore multifaceted, as we are looking for the different modules of our timing
104 system, from the attention to duration to the retrieval of specific intervals, including the
105 formation in memory of temporal associations between events. **The literature we review**
106 **here is not intended to be exhaustive, but rather to cover a large range of behavioral**
107 **tasks and highlight various examples from the literature in order to bring together**
108 **different angles of view on potential neural correlates of time processing.**

109

110

111 1.2 Neurobiological basis of the internal clock

112

113 Although the scalar expectancy theory explains most behavioral results, **it has not**
114 **yet been supported at the neurobiological level.** Pharmacological, lesion and human
115 imaging studies have highlighted the importance of several brain areas in interval timing,

116 results that have been discussed many times before, and will not be part of this review.
117 Briefly, a few structures have been detected as playing a role in timing across a lot of
118 studies: the supplementary motor area (SMA), the pre-SMA, the prefrontal cortex (PFC),
119 the striatum, the *substantia nigra*, the inferior parietal cortex and the cerebellum (e.g.
120 Brannon et al., 2008; Buhusi and Meck, 2005; Coull et al., 2011; Harrington et al., 2010,
121 2004; Lewis and Miall, 2006; Wiener et al., 2010). For example, in Huntington's disease,
122 in which the striatum is degenerating, temporal deficits have been reported (Garces et al.,
123 2018; Höhn et al., 2011; Paulsen et al., 2004; Rowe et al., 2010; Zimbelman et al., 2007).
124 Patients with Parkinson's disease show impaired timing in motor and sensory tasks,
125 linked with the degeneration of their dopaminergic neurons (e.g., Pastor et al., 1992).
126 Pharmacological studies in animals confirm a role of dopamine in timing (Drew et al.,
127 2003; Kim et al., 2016; Meck, 1996), although its function is complex (in part related to
128 its multi-structures targets), and interacts with motivational states (for a recent review,
129 see Balci, 2014). Meanwhile, the prefrontal cortex is critically involved in simultaneous
130 temporal processing, as shown in lesion studies in rodents (Meck and MacDonald, 2007;
131 Olton et al., 1988; Pang et al., 2001).

132 One of the core debates on the neurological basis of timing is whether it is dependent
133 on one central timing center, or whether timing is present all over the brain in separate
134 clusters. One argument for a central clock is the fact that, in different tasks, there is a
135 similar temporal variance, at least for intervals larger than hundreds of milliseconds
136 (Gibbon et al., 1997). There is also a strong correlation between performance in self-
137 paced timing tasks and duration discrimination, implying, again, the use of a common
138 timing mechanism (Keele et al., 1985). However there are also studies showing that brain
139 slices can encode durations (up to 2s) which implies that a very restricted amount of

140 connected neurons is sufficient for simple temporal encoding (Chubykin et al., 2013; Goel
141 and Buonomano, 2016; Johnson et al., 2010).

142 Differences in neural encoding may relate to differences in the timing process
143 involved, e.g. whether it is of implicit or explicit nature. In implicit tasks, a subject's
144 knowledge of the durations experienced is not required for its performance, that is, the
145 subject does not have to time during the task but may do so nonetheless (like during
146 Pavlovian conditioning, working memory tasks and entrainment). In these tasks, accurate
147 timing may facilitate detection of a stimulus or allow for a better regulation of behavior,
148 but is not necessary to perform. In explicit tasks, durations have to be processed for the
149 subject to respond accurately and learning of the duration is necessary (like in temporal
150 discrimination, temporal production and reproduction tasks). To what extent these two
151 types of timing task rely on distinct or overlapping neural networks is still debated.
152 However, in humans at least, explicit timing seems to involve a fronto-striatal network
153 (SMA, right inferior frontal cortex and basal ganglia) (Coull et al., 2013; Wiener et al.,
154 2010) whereas implicit timing activates the left inferior parietal cortex and the right
155 prefrontal cortex (Coull et al., 2000; Coull and Nobre, 1998; Vallesi et al., 2009).

156 To address the issue of the origin of the internal clock, assuming there is one, we
157 must look at neuronal activity from individual neurons to groups of neurons in a large
158 range of brain areas and in different types of timing tasks. *In vivo* deep brain recording in
159 the awake behaving animal gives access to single cell and population neuronal activity
160 with high temporal resolution in any brain area during behavioral tasks with a large range
161 of cues' duration. Patterns of single cell firing activity and synchronous spike activity of
162 neural ensembles could reflect a local processing of time. This synchronous cell activity
163 can generate depolarization/hyperpolarization oscillatory rhythms either locally (through
164 recurrent networks) or in distant brain areas, which can be recorded with local field

165 potentials (LFP). Neural oscillations also give access to subthreshold depolarization,
166 which may not be translated into spikes by the integrating neurons. As such, recordings
167 of spike activity and oscillations provide complementary, non-fully-overlapping,
168 information. Neural oscillations are an ubiquitous property of brain function and have
169 important roles in learning, memory and cognitive processes such as those involved in
170 timing and time perception (for reviews, Buzsáki et al., 2013; Buzsáki and Draguhn,
171 2004; Hanslmayr and Staudigl, 2014; Matell and Meck, 2004). Slow (<50Hz) oscillations
172 are associated with large fluctuations of neurons' membrane potential and are considered
173 to cover large brain areas, whereas fast oscillations result from smaller fluctuations in
174 membrane potential and should be restricted to smaller neural volumes. Changes in
175 oscillatory rhythms' frequency or power may represent timing function at a network level.

176 Here we have selected studies in the animal literature - not only in tasks designed to
177 study timing, but also in tasks studying other aspects of learning in which time was
178 involved or manipulated - to see whether general principles emerge on how duration can
179 be encoded/decoded in the brain. We classify the studies between explicit and implicit
180 timing tasks as a way to determine if they may rely on different neural systems or if they
181 belong to a common network that could represent 'pure' timing. **To help the reader for
182 having a global view of the literature reviewed here, we summarize it in table
183 formats, organized around the type of tasks and neurophysiological correlates.**

184

185 **2. Can time be encoded by a single neuron activity?**

186

187 Since the pioneering study by Fuster & Alexander (1971) which pointed to cells in
188 the prefrontal cortex modulating their firing during a delay in monkeys performing a
189 delayed response task, many different studies have been interested in determining how

190 single neuron activity (i.e. spikes) can encode durations; and it is a growing field of
191 research, as about 30% of these studies have been published within the last five years.
192 Indeed, how can an event of less than ten milliseconds encode durations of several
193 seconds to minutes? We are compiling here more than 80 studies that have in some way
194 looked at different patterns of single neuron firing that can represent time in explicit
195 (Table 1) or implicit (Table 2) temporal tasks. We have organized these studies according
196 to the type of task used, as well as the brain area where timing-related activity was
197 reported. The studied species, as well as the range of durations used, are also mentioned.
198 We have categorized the modification of neurons' firing patterns, as compared to baseline
199 activity, in four types (see Figure 1 for a schematic representation of the different activity
200 patterns): (1) sustained change, (2) phasic change in activity at the stimulus onset or
201 offset, whose amplitude and/or duration is proportional to the duration of the event, (3)
202 peak modulation at a specific time point ('event time' cells), and (4) ramping activity.
203 The changes reported are in majority in the direction of an increased cell firing, but several
204 studies have also reported a decrease in cell firing, in particular when baseline levels of
205 activity are high (e.g. Fuster and Alexander, 1973; Oshio et al., 2006).

206

207 2.1 Sustained change in cell's firing

208

209 Sustained change in activity is often described in working memory tasks, and may
210 represent the temporary maintenance in memory of a stimulus until a response has to be
211 produced (e.g., Hampson and Deadwyler, 2003; Hikosaka et al., 1989; Narayanan and
212 Laubach, 2009; Ohmae et al., 2008; Soltysik et al., 1975; Tremblay et al., 1998).
213 Sustained increase or decrease in the number of spikes for the whole duration of a
214 stimulus has been observed in 21 studies, in both implicit and explicit tasks. This pattern

215 has mostly been observed in the cortex, except for the four following studies. Pendyam
216 et al. (2013) reported sustained activity in the basal amygdala of rats in a Pavlovian
217 aversive conditioning between the onset of a tone used as a conditioned stimulus (CS)
218 and the arrival of the footshock (used as an unconditioned stimulus, US). **In Pavlovian**
219 **associative tasks, animals not only learn the association but also memorize the**
220 **interval between the CS and US, whether they co-terminate, as in delay**
221 **conditioning, or are separated by a gap, as in trace conditioning (for a review,**
222 **Balsam et al., 2010), and it has been suggested that the amygdala plays a role in**
223 **processing the CS-US interval (Díaz-Mataix et al., 2014).** Soltysic et al. (1975) and
224 Hikosaka et al. (1989) observed this pattern in the basal ganglia of monkeys engaged in
225 a working memory task, and Hampson and Deadwyler (2003) saw it in the subiculum of
226 rats in a similar task.

227 However, when the stimulus is present during the whole duration to be timed, it
228 is difficult to differentiate a sustained change in activity due to the presence of the
229 stimulus, from one representing the online processing of duration. Circumventing this
230 issue, Namboodiri et al (2015) have shown recently that the primary visual cortex can
231 encode time with sustained modulation in the absence of a continuous stimulus, allowing
232 us to better sort out sensory from temporal encoding. They used a task somewhat related
233 to a DRL-LH (differential reinforcement of low rates with limited hold) task, in which a
234 brief (100 ms) visual stimulus delivered through goggles indicates the availability of a
235 reward for a fixed amount of time (1.5 s), but with increasing reward value (i.e. quantity
236 of liquid) as time passes. Thus, the rat has to perform in a temporally precise manner to
237 optimize the amount of reward. After a substantial amount of training, the rats developed
238 a stereotyped behavior with an optimal time of responding very close to the programmed
239 optimum (~1.1 s). The authors determined that 10% of the cells they recorded in the

240 primary visual cortex were timing units, as their sustained change in activity was highly
241 correlated with the behavioral timing, but only on trials on which the action was correctly
242 timed. Furthermore, the temporal information encoded by these neurons before the start
243 of the action was predictive of timing behavior. Optogenetic modulation of primary visual
244 cortical neurons' activity induced a shift in behavior to earlier responding, showing that
245 the primary visual cortex participates in the temporal control of this highly stereotyped
246 action.

247 Sustained activity does not seem sufficient to encode duration by itself, but could be
248 used as a pacemaker in an internal clock model with each spike representing a 'tick'. The
249 activity from the 'sustained' cells would need to be accumulated and transformed to be
250 memorized, and then retrieved for comparison to previous durations. Therefore, it does
251 require other forms of activity, either from the same brain area or from others, to form a
252 complete internal clock. It may thus not be surprising that, most of the time, this type of
253 activity was observed at the same time as other patterns of activity in the same brain area
254 (see Table 1 and 2).

255

256 2.2 Phasic response at onset or offset of the stimulus

257

258 Neuronal activity at either the onset or the offset of a stimulus may encode its duration
259 through changes in the firing rate at its onset for representing its expected duration or at
260 its offset for representing its passed duration. Such type of neural encoding has been
261 observed for a large range of durations (from 1 to tens of seconds), and often when several
262 durations are presented within the task, suggesting that it may have a role in
263 differentiating durations (Chiba et al., 2015, 2008; Fiorillo et al., 2008; Jaramillo and
264 Zador, 2011; Ohmae et al., 2008; Roux et al., 2003; Sakurai et al., 2004; Yumoto et al.,

265 2011). For example, Fiorillo et al. (2008) used a Pavlovian appetitive task where each of
266 four CSs predicted different intervals (from 1 to 8 seconds) between the CS onset and the
267 US. The authors showed that dopaminergic neurons from the *substantia nigra* and ventral
268 tegmental area of trained monkeys respond less to the CS onset and more to the US for
269 longer CS-US intervals, and that the response to the US was also modulated when it was
270 delivered earlier or later than expected. The lawful relationship between US-evoked
271 responses and time is indicative of some underlying mechanisms of temporal encoding,
272 and may be the expression of it, but is not the neural encoding of time *per se*. The
273 modulation of neural responses to the CS onset may, on the contrary, be decoded as the
274 length of time that the animal expects to wait before receiving the US, since one of the
275 elements recalled when a CS is presented is the CS-US interval. The issue, though, is that
276 expectation of the reward includes also its salience, a reward closer in time being more
277 rewarding.

278 To isolate time encoding *per se* would necessitate a task without reward. Yumoto and
279 colleagues (2011) recorded activity in the PFC (area 9) of monkeys during a temporal
280 reproduction task of a visual stimulus, in which the duration of the stimulus was not linked
281 to the wait for the reward, thus allowing separation between duration and salience. They
282 observed that some neurons showed phasic activity after the offset of a visual stimulus of
283 a specific duration (neurons called “duration-recognizing”), whereas other neurons
284 showed sustained activity during the production of a specific duration (neurons called
285 “interval-generating”). Very rarely (less than 10%) a neuron had both roles. The authors
286 further demonstrated a role for area 9 of the PFC in timing by showing that an injection
287 of muscimol (a GABA_A agonist that induces an inhibition of neuronal activity) resulted
288 in an increase in the temporal error rate as well as a shift to earlier responding.

289 Even though it has been described in fewer studies (only 14) than for other patterns,

290 duration-related phasic activity has been observed in a wide variety of brain areas, from
291 cortical structures to hippocampus and *substantia nigra*. Interestingly, this pattern seems
292 to represent a discriminative response, and thus probably makes differentiation of
293 durations more efficient. It appears in both implicit and explicit tasks, strengthening the
294 idea that learning durations and discrimination between durations is important even in
295 implicit tasks. However, this phasic activity represents durations relative to one another
296 and not their absolute time.

297

298 2.3 'Event time' cells

299

300 'Event time' activity relates to a transient increase or decrease of the firing rate of a
301 neuron at the end of a learned interval, usually reinforcement time or when the animal
302 must respond. One well-known example of such activity, described by Schultz et al.
303 (1992), is the decrease of firing of dopamine neurons at the time of an expected, but
304 omitted, reward. To detect an 'event time' activity requires paradigms in which the period
305 post-expected reinforcement can be studied; for example, by using probe trials where the
306 cue is presented for a longer duration and in the absence of reinforcement. Therefore,
307 unlike the previous two patterns, it is not dependent on the presence vs. absence of an
308 external stimulus but only on the memorized duration.

309 'Event time' activity has been observed in the cortex (prefrontal, premotor, motor and
310 visual), striatum and hippocampus, and for a wide range of durations. Most of these
311 structures are part of the SBF and/or have been studied in the context of timing for a long
312 time. 'Event time' activity has also been observed in a peak interval timing task, when
313 unreinforced probe trials are introduced in a fixed-interval task (where the reward is
314 available after a certain amount of time has passed since a stimulus). In such a paradigm,

315 the animal develops a pattern of responding that is time-appropriate which, on average,
316 follows a Gaussian curve with a peak around the expected time of reward in probe trials.
317 Using this task in rats, Matell et al. (2003) have shown that some neurons in the PFC and
318 in the dorsal striatum (the two main brain areas of the SBF model) follow patterns of
319 responding that are very similar to the temporal behavior of the animal, that is, their
320 activity reaches a maximum around the expected time of arrival of the reinforcement.
321 ‘Event time’ cells have also been described in implicit timing tasks, such as Pavlovian
322 conditioning and entrainment. In entrainment paradigms, the regular repetition of a
323 stimulus is interrupted and the expectation of the next stimulus can thus be recorded
324 without the interference associated to its presentation (Bartolo et al., 2014; Crowe et al.,
325 2014; Merchant et al., 2013b, 2011). In a Pavlovian tone-shock conditioning paradigm,
326 Armony et al. (1998) and Quirk et al. (1997) described a late tone-induced response that
327 appeared in the auditory cortex of rats after a single session of twenty CS-US trials. An
328 increase in firing was observed late during the CS, just before the arrival of the US,
329 suggesting that it reflected the higher expectation of the US near its time of arrival.
330 Although the US was not omitted, this neural activity close to the time of the US arrival
331 could reflect an ‘event time’ neural correlate.

332 The ‘event time’ activity seems to encode the expected arrival of the reinforcement,
333 or of the next event. We can wonder how it bridges the duration between the CS onset
334 and the US, presumably through other patterns of activity such as sustained changes.

335

336 2.4 Ramping activity

337

338 Ramping activity, when a neuron’s firing rate increases or decreases gradually with
339 passing time, either from baseline level or after an initial abrupt change in activity, has

340 been observed in a majority of studies (e.g., Donnelly et al., 2015; Fuster et al., 1982;
341 Knudsen et al., 2014; Kojima and Goldman-Rakic, 1982; Paz et al., 2006; Sakai, 1974;
342 Soltysik et al., 1975) and may represent the gradual increase in expectation of the animal.
343 A neuron discharges more and more (or less and less) as time passes until it reaches a
344 threshold which induces a specific response that is time appropriate. Ramping activity
345 has been described in most brain structures, in diverse cortical areas, but also in
346 subcortical structures such as the hippocampus and the basal ganglia. It thus does not
347 seem specific to a brain region. In the absence of probe trials, it can difficult to distinguish
348 between ramping and ‘event time’ cells, because we cannot see the post-expected
349 reinforcement activity. For example, Narayanan and Laubach (2009) showed ramping
350 activity in the dorsomedial PFC, which seems to reach a plateau just before the arrival of
351 the reinforcement; adding probe trials without reinforcement would have differentiated
352 activity related to a specific time from simple accumulation of time, as it would have
353 peaked and gone back to baseline level after the expected time of reinforcement in the
354 first case, but would have continued to increase as long as the stimulus was present in the
355 second case.

356 Ramping activity has often been described in delayed matching-to-sample or non-
357 matching-to-sample (i.e., working memory) tasks, and in expectation tasks, where the
358 animal waits for a stimulus. These tasks are not typical timing tasks, but have a temporal
359 component that can be modulated, *i.e.* the wait between the first and the second stimulus.
360 The increased activity during the delay could represent an encoding of the hazard rate,
361 that is, the longer the duration, the more likely the stimulus is to appear (Heinen and Liu,
362 1997; Janssen and Shadlen, 2005; Leon and Shadlen, 2003; Lucchetti and Bon, 2001;
363 Renoult et al., 2006; Riehle et al., 1997). It is difficult to know whether expectation is
364 similar to timing, as it may involve different mechanisms, such as the accumulation of

365 activity over time or an increase in attention until a given stimulus has finished, rather
366 than precise temporal control.

367 Trying to parse the role of ramping activity in increased expectation *vs.* precise
368 temporal control, Donnelly et al. (2015) used an attention task (5-CSRTT) in which a 5s
369 waiting period without making a nose poke is imposed after the onset of the trial, before
370 a brief (500ms) light indicates in which hole the rat must go for getting a reward, a task
371 which requires a high attention level to detect the light cue. The authors, comparing
372 correct responses with premature responses (when the animal did not wait for the light
373 cue to respond), found that positive and negative ramping activity in both PFC and ventral
374 striatum started earlier in premature trials, but with similar ramping rate, so that the
375 activity reached the threshold for action earlier on premature trials than on correct trials.
376 No ramping activity was observed in trials where the animal did not respond. When the
377 waiting period was varied, ramping activity on correct trials was found to reach its
378 maximum at the earliest time of possible appearance of the visual stimulus, then
379 remaining at this level until the emission of a response. Thus, ramping activity up to a
380 threshold may indeed be a correlate of precise temporal control, and premature response
381 may result from an aberrant start of a timing signal that may originate from somewhere
382 else.

383 Like any unbounded accumulator, however, it seems biologically impossible to
384 encode long durations of more than a minute with ramping activity. There is a limit to the
385 number of spikes a single cell can produce in a definite amount of time. This is where
386 population coding might come into play by having different populations activating each
387 other to represent longer durations than a single cell can.

388

389 **3. Can neurons form a network to encode time?**

390

391 As we have seen previously, single cells can encode durations but they are limited
392 biologically in how high their firing rate can be, and other mechanisms have to be at play
393 to make them fire at a specific time (outside of the presence of external stimuli).
394 Therefore, to span complete and/or longer durations, other forms of temporal encoding
395 are necessary, at a network level. In addition to recordings of several individualized cells
396 at a time, other techniques in animals can give us a view of neural activity at the
397 population level, such as multi-unit recordings, local field potentials (LFPs), calcium
398 imaging, micro-dialysis and PET-scan (Positron Emission Tomography), but with a wide
399 range of temporal resolution (from the millisecond to the minute). Patterns of activation
400 similar to the ones observed with single unit can be observed with other techniques that
401 have good temporal resolution, such as multi-units, LFP and, in a slightly less precise
402 way, calcium imaging. In comparison to the studies of single cell encoding of durations,
403 fewer papers have focused on activity related to time at a population level in animals (see
404 Table 3 for explicit tasks and Table 4 for implicit tasks). Nonetheless, they cover a large
405 range of model species and of time intervals, as well as explicit and implicit tasks similar
406 to the ones studied with unit recordings.

407

408 3.1 Sequential time cells

409

410 Sequential time cells (also known as ‘time cells’) fire one after the other, creating, as
411 a population, a range of firing across time which forms a bridge of activity between events
412 separated by a constant time interval, thus encoding as a whole the event’s duration or the
413 interval between events (Figure 2A). **Interestingly, the response field of cells that fire**
414 **later in a sequence is larger than for cells firing early (e.g., Kraus et al., 2013), which**

415 **could be consistent with scalar timing.** Sequential time cells have been described in the
416 hippocampus (Kraus et al., 2013; MacDonald et al., 2013, 2011; Pastalkova et al., 2008),
417 in the PFC (Horst and Laubach, 2012; Jin et al., 2009; Kim et al., 2013; Kojima and
418 Goldman-Rakic, 1982; Oshio et al., 2008; Sakurai et al., 2004), in the premotor cortex
419 (Merchant et al., 2011), and in the basal ganglia (Jin et al., 2009; Mello et al., 2015).
420 MacDonald et al. (2011) have differentiated cells depending on whether or not they
421 modify their peak firing time when the duration of the interval is changed. They named
422 ‘absolute time cells’ cells that show a peak response at a specific time point during the
423 interval with a pattern that does not rescale when the duration is modified. ‘Relative time
424 cells’ show a similar peak response at a specific time but their activity is rescaled
425 depending on the duration of the timed interval. Other cells may either lose their activity
426 or change their activity to a non-similar and non-rescaled time point when the interval is
427 modified. Other studies have also highlighted the dichotomy between relative *versus*
428 absolute time cells (Kojima and Goldman-Rakic, 1982; Merchant et al., 2011).

429 To describe these sequential time cells, MacDonald and collaborators (2011) used a
430 go/no-go paradigm with a delay. The rats were trained to pair objects and odors, such that
431 they had to retain in memory for 10s the object that was presented at the beginning of a
432 trial to know whether or not they should dig into a scented pot to get a reward. During the
433 10s delay, neurons in the hippocampus fired sequentially to cover the whole duration with
434 a firing pattern that was rearranged when the duration was changed. Most neurons were
435 modulated by both space and time, and in a manner independent of locomotion, speed, or
436 head placement. In another study, it was shown that very few neurons depend only on
437 time (MacDonald et al., 2013, 2011). Therefore, these sequential time cells seem similar,
438 or even identical, to the place cells described in the hippocampus (O’Keefe and
439 Dostrovsky, 1971) and may interact with those cells to form spatiotemporal maps of the

440 environment. More recently, Mello et al. (2015) have reported that 68% of cells recorded
441 in the dorsal striatum of rats performing a serial fixed-interval task (from 12s to 60s) were
442 relative time cells (i.e. active at specific time points during the fixed-interval). The pattern
443 of activity was modulated by the duration of the interval but not correlated to motor
444 responses, thus demonstrating a scalable population of neurons which conformed to the
445 scalar property. **As can be seen from the studies described above, sequential time cells**
446 **have been evidenced in both explicit and implicit timing tasks.**

447 These sequential time cells seem to constitute a “pure” time encoding which can
448 support the encoding of long durations and, even, parallel encoding of multiple durations
449 simultaneously. However, the questions remain of what makes these cells fire at a specific
450 time (e.g., does it result from a local process or do they receive a temporal input from an
451 upstream brain area), and of to separate the different sub-populations representing
452 different durations in different contexts.

453

454

455 3.2 Non-electrical activity measures

456

457 Using Positron Emission Tomography (PET) scan imaging in monkeys performing a
458 visual temporal discrimination task, Onoe et a. (2001) showed blood flow modulation
459 (increase in blood flow is correlated with an increase in neural activity) in specific
460 structures that was correlated with the length of the estimated interval (within a 0.4 to
461 1.5s range). These structures included the dorsolateral PFC, the posterior inferior parietal
462 cortex, the posterior cingulate cortex, and the basal ganglia. Meanwhile, micro-dialysis
463 can give access to dynamic release of neurotransmitters, albeit with a temporal resolution
464 of around a minute at the maximum resolution. In an olfactory Pavlovian aversive

465 conditioning in which CS-US trials were given at a regular pace (4 min), Hegoburu et al.
466 (2009) saw transient amino acid increases (GABA and glutamate) in the piriform cortex
467 of rats (but not in the amygdala) near the expected time of the CS-US trial when the trial
468 was omitted after training. These increases may thus be correlates of the encoding of the
469 inter-trial interval (ITI). Unfortunately, these two techniques lack good temporal (from
470 tens of seconds to a few minutes) and/or spatial resolution (from a few millimeters to a
471 few centimeters) compared to other types of recordings, meaning that it is not possible to
472 separate the different steps of accumulating, encoding and decoding duration.

473 Calcium imaging in behaving animals is a recent technique which looks at the activity
474 of single cells using fluorescent calcium indicators. This technique adds the very
475 interesting aspect of being able to give spatiotemporal information on neuronal activation,
476 albeit at the expense of a lower (~100ms) temporal precision compared to electrical unit
477 recordings (~40 μ s). Furthermore, it also gives the opportunity to record from a large
478 number of cells at the same time, while individualizing them spatially. Using this
479 technique in zebrafish larvae (which are transparent), entrainment to a visual stimulus
480 was observed in the lateral habenula (similar to the mammalian habenula) through an
481 increased calcium metabolism at the expected time of arrival of a neutral stimulus (Cheng
482 et al., 2014). Also, in mice, a ramping pattern of activated neurons was detected in the
483 hippocampus during the delay between CS offset and US in a trace conditioning task
484 (Modi et al., 2014). While the authors did not observe a specific spatial organization of
485 the time-tuned cells, they observed that cells with highly correlated spontaneous activity
486 formed clusters that were modified with learning.

487

488 3.3 Monotonic change of neuronal population activity across time

489

490 Studying episodic memory, (Manns et al., 2007) have shown in rats that events
491 closer in time are associated with spatial ensemble activities in CA1 that are more
492 similar than for events farther in time. They taught the rats to choose an odor
493 according to when in a sequence of odors it had been presented before, and showed
494 differences in cell firing encoding between earlier and later odors on correct trials,
495 but not on incorrect trials. These ensembles of cells in CA1 change their patterns of
496 activity monotonically across time and could provide a temporal context, a way to
497 encode and differentiate similar memories that are separated in time. This has also
498 been shown in the hippocampus of primates (Naya and Suzuki, 2011). Within the
499 hippocampus, CA2, and to a lesser extent CA1, networks show changes of activity
500 over time in stable spatial environments, providing a temporal coding at the scale of
501 hours, in contrast to a highly consistent time-independent CA3 network activity
502 (Mankin et al., 2015, 2012). These changes over time do not impede the decoding of
503 the spatial information that is also encoded (Rubin et al., 2015).

504 Interestingly, sequential time cells that code time in the range of seconds to
505 minutes may also exhibit this type of ensemble timing (in the range of hours to days).
506 Indeed, using calcium imaging *in vivo* in mice running timed laps on a treadmill,
507 Mau et al. (2018) showed that a population of sequential time cells in CA1 that
508 encoded a 10s duration would change gradually over days, therefore encoding time
509 on a larger scale as well.

510

511 3.4 Local field potentials (LFPs)

512

513 LFPs represent the sum of depolarization/hyperpolarization of a population of
514 neurons, reflecting action potentials as well as subthreshold electrical modulation such as

515 EPSPs (excitatory post-synaptic potentials) and IPSPs (inhibitory post-synaptic
516 potentials) (Buzsáki et al., 2012). It is important to note that LFPs represent both input
517 activity (i.e. coming from upstream brain areas) as well as local computations and output,
518 in contrast to single unit or multi-unit recordings which only reflect spikes, and thus
519 output data of the recorded area. Some LFP modulations are time-locked to the onset of
520 a stimulus and are called event related potentials or ERP (Figure 2B). They can be
521 observed when averaging a large number of trials under constant conditions. The raw LFP
522 signal (Figure 2C) recorded from a brain area can also be decomposed in different
523 frequency components (i.e., oscillations) that are considered to have different roles in
524 neural processing. Data on oscillations are often presented in the form of power spectrum
525 density (PSD), which represents the strength of different frequency bands in a signal.
526 When looked at in a time-frequency manner, one can ask how the power of different
527 frequency bands varies across a trial. Most frequency bands - from slow oscillations (like
528 delta and theta) to mid-range (like alpha and beta) and even high frequency oscillations
529 (like gamma and epsilon) - have been described in several mammalian species, and neural
530 oscillations seem to be a conserved phenomenon across mammalian evolution (Buzsáki
531 et al., 2013). However, depending on the task and on the brain area under study, the exact
532 parameters of these oscillatory bands may differ. We will thus refer to the specific
533 frequency ranges rather than the sole classification range, in order to keep accuracy and
534 avoid misinterpretation.

535 Neuronal oscillations have long been hypothesized as the major constituent of the
536 internal clock (Buhusi and Meck, 2005; Treisman, 1963). Oscillations also seem to be
537 involved in structuring events in time (for example events can be associated with the
538 specific phase of an oscillation) (Köseme et al., 2014; Mizuseki et al., 2009). They present
539 a further interest, as they provide potential comparison with human studies where most

540 of the data are in the form of oscillatory activity measured in a non-invasive manner
541 (Electroencephalogram (EEG) and Magnetoencephalogram (MEG)). In contrast to the
542 large number of studies done using EEG and MEG in humans for the past two decades,
543 studies on LFP and interval timing in animals are rather recent but reflect a growing
544 interest in the neuroscience community.

545

546 *3.4.1 Explicit tasks*

547

548 Comparing an auditory temporal discrimination task with a simple auditory
549 reaction time task in rats, Onoda and collaborators showed that ERPs can be modulated
550 by timing. They showed an involvement of the frontal cortex, the hippocampus and the
551 cerebellum in discriminating between 2s and 8s (Onoda et al., 2003) and of the frontal
552 cortex, striatum and thalamus for durations shorter than 2s (Onoda and Sakata, 2006).
553 Matell and Meck (2004) have proposed, within the frame of SBF model, that the ERP
554 signal could be representative of a reset of cortical neurons at the beginning of a stimulus,
555 which seems coherent with the observation of a time-dependent ERP in the frontal cortex
556 for all tested durations. These results confirm the lesions and inactivation studies showing
557 the importance of the striatum and PFC in interval timing while implying an involvement
558 of other structures that have also been suggested to play a role in timing (i.e., cerebellum,
559 thalamus and hippocampus). However, ERPs do not give information on whether nor how
560 these structures are involved in further temporal processing beyond a reset mechanism.

561 Low frequency oscillations have been associated with explicit temporal
562 processing in several structures, mostly in the hippocampus, striatum and PFC.
563 Concerning the hippocampus, the results are somewhat contradictory depending on the
564 durations studied. Nakazono et al. (2015) showed a transient increase in theta power (4 -

565 9 Hz) during the comparison between a 1s and a 3s stimulus in a temporal discrimination
566 task. However, looking at longer intervals (30s) in a peak interval task, Hattori and Sakata
567 (2014) found that the power increase in the 6-12 Hz band was not modulated by time in
568 the hippocampus, while it was so in the striatum. Looking at both the striatum and the
569 PFC, Emmons et al. (2016) showed a correlation between timing behavior in rats engaged
570 in a fixed interval task (with intervals ranging from 3 to 16s) and the theta band (4 – 8
571 Hz) within the PFC as well as with the delta band (1 – 4 Hz) of the striatum. Interestingly,
572 timing behavior was impaired when disrupting dopamine signaling in the PFC, in
573 correlation with a decreased 4 Hz power in the PFC (Kim et al., 2016; Parker et al., 2014).
574 Furthermore, these impairments were rescued by stimulation of the lateral cerebellar
575 nuclei projection to the thalamus (Parker et al., 2017). No study has reported an
576 involvement of higher frequencies in explicit timing, but it may reflect a simple neglect
577 of analysis. While these experiments show an important role of a PFC-striatum-thalamo-
578 cerebellum network in timing behavior, further experiments are needed to give more
579 insight on potential larger networks (e.g., other cortical areas, hippocampus) and their
580 specific involvement in the processing of time when the subject is engaged in explicit
581 timing.

582

583 3.4.2 *Implicit tasks*

584

585 So far, eleven studies using various implicit timing tasks have reported changes in
586 neural oscillations in several brain areas and from low to high frequency ranges. In
587 entrainment tasks, in which a stimulus is presented at regular intervals, the observed
588 change is usually an increased activity at the entrained frequency even in absence of the
589 stimulus. For example, Abe et al. (2014) showed that hippocampal oscillations could be

590 entrained at a theta (4-12 Hz) frequency but not at higher frequencies (above 20 Hz).
591 Bartolo et al. (2014) showed entrainment in beta (10-30 Hz) and gamma (30-80 Hz)
592 ranges in the striatum of monkeys during an internally-driven rhythmic tapping task with
593 intervals ranging from 450ms to 1s.

594 Changes in power from low to mid frequency ranges have also been reported in
595 several cortical areas in tasks involving holding attention for a given amount of time. In
596 a sustained attention task, in which the rat had to pay attention for 8s to detect a visual
597 stimulus that indicated which hole to choose between three to get a reward, Totah and
598 collaborators (2013b) reported changes during the delay on correct trials (incorrect trials
599 being any trials during which the animal chose the wrong hole) in two regions of the PFC,
600 the anterior cingulate cortex (ACC) and the prelimbic cortex (PL). They observed an
601 increase in delta oscillations power (1-4 Hz) in a ramping manner in the ACC, while the
602 increase was sustained in the PL. Either of these patterns could be interpreted as a
603 representation of expectation and time. Kilavik et al (2012) showed an increase in power
604 in a 12 to 40 Hz range in the motor cortex that was related to the temporal motor
605 preparation of monkeys performing a reaching task with two different delays. The short
606 durations used (0.7 – 2 s range) may not have made the characterization of a ramping
607 pattern possible. Zold and Hussain Shuler (2015) described a modulation of a 6-9 Hz
608 frequency band in the primary visual cortex during a reward expectation task in rats, the
609 duration of which evolved with training from being initially related to physical parameters
610 of the stimulus used (i.e. the visual stimulus intensity) to being correlated to the reward
611 time. However, as it was also correlated with the rate of reward (i.e. performance), it is
612 difficult to ascertain that it represented temporal coding rather than saliency/motivation
613 encoding.

614 Changes have also been reported in ranges from low to high frequency, most often in
615 the amygdala, but also in other subcortical and cortical areas, in associative conditioning
616 tasks. In these tasks, in which the CS predicts the arrival of a US, at a given time, usually
617 at the end of the CS (delay conditioning) or after a stimulus-free period (trace
618 conditioning), changes in neural oscillations have been observed in a manner compatible
619 with increasing temporal expectancy for the US arrival. An increase in synchronicity
620 within the theta range (4-7 Hz) has been observed in the lateral nucleus of the amygdala
621 (LA) in aversive conditioning in cats (Paré and Collins, 2000), while a sudden increase
622 in power in the gamma range (50-80 Hz) followed by a progressive return to baseline,
623 and a decrease in power of lower frequency oscillations (10-30 Hz), have been reported
624 in the auditory cortex in a similar task in rats (Headley and Weinberger, 2013). In
625 appetitive Pavlovian trace conditioning in cats, Bauer et al. (2007) observed a ramping
626 low gamma activity (35-45 Hz) peaking just before the reward for the basolateral nucleus
627 of the amygdala (BA) and earlier for the rhinal cortices. Interestingly it emerged with
628 training. However, in all these studies, the lack of recordings during post-reinforcement
629 time and the use of a single CS-US interval render difficult to determine whether these
630 changes in neural activity really represent timing of the CS-US interval, rather than a
631 simple increased US expectancy as time passes. In a specifically designed Pavlovian
632 aversive task in which the US was embedded within a long 60s CS and probe non-
633 reinforced CS alone trials were interleaved between CS-US pairing trials, allowing to
634 follow both the ascending and descending parts of the US expectancy, Dallérac et al.
635 (2017) showed a bell-shape pattern of increased power that followed closely the temporal
636 behavior pattern, in the theta (3-6 Hz) and gamma (60-70 Hz) ranges for both the BA and
637 the dorsomedial striatum. Importantly, these patterns shifted in time with a shift in the
638 CS-US interval and followed the scalar property of time.

639 While changes in oscillatory power points to the involvement of a given brain area
640 in timing - although the function of specific frequencies remains to be resolved - it does
641 not give access to the recruitment of potential networks encompassing several structures.
642 Synchronicity of oscillations between different structures, also called coherence (Figure
643 2D), gives information about the communication between structures. When two structures
644 are highly coherent, it is thought to make information transfer easier because the other
645 structure is already primed to receive the spiking activity from the first (cf. the
646 communication through coherence hypothesis, Fries, 2005). Only four studies have
647 reported increased coherent activity between brain areas, all of them involving the
648 amygdala in associative tasks. Pape and collaborators (2005) were the first to note a
649 progressive increase in correlated theta (5-6 Hz) between CA1 of the hippocampus and
650 the lateral amygdala (LA) across the CS in an aversive Pavlovian delay conditioning
651 paradigm in mice. Popescu et al. (2009) detected an increase in gamma band (33-45 Hz)
652 coherence between the BLA and the posterior striatum during the CS, with a peak
653 immediately before the arrival of the reward that was bigger for the CS⁺ (associated with
654 the US) than for the CS⁻ (not associated with the US). This increased coherence emerged
655 with repeated training, and may thus represent a correlate of some expectancy-related
656 behavior rather than the initial temporal learning (which happens from the start of
657 associative learning, Balsam and Gallistel, 2009). Totah and collaborators (2013b)
658 showed that coherence in a 8-12 Hz band between two sub-areas of the PFC (ACC and
659 PL) was increased in a ramping manner during the 8s preparatory period predicting a very
660 brief visual stimulus the rat had to detect. More recently, Dallérac et al. (2017) showed a
661 temporally-linked increase in coherence in the 3-6 Hz theta (but not the 60-70 Hz gamma)
662 range between BA and dorsomedial striatum that peaked at the expected time of an
663 aversive US arrival and returned to baseline level, in trials in which the US was omitted.

664 This increased coherence was shifted following a scalar-related variance when changing
665 the CS-US duration. These results suggest that the dynamics of functional connectivity,
666 as reflected through coherence, may indicate time-based recruitment of large neural
667 networks. Although these types of investigation are yet too few to give a good idea of the
668 network(s) involved in different timing tasks, it seems that the amygdala, prefrontal
669 cortex and striatum may enter in active interaction during temporal expectancy.

670

671 **3.5 Modulating neuronal activity**

672

673 **Thanks to recent methodologies permitting a highly precise temporal control of**
674 **cells' activity, there is an increasing interest in investigating how modulating activity**
675 **of specific neuronal populations could influence interval timing. In a task where rats**
676 **learned to optimize their wait time (~1.1s) after a visual cue in order to get the**
677 **biggest reward, Namboodiri et al, in (2015) , have shown that stimulating, for 200ms,**
678 **V1 neurons 300ms after the visual cue, shifted the entire distribution of the animal's**
679 **waiting times, and thus delayed its timed actions. Three papers from the**
680 **Narayanan's lab have looked at how to rescue behavioral timing impairment due to**
681 **a disruption of the medial frontal cortex (MFC) functioning. Stimulating D1**
682 **dopamine receptors in the MFC of DA-depleted transgenic mice or stimulation the**
683 **lateral cerebellar projection to the thalamus at 2Hz frequency in rats with D1-**
684 **inhibited MFC, which both increased the ramping activity in the MFC (a well**
685 **described characteristic of timing, (Emmons et al., 2017; Kim et al., 2016; Parker et**
686 **al., 2015), or 20Hz activation of MFC axons in the dorsomedial striatum (DMS)**
687 **which rescued the time-related ramping activity in the DMS in MFC muscimol-**
688 **inhibited rats, all these rescued the animal's temporal behavior in a 12s fixed**

689 **interval task that was otherwise disrupted by MFC dysfunction** (Emmons et al., 2019;
690 Kim and Narayanan, 2019; Parker et al., 2017).

691 **Soares and collaborators, in (2016), have shown that activation of the**
692 **dopaminergic neurons in the substantia nigra *pars compacta* in mice during the**
693 **entire interval produced a shift to the right of the temporal bisection curve (range**
694 **0.6-2.4s), suggesting a slowing down of internal time, whereas inhibition of those**
695 **neurons produced a shift in the opposite direction, compatible with an acceleration**
696 **of internal time. Targeting the GABAergic projection from the substantia nigra *pars***
697 ***reticulata* (controlled by outputs from the striatum) to the superior colliculus in mice**
698 **performing in a 10s fixed-time schedule with delivery of sucrose reward, Toda et al.**
699 **(2017) showed that, depending on the frequency of stimulation as well as when the**
700 **stimulation was done during a trial, stimulating this nigrotectal pathway not only**
701 **stopped the on-going licking behavior but could also produce a shift in anticipatory**
702 **licking on the next trial, and thus disrupted interval timing.**

703 **All these studies not only confirm the suspected critical role of some brain areas**
704 **(prefrontal cortex, striatum) or neuromodulators (dopamine), but also bring novel**
705 **information on neural networks and the frequencies at which they should function**
706 **for optimal interval timing. Nevertheless, more such studies aiming to modulate the**
707 **activities previously correlated with passing time are necessary to help us distinguish**
708 **the essential neural patterns for time from the non-essential.**

709

710 **4. Open questions**

711

712 **4.1 Neural syntax of timing from single cells to networks**

713

714 How the animal brain encodes time remains a challenging question. As we just
715 reviewed above, a large range of activity patterns (ramping, sustained and phasic) could
716 be considered to be associated with passing time and this suggests that it may be their
717 combined activities that underlie timing.

718 At first, it is tempting to think that sequential time cells could be the main tool the
719 brain uses for time encoding; however, are they sufficient? Could these cells be at the
720 origin of the other patterns of activity that have been described or are they the end results
721 of other neural computations? Sequential time cells may share the role of single unit's
722 sustained activity but for longer durations that cannot be coded by a single cell. Sequential
723 time cells need to be part of sets (i.e. functional populations) with each set involved in
724 encoding a specific duration, this allows for multiple durations to be encoded and decoded
725 at the same time.

726 Oscillations may provide a good way to produce those sets either through the phase
727 locking of spikes to different phases of a frequency band (i.e. whether spikes are
728 repeatedly more present at specific phases of the oscillations), or through phase amplitude
729 coupling (PAC) of high frequency oscillations' power with low frequency oscillations'
730 phase. To our knowledge very few studies studies have looked at this aspect of neuronal
731 encoding in a timing task. Phase-locking of spikes to delta oscillations (centered at 1.6Hz)
732 in the ACC have been reported to correlate with the growing expectation of a reward in a
733 sustained attention task (Totah et al., 2013a). In that study, the phase-locking was
734 increased significantly more in correct than incorrect trials within the 2s period before the
735 presentation of the stimulus indicating which hole to choose to get a reward (2s before).
736 A similar pattern was observed in the PL, but with phase-locking of spikes to beta
737 oscillations (centered at 17 Hz). However, Nakazono et al. (2015), looking at single units
738 and theta oscillations in the hippocampus in a temporal discrimination task, showed that

739 only few cells were time-locked to the oscillations compared to the study by MacDonald
740 et al. (2013). The authors suggested that the two types of activity may have different roles,
741 albeit both related to time: theta oscillations might help the hippocampus to interact with
742 the PFC at the correct time, whereas the spikes may encode both temporal and
743 spatial/sensory information.

744 Clearly, more studies specifically devoted to timing are needed to decipher the
745 respective roles of the different types of neural activities, how these patterns emerge, and
746 how their intricate intertwined activities may possibly create time representations in the
747 brain. In this venture, it will be critical to also identify which ones are required for timing
748 per se versus other aspects of the task (e.g., motivation, motor preparation, ...).

749

750 **4.2 Neural correlates of time associated with models**

751

752 **A number of models of interval timing have been proposed, but neural proofs**
753 **can be contradictory and do not, for now, allow for choosing one specific timing**
754 **model. As the subject is quite large and beyond the purpose of this review, we will**
755 **only quickly discuss to what extent the available data support some of these timing**
756 **models.**

757 **The main group of internal clock models are pacemaker accumulator models**
758 **(PA). Taking into account the intrinsic functioning of neurons and known network**
759 **connectivity, Matell and Meck (2000) proposed the Striatal Beat Frequency model**
760 **(SBF). It involves numerous cortical oscillators (representing the pacemaker and**
761 **accumulator), and the detection of their coincident activation by the medium spiny**
762 **neurons of the striatum on which they project. At the start of a stimulus, the**
763 **oscillators are synchronized (maybe by a dopamine burst, Kononowicz, 2015) while**

764 keeping their own distinct frequencies, meaning that they will not remain
765 synchronized over time. When a significant event happens (e.g., at the end of the
766 stimulus or at the appearance of a reinforcement), the state of these different
767 oscillators is encoded and stored by the striatum. By comparing the oscillators'
768 ongoing activity to the memorized patterns, it is possible for the striatum to
769 determine how much time has passed, provided that the oscillatory activity remains
770 very stable across time. Recently, replacing the memory and decision stage of the
771 SBF by the ones from a well characterized cognitive architecture (the adaptive
772 control of thought-rational, ACT-R), which has defined default parameters, has
773 improved modeling of more complex temporal behaviors (such as timing of multiple
774 overlapping intervals) (van Rijn et al., 2014). These systems from ACT-R may
775 involve other brain areas (e.g., the hippocampus) for memory and decision-making
776 processes.

777 Oscillations in the frontal cortex seem to be important for timing (e.g. Parker et
778 al, 2014, and duration-related increased neuronal oscillations have been reported in
779 the dorsomedial striatum (Dallérac et al, 2017) that could reflect a read-out of
780 convergent oscillations from cortical neurons. However, no study has yet shown
781 increased coherence between striatum and prefrontal cortex during interval timing.
782 Potentially adding on to the SBF model, data from our lab seems also to implicate
783 the amygdala as a modulator of cortico-striatal synapses to maintain the memory of
784 a previous duration when learning a new duration. So both memories are
785 maintained even though behavioral expression shifts quickly to the new duration
786 (Dallérac et al. 2017, see Figure 10). However, some of the expected signs of the SBF
787 model, such as phase reset at the beginning of the interval, have not been described
788 in neurophysiological studies (Kononowicz and van Wassenhove, 2016).

789 **The TopDDM (Time Adaptative Opponent Poisson drift-diffusion model) is also**
790 **a PA model, but based on the drift-diffusion model of decision-making (Balci and**
791 **Simen, 2016; Simen et al., 2011). It considers, in very general terms, that the**
792 **accumulation of time should be represented by a ramping activity which rate is**
793 **inversely proportional to the duration encoded. As reported above, this type of**
794 **activity has been described in multiple papers (e.g. Komura et al., 2001; Lebedev et**
795 **al., 2008; Murakami et al., 2014).**

796 **There are also non-clock-based models; they require a population of units (can**
797 **be neurons or group of neurons) that respond differently across time, which is**
798 **consistent with the existence of sequential time cells. Included in those models is the**
799 **TILT (Timing from Inverse Laplace transform) model from Shankar & Howard**
800 **(2012), as well as the multi-timescale model (MTS) from Staddon et al. (Staddon**
801 **and Higa, 1999), and the Spectral Timing Model (Grossberg and Merrill, 1992).**
802 **TILT model can also explain the scalar property of time as well as the recency effect**
803 **of episodic memory (Howard et al., 2015). Its principle is that the presentation of a**
804 **stimulus will activate a certain number of t nodes which will maintain a stable firing**
805 **rate across the period of to-be-encoded time, and after the end of the interval decay**
806 **exponentially to result in the activation of T nodes through an inverse Laplace**
807 **transform. This will produce units that are active at a specific time point after the**
808 **beginning of the stimulus. The different T nodes are activated sequentially and do**
809 **not influence one another, they are instead influenced by the activity in the t nodes.**
810 **Activities resembling to t nodes (stable increased firing) and to T nodes (sequential**
811 **time cells) that when active during the early part of the interval have smaller spread**
812 **of activity than cells activated later have both been reported in the literature.**

813 **However, it remains to be determined to what extent they are found in all brain**
814 **areas.**

815 **Clearly, more studies are necessary to improve our models of timing, to try and**
816 **disprove some of them, and choose between clock and non-clock-based models.**

817

818 4.3 Clock(s)

819

820 The question of how time is “written” in the brain opens another question of whether
821 there is one clock, multiple clocks, or any clock at all. As Staddon & Higga (1999) have
822 proposed, time may be encoded in the decaying function of memory strength, and would
823 therefore be present in all brain areas that are involved in a specific task. If so, time-
824 related patterns of neural activities may simply reflect the resulting read-out of these
825 memory strengths at each storage sites.

826 Neural correlates of time have been observed in most parts of the brain, depending on
827 the duration and the context of the task, making it difficult to determine the potential
828 origin of time. In particular, sequential time cells have been recorded not solely in the
829 hippocampus, but also in other brain areas that are involved in timing (PFC, premotor
830 cortex, basal ganglia). Also, as multiple durations are processed and encoded at every
831 moment, context might be critical to distinguish which intervals are essential in a specific
832 situation. Indeed, duration and spatial location are learned and processed together as
833 shown through space-time-context binding (Malet-Karas et al., 2019). It would seem
834 important to store durations and contextual cues in the same anatomical regions, therefore
835 going in the direction of multiple clocks.

836 The possibility of multiple clocks is suggested by the fact that some individual
837 neurons have an intrinsic oscillating activity, *in vitro* (e.g. Grace and Onn, 1989;

838 Hutcheon and Yarom, 2000; Steriade et al., 1993) and *in vivo* (Hyland et al., 2002).
839 **Furthermore, it has been shown that Purkinje cells in the cerebellum can produce a**
840 **timed pause in activity by themselves, i.e. intracellularly** (Johansson et al., 2014) **and**
841 **can even encode two durations** (Jirenhed et al., 2017). Therefore, a single cell might
842 represent the smallest unit for an internal clock.

843 This could lend some credence to the hypothesis that a small part of the brain is
844 sufficient for timing, without a need for inputs from external activity (Chubykin et al.,
845 2013; Goel and Buonomano, 2016; Johnson et al., 2010). In effect, Johnson and
846 collaborators (2010) showed that chronic rhythmic stimulation in organotypic cortical
847 slices (auditory and somatosensory) can entrain the cell activity to reflect the interval
848 between stimulations, in the hundreds of milliseconds range. Chubykin and colleagues
849 (2013) have also shown that it is possible to « teach » an interval of time to a slice of
850 primary visual cortex by using a carbachol infusion as a US and electrical stimulation of
851 the underlying white matter as a CS. Changing the interval between the CS and the US
852 induced a shift of cortical layer 5 neurons responses to the new time. *In vivo*, Namboodiri
853 et al. (2015) have demonstrated that it is possible for the primary visual cortex alone to
854 encode and influence highly stereotyped and quick motor actions. Although this remains
855 to be tested for longer durations, all these studies support the hypothesis that every cortical
856 circuit has the capacity to time and that there are local clocks that are activated depending
857 on the type of task or stimuli (Karmarkar and Buonomano, 2007). However, these may
858 be restricted to rather simple timing demands and may not be sufficient for more complex
859 timing tasks. It is conceivable that, with increasing complexity and demand, rather than
860 processing time within a brain area, larger networks may be involved, and improvement
861 of communication between different brain areas during salient time periods may be
862 necessary to encode duration, especially when it is long. Interestingly, Emmons et al.

863 (2016) showed that the inactivation of the PFC inhibits the ramping activity in the
864 striatum and disrupts temporal behavior, suggesting a role of between brain connectivity
865 in interval timing. Functional connectivity between brain areas can be measured in
866 various ways, through coherence (synchronization of the two LFP signals), PAC between
867 structures or phase-locking between oscillations and spikes (see a few examples at the
868 end of 3.3.2). Although the data are yet too few to draw a picture of time encoding at the
869 scale of large networks, it is a promising research avenue toward our understanding of
870 the neural syntax of timing.

871 It is thus possible that simple timing processing can be done in the brain area involved
872 in the task but that, for more complex paradigms, a larger network is at play (possibly
873 including PFC and striatum). This seems to be the case during development, as pre-
874 weaning age rats (around PN18-20), when prefrontal cortex, striatum and hippocampus
875 are not yet adult-like (Tallot et al., 2015), can still learn and memorize simple intervals
876 (Tallot et al., 2017). This simple/complex dichotomy may also apply in humans when
877 comparing explicit and implicit timing in children *vs.* adults
878 (Droit-Volet and Coull, 2016).

879

880 4.4 Temporal learning vs. temporal behavior

881

882 One parameter that has been overlooked so far in the literature is the amount of
883 exposure to the duration that is encoded. In effect, when looking at the experiments
884 described in the present review, we can notice that most of them are done in well trained
885 animals, and we can wonder whether different neurophysiological substrates may
886 underlie timing depending on the level of training of the animal; especially because
887 precise temporal behavior usually appears after at least a few hundred trials, although

888 duration is discriminated and learned much earlier (Balsam et al., 2010). In addition,
889 going even further in training, the animal may enter into habitual behavior, defined as
890 insensitive to devaluation of the reward, a process which may not happen at the same rate
891 depending on the duration and the task (Araiba et al., 2018). Habit may require a different
892 neural encoding than initial learning and, even, than optimized behavioral output,
893 although the network may remain the same (Doyère and El Massioui, 2016).

894 A single time interval can be learned in as little as one conditioning trial, as shown in
895 Diaz-Mataix et al. (2013), in which a change in CS-US interval is detected, that triggers
896 plasticity in the amygdala. Noticeably, this experiment is an example of a true
897 retrospective timing task, as the animal is “asked” only once whether the CS-US interval
898 during reactivation differs from the one presented during conditioning. When adding
899 more training/testing sessions, the animal enters into prospective timing which is the
900 domain of most of the studies described in our review. Whether prospective timing is at
901 play from the second trial or after several repetitions is not known, nor is it known whether
902 prospective timing would also engage time-stamping mechanisms, which retrospective
903 timing likely relies on.

904 Importantly, learning a duration and optimizing temporal behavior may involve
905 different mechanisms. This has been well exemplified by the study of Ohyama and Mauk
906 (2001) using eyeblink conditioning. Rabbits were trained on a first duration only for a
907 few sessions (i.e. before expression of temporal behavior) and then trained on a new
908 duration for hundreds of trials, resulting, once the behavior had been optimized, in a dual
909 response, one at each duration, and thus unravelling the initial, yet hidden, learning of the
910 first duration.

911 Only very few studies have tried to look at how neural correlates emerges with
912 training. Using calcium imaging, Modi et al. (2014) evidenced the modification of spatial

913 patterns of neuronal activation depending on the level of training, which could represent
914 progressive learning of the duration and improvement in precision. In mice navigating in
915 a virtual environment, Heys and Dombeck (2018) recorded sequential time cells' calcium
916 activity in the medial entorhinal cortex when animals spontaneously stopped to move and
917 for the duration of inactivity, as a way to see how animals record passing time in the
918 absence of changes in space or in motor output. By changing the environment sufficiently
919 to get a global remapping of space and sequential time cells, they considered that they
920 were looking at the initial encoding of time in that new environment. They showed that
921 sequential time cells' activity was very stable from the beginning of the session, from the
922 first trial even. Another proxy of early learning of duration can be to change the learned
923 duration to a new one, forcing the system to re-encode. However, the temporal behavior
924 is shifted in time very quickly and it can be difficult to separate learning the new duration
925 and forgetting or eliminating responses to the previous one, each process possibly relying
926 on different brain areas (Dallérac et al., 2017).

927 Beside the effects of training on the neural encoding of time, the behavioral output of
928 the animal per se may modify how passing time is encoded, as has been shown in the
929 lateral entorhinal cortex (Tsao et al., 2018). On one hand, when behavior is stable across
930 trials, then encoding of time becomes relative to these trials, and it is difficult to
931 differentiate a trial at the beginning of the session from a trial at the end of the session,
932 and time within a trial is very well encoded. On the other hand, in free exploration, the
933 flowing of time across the whole session is encoded, even if there are temporal cues
934 intrinsic to the session that can separate it into trials. Therefore, behavioral output may
935 change how the animal perceives time. This is similar to what was implied in the
936 Behavioral Theory of Timing, where behavioral states are used as temporal counters
937 (Killeen and Fetterman, 1988).

938

939 4.5 Animal vs. Human

940

941 Some aspects of timing may differ between humans and animals, potentially due to
942 the fact that animals need a lot of training to understand the task or express temporal
943 control in their behavior, while reading instructions is sufficient in most cases in humans.
944 The fact that there has not been much attempt to record brain activity in paradigms
945 enabling comparison between animal and human data makes it difficult to extract a global
946 picture across species. Indeed, the types of tasks and of durations used are very different
947 between the human and animal research, as well as the types of recording. The neural
948 correlates of time have been studied a lot in humans using different techniques ranging
949 from functional magnetic resonance imaging (fMRI) to magnetoencephalography
950 (MEG). We will not go into details since the subject has already been covered by several
951 reviews (Allman et al., 2014; Coull et al., 2011; Merchant et al., 2013a). As a brief
952 summary, several structures have been detected as active during timing tasks across many
953 different studies, such as the supplementary motor area (SMA), the pre-SMA, the
954 prefrontal cortex, the striatum, the inferior parietal cortex and the cerebellum (Brannon et
955 al., 2008; Coull and Nobre, 2008; Harrington et al., 2004; Lewis and Miall, 2003; Rubia
956 and Smith, 2004; Wiener et al., 2010; Wittmann et al., 2011). The pre-SMA (or rostral
957 SMA) seems more involved in perceptually-based timing in the supra-second range,
958 whereas the caudal SMA may be more important for sensorimotor-based timing in the
959 sub-second range (Schwartz et al., 2012). However, timing of a stimulus offset seems to
960 be encoded in the related sensory cortex (van Wassenhove and Lecoutre, 2015). In a meta-
961 analysis, Wiener et al. (2010) highlighted the fact that the structures involved often
962 depend on the type of task and on the durations used. They concluded that two main

963 structures are involved in temporal encoding only: the prefrontal cortex and the SMA. In
964 contrast, Harrington and collaborators (2010) showed that the striatum is the only
965 structure that is more active during the encoding of durations than during their
966 maintenance in memory. In their study, the SMA and pre-SMA had a high activity for
967 both encoding and maintenance phases, while the cerebellum and frontal cortex were
968 more active in the time paradigm only at the decision stage.

969 Unfortunately, the SMA and pre-SMA have not been studied much in animals' timing
970 studies, in contrast to the prefrontal cortex, the striatum and the *substantia nigra*. Striatum
971 and *substantia nigra* are deep brain structures that cannot be recorded easily in humans
972 at least on a rapid timescale. Therefore, the question of to what extent time is encoded
973 similarly between animals and humans may not find a complete answer - without
974 technical improvement of recordings in humans - but there is space for advancement in
975 species comparability.

976

977 4.6 Concluding remarks

978

979 As we have seen in the previous pages, the neural processing and encoding of time
980 has been studied in animals for ~50 years using a large range of techniques, giving us
981 insight from individual neurons to the interaction of separate brain areas. However,
982 compared to other types of neural computation (such as spatial encoding), we are still
983 very much unsure of the exact neural correlates of interval timing. To process long
984 durations, interactions between populations of neurons, and even maybe between brain
985 areas, might be necessary (as ramping and sustained activity cannot be maintained over
986 long periods of time), but it has almost never been studied in that aspect.

987 In this review, we have pointed to studies where temporal patterns of brain activity
988 were observed, but for the most part, the studies described here did not directly have the
989 purpose of searching for timing related activity, in particular in the case of implicit timing
990 tasks. This puts into focus the necessity to use the decades of psychological research on
991 timing to create specific protocols and paradigms to determine how time can be processed
992 and encoded in the brain, and how these processes may be modified depending on task's
993 demand. For example, although testing for the scalar property of time is an essential
994 parameter of a temporal task, very few studies have looked at it while recording brain
995 activity (see Dallérac et al., 2017; Mello et al., 2015). It is also very important to look at
996 both the pre-reinforcement as well as the post-reinforcement periods, for example by
997 using non-reinforced probe trials, as some patterns of encoding cannot be detected when
998 looking only at the expectancy period. Also, specific controls may be necessary to isolate
999 temporal information from saliency of stimuli or of reinforcement. In addition, looking
1000 in a wide variety of brain areas, not necessarily involved in the task at hand, could help
1001 determine if timing is ubiquitous in the brain. Finally, cross-species comparison, using
1002 virtually identical tasks, is critical in order to dissociate general principles of timing
1003 mechanisms from species-specific time-associated behaviors, thus optimizing the
1004 potential generalization of findings to human brain function.

1005

1006

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1010

1011 **References**

1012

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1623

1624

1625 **Figure captions**

1626

1627 Figure 1: Schematic representation of the different patterns of changes in the number of
1628 spikes of single neurons in relation to the encoding of temporal durations (here two
1629 durations are represented, one in black and one in red). All of these patterns can also be
1630 observed in a negative variation.

1631

1632 Figure 2: Schematic representation of possible encoding of time through modulation of
1633 population neural activity either through organization of single cells activity (A), or
1634 through local field potentials modulations (B-D).

1635

1636 **Tables captions**

1637

1638 Table 1: Single unit studies in explicit timing tasks

1639

1640 Table 2: Single unit studies in implicit timing tasks

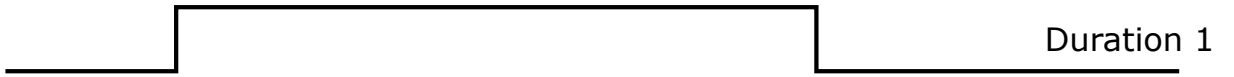
1641

1642 Table 3: Population-level studies in explicit timing tasks

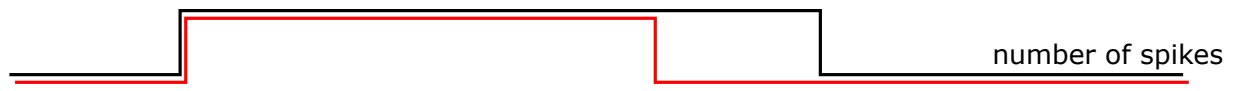
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1644 Table 4: Population-level studies in implicit timing tasks

1645



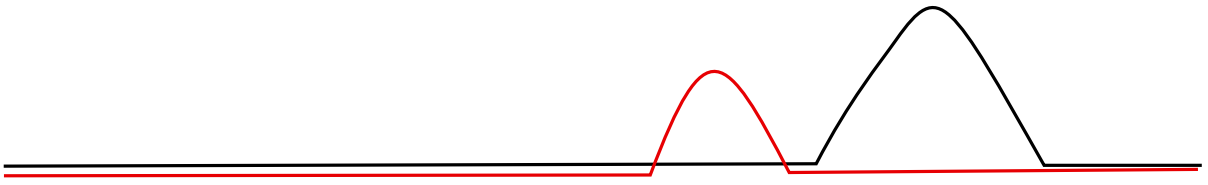
Sustained



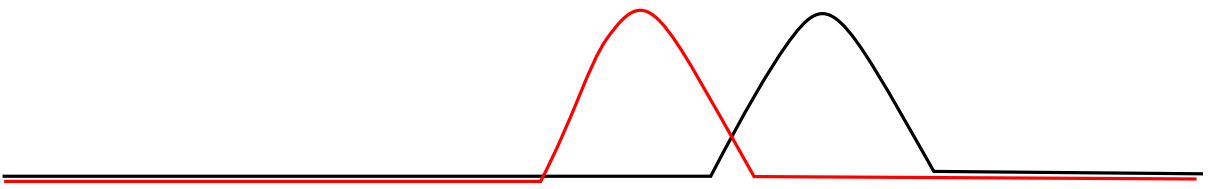
Phasic onset



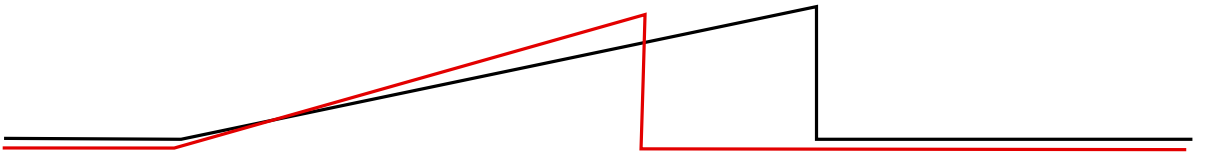
Phasic offset



'Event time' cells

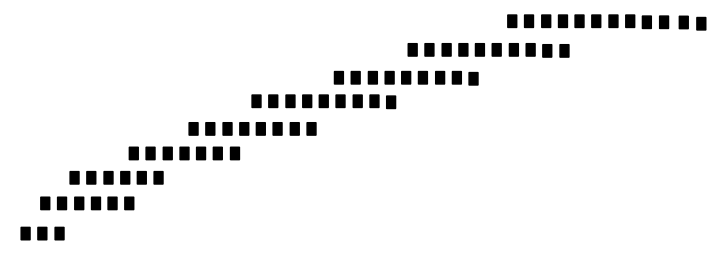


Ramping

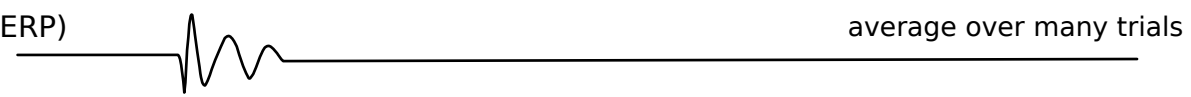




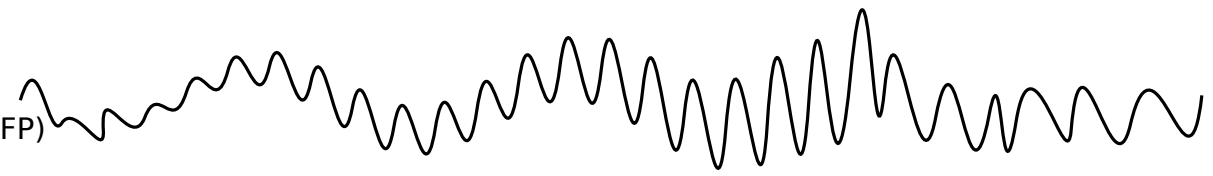
A Sequential Time cells



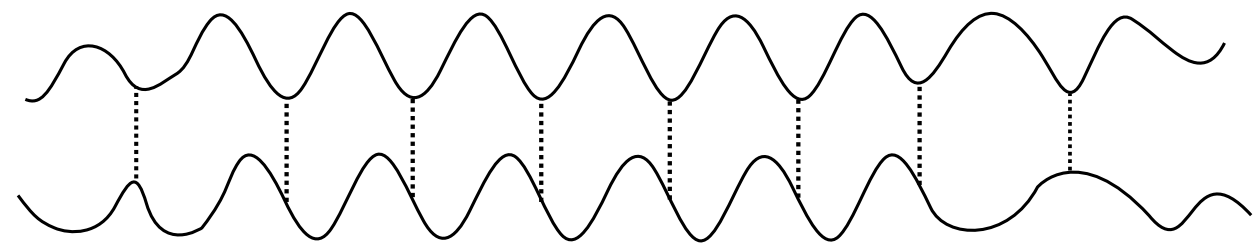
B Evoked Related Potential (ERP)



C Local Field Potential (LFP)



D Coherence



Tasks	Brain structures	Species	Durations (in s)	Results			References	
				Sustained activity	Phasic response at onset or offset of cue	Event time		Ramping activity
Time production	Motor Cx	rat	1 - 2	a		a	Knudsen et al. (2014) (a)	
	Premotor Cx	monkey	2.5 - 4.5			a	Lebedev et al. (2008) (a)	
	Parietal Cx	monkey	0.5 - 1			a	Jazayeri and Shadlen (2015) (a)	
	Presupplementary Cx Supplementary motor	monkey	2 - 8			a, b	Mita et al. (2009) (a); Roux et al. (2003) (b)	
Time reproduction	Prefrontal Cx	monkey	2 - 7	a	a		Yumoto et al. (2011) (a)	
	Parietal Cx	monkey	0.5 - 1			a	Jazayeri and Shadlen (2015) (a)	
	Premotor Cx	monkey	0.45 - 1			a	Merchant et al. (2013b) (a)	
Peak interval	Prefrontal Cx	rat	1.5 - 2.5			a	Xu et al. (2014) (a)	
			10 - 40			b	a	Parker et al. (2014) (a); Matell et al. (2003) (b)
	Lateral agranular Cx	rat	10 - 40			a	Pang et al. (2001) (a)	
	Medial agranular Cx	rat	10 - 20			a	a	Matell et al. (2011) (a)
	Primary visual Cx	rat and mice	1 - 2	a, b		a, b, c	Chubykin et al. (2013) (a); Liu et al. (2015) (b); Hussain Shuler and Bear (2006) (c)	
	Dorsal striatum	rat	10 - 40			a, b	Matell et al. (2003) (a); Portugal et al. (2011) (b)	
Differential reinforcement of low rates (DRL)	Secondary motor Cx	rat	1 - 4		b		a, b	Murakami et al. (2014) (a); (2017) (b)
	Prefrontal Cx	monkey	2	a			a	Niki and Watanabe (1979) (a)
	Hippocampus	rat	15				a	Young and McNaughton (2000) (a)
Limited hold (LH)	Prefrontal Cx	pigeon	1.5				a	Kalenscher et al. (2006) (a)
	Ventral striatum	monkey	1				a	Shidara et al. (1998) (a)
	Primary visual Cx	rat	1.5	a			a	Namboodiri et al. (2015) (a)
Temporal discrimination	Parietal Cx	monkey	0.3 - 0.8				a	Leon and Shadlen (2003) (a)
			0.2 - 2	d	a, b, c, d		a, b, c, d	Genovesio et al. (2006) (a), (2009) (b); Oshio et al. (2006) (c), (2008) (d)
		rat	3 - 4				a	Kim et al. (2013) (a)
	Motor Cx	monkey	0.6 - 1.2		a		a	Roux et al. (2003) (a)
	Dorsal striatum	monkey and rat	0.2 - 2.4		a, b	c		Chiba et al. (2008)(a), (2015)(b); Gouvêa et al. (2015)(c)
	Hippocampus	rat	1 - 3			a		Nakazono et al. (2015) (a)
Fixed interval	Medial prefrontal Cx	rat and mice	12				a, b, c, d	Emmons et al. (2017)(a); Kim et al. (2016) (b); Parker et al. (2015) (c); (2017) (d)
	Cerebellum	rat	12				a, b	Emmons et al. (2017)(a); Parker et al. (2017) (b)
Serial fixed interval	Dorsal striatum	rat	10 - 60			a		Mello et al. (2015) (a)

Tasks	Brain structures	Species	Durations (in s)	Results				References	
				Sustained activity	Phasic response at onset or offset of cue	Event time	Ramping activity		
Pavlovian aversive delay	Auditory Cx	rat	2			a, b	Armony et al. (1998) (a); Quirk et al. (1997)		
	Prefrontal Cx	rat	30	a			Pendyam et al. (2013) (a)		
	Basal amygdala	rat	30	a			Pendyam et al. (2013) (a)		
Pavlovian aversive trace	Prefrontal Cx	rat	20			a	Gilmartin and McEchron (2005) (a)		
	Hippocampus	rabbit	10 - 20			a, b	McEchron et al. (2003) (a)		
Pavlovian appetitive delay	Amygdala	monkey	2			a	Bermudez et al. (2012) (a)		
	Nucleus accumbens	rat	10	a			Day et al. (2006) (a)		
	Substantia nigra	monkey	1 - 16		a		Fiorillo et al. (2008) (a)		
	Ventral tegmental area	monkey	1 - 16		a		Fiorillo et al. (2008) (a)		
Pavlovian appetitive trace	Orbitofrontal Cx	mice	2	a			Zhou et al. (2015) (a)		
	Basolateral amygdala	cat	1.5			a	Paz et al. (2006) (a)		
Delayed matching to sample / working memory	Parietal Cx	monkey	0.5 - 2			a	Janssen and Shadlen (2005) (a)		
	Prefrontal Cx	monkey	0.5 - 60	b, g	c	b, e	a, b, c, d, f, g, h, i, j	Brody et al. (2003) (a); Fuster and Alexander (1971) (b); Fuster et al. (1982) (c); Jin et al. (2009) (d); Joseph and Barone (1987) (e); Kojima and Goldman-Rakic (1982) (f); Machens et al. (2010) (g); Rainer et al. (1999) (h); Sakurai et al. (2004) (i); Tsujimoto and Sawaguchi, (2005) (j)	
	Orbitofrontal Cx	monkey	0.5 - 2.5		a			Roesch and Olson (2005) (a)	
	Inferotemporal Cx	monkey	5 - 8				a	Reutimann et al. (2004) (a)	
	Motor Cx	monkey	0.5 - 3	a	b		a, b, c	Narayanan and Laubach (2009) (a); Ohmae et al. (2008) (b); Rossi-Pool et al. (2019) (c)	
	Premotor Cx	monkey	15 - 60	a			a, b	Fuster and Alexander (1971) (a), (1973) (b)	
	Striatum	monkey	2 - 4	a, b, c		c	a, b	Hikosaka et al. (1989) (a); Jin et al. (2009) (b); Tremblay et al. (1998) (c)	
	Ventral striatum	monkey	2 - 5			a	a	Schultz et al. (1992) (a)	
	Subiculum	rat	1 - 30	a			a	Hampson and Deadwyler (2003) (a)	
	Hippocampus	monkey	0.7 - 1.2				a	Sakon et al. (2014) (a)	
	Expectation	Primary auditory Cx	rat	0.3 - 1.5		a			Jaramillo and Zador (2011) (a)
		Prefrontal Cx	monkey and rat	3-6			b	a, b	Donnelly et al. (2015) (a); Sakai (1974) (b)
		Motor Cx	monkey and rat	0 - 5				a, b	Lucchetti and Bon (2001) (a); Lucchetti et al. (2005) (b)
		Premotor Cx	rat	up to 80 min				a	Tsao et al. (2018)
		Lateral entorhinal Cx	rat	0 - 2				a	Komura et al. (2001) (a)
Posterior thalamus		rat	1.5 - 20	a				Miyazaki et al. (2011) (a)	
Dorsal raphe		rat	8				a	Totah et al. (2013b) (a)	
Ventral tegmental area		monkey	1.5 - 4.5	c			a, b, c	Apicella et al. (1992) (a); Hikosaka et al. (1989) (b); Sardo et al. (2000) (c)	
Striatum (caudate and putamen)		rat	1 - 5			a	b	Donnelly et al. (2015) (a); Khamassi et al. (2008) (b)	
Ventral striatum		mice	1				a	Wagner et al. (2017) (a)	
Entrainment	Cerebellum	monkey	0.45 - 1	b		a, b, c	b	Crowe et al. (2014)(a); Merchant et al. (2011) (b), (2013b) (c)	
	Striatum	monkey	0.45 - 1			a		Bartolo et al. (2014) (a)	

Tasks	Brain structures	Species	Durations (s)	Results			References
				PSD	Coherence	Other	
Time production	Parietal Cx	monkey	1			multiunits	Schneider and Ghose (2012)
Temporal discrimination	Prefrontal Cx	monkey	0.2 - 2			Single unit recordings	Oshio et al. (2008)
		rat	3 - 4			Single unit recordings	Kim et al. (2013); Tiganj et al (2017)
	Frontal Cx Hippocampus Cerebellum	rat	2 - 8			ERP	Onoda et al. (2003)
	Frontal Cx Striatum Thalamus	rat	0.5 - 2			ERP	Onoda and Sakata (2006)
	Hippocampus	rat	1 - 3	theta (4-9 Hz)			Nakazono et al. (2015)
	Substantia nigra	mice	0.6 - 2.4			Single unit recordings	Sakurai (2002)
	Dorsolateral prefrontal Cx Posterior inferior parietal Cx Posterior cingulate Cx Striatum	monkey	0.4 - 1.5			Calcium imaging	Soares et al. (2016)
Peak interval	Striatum	rat	30	theta (6-12 Hz)			Hattori and Sakata (2013)
Limited Hold (LH)	Medial entorhinal Cx	mice	6			Calcium imaging	Heys and Dombeck (2018)
Fixed interval	Medial prefrontal Cx	rat and mice	12	delta (4 Hz)			Parker et al. (2014); (2017)
				delta (1 - 4 Hz)			Kim et al. (2016)
	Medial prefrontal Cx Striatum	rat	3 - 12	delta (1 - 4 Hz) theta (4 - 8 Hz)			Emmons et al. (2016)
	Striatum	rat	12			Single unit recordings	Emmons et al. (2019)

Tasks	Brain structures	Species	Durations (in s)	Results			References
				PSD	Coherence	Other	
Pavlovian appetitive delay	Substantia nigra	monkey	2 – 16			Multiunits	Kobayashi and Schultz (2008)
	Striatum Basolateral amygdala	cat	3			gamma (35-45 Hz)	Popescu et al. (2009)
Pavlovian aversive delay	Auditory Cx	rat	10	gamma (50-80 Hz) beta (10-50 Hz)			Headley and Weinberger (2011); (2013)
	Dorsomedial striatum Basolateral amygdala	rat	10 – 30	theta (3-6 Hz) gamma (60-70 Hz)	theta (3-6 Hz)		Dallérac et al. (2017)
	Lateral amygdala	cat	15			Multiunits and cross- correlograms	Paré and Collins (2000)
	Hippocampus Lateral amygdala	mice	10		theta (5-6 Hz)		Pape et al. (2005)
	Rhinal Cx Basolateral amygdala	cat	1.5	gamma (35-45 Hz)			Bauer et al. (2007)
Pavlovian appetitive trace	Medial entorhinal Cx	mice	5.5			Calcium imaging	Heys and Dombeck (2018)
Pavlovian aversive trace	Hippocampus	mice	0.25			Calcium imaging	Modi et al. (2014)
Delayed matching to sample / working memory	Prefrontal Cx	monkey	0.5 - 20			Single unit recordings	Fuster et al. (1982); Jin et al. (2009); Narayanan and Laubach (2009); Tiganj et al. (2018)
		rat	0 - 20			Single unit recordings	Horst and Laubach (2012)
	Striatum	monkey	2 - 4			Single unit recordings	Soltysik et al. (1975)
	Hippocampus	monkey	0.5 - 1			Single unit recordings	Naya & Suzuki (2011)
		rat	10 - 20			Single unit recordings	Gill et al. (2012); Kraus et al. (2013); MacDonald et al. (2011), (2013); Manns et al. (2007); Pastalkova et al. (2008); Salz et al. (2016); Robinson et al. (2017)
Expectation	Anterior cingulate Cx Prelimbic Cx	rat	8	delta (1 - 4 Hz) theta (8 - 12 Hz)			Total et al. (2013a)
	Hippocampus (CA1)	mice	10			Calcium imaging	Mau et al. (2018)
	Primary visual Cx	rat	1 - 2	theta (6-9 Hz)			Zold and Shuler (2015)
	Lateral entorhinal Cx	rat	up to 80 min			Single unit recordings	Tsao et al. (2018)
	Motor Cx	monkey	0.7 - 2	beta (12-40 Hz)			Kilavik et al. (2012)
Entrainment	Lateral habenula	zebrafish	20 - 30			Calcium imaging	Cheng et al. (2014)
	Hippocampus	mice	0.15	theta (4-12 Hz)			Abe et al. (2014)
	Striatum	monkey	0.45 - 1	beta (10 - 30 Hz) gamma (30 - 80 Hz)			Bartolo et al. (2014)
	Piriform Cx	rat	240			glutamate and GABA micro- dialysis	Hegoburu et al. (2009)
Free exploration	Hippocampus	rat	hours to days			Single unit recordings Calcium imaging	Mankin et al. (2012), (2015) Rubin et al. (2015)