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Commentary

Temporal Processing by Intrinsic Neural Network Dynamics

Elijah A. Petter^{1,*} and Hugo Merchant²

¹Department of Psychology and Neuroscience, Duke University, Durham, NC, USA

²Instituto de Neurobiología, UNAM, Campus, México

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Abstract

It is becoming more apparent that there are rich contributions to temporal processing across the brain. Temporal dynamics have been found from lower brain structures all the way to cortical regions. Specifically, *in vitro* cortical preparations have been extremely useful in understanding how local circuits can time. While many of these results depict vastly different processing than a traditional central clock metaphor they still leave questions as to how this information is integrated. We therefore review evidence to place the results pertaining to local circuit timers into the larger context of temporal perception and generalization.

Keywords

Intrinsic timers, generalization, interval timing, time perception, basal ganglia, cortex, hippocampus

1. Introduction

A question that remains unanswered in the field of timing and time perception is whether temporal processing in the brain relies on intrinsic versus dedicated circuits (Buonomano, 2014; Van Rijn et al., 2014). This dichotomy, as is the case with most 'black and white' depictions, does not fully elucidate how the brain keeps track of time. Instead there is likely a combination of both types of temporal processing. This commentary addresses recent findings on the importance of intrinsic timing and puts forth proposals for how local timers can be integrated with centralized temporal processing circuits as illustrated in Fig. 1 (Merchant et al., 2013a). It is important to note that these centralized timers are not circuits with the sole purpose of keeping time, but instead is a circuit involved in creating a unified perception of time (Merchant & de Lafuente, 2014). Historically, the neural mechanisms of interval timing have been interpreted through internal

* To whom correspondence should be addressed. E-mail: elijah.petter@duke.edu.

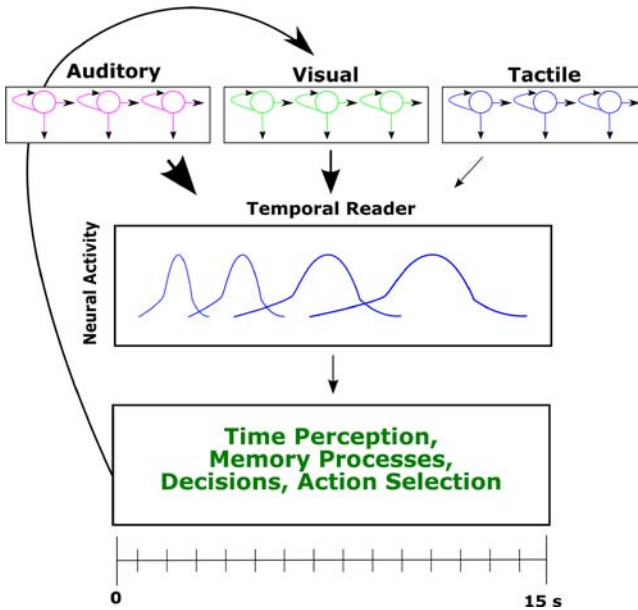


Figure 1. Interaction of intrinsic and centralized timing networks. Evolving activity of recurrent cortical networks allows for the readout of events in time. Different cortical networks contribute with varying weights (as indicated by arrow size) to a centralized region that is involved in temporal generalization across behavioral tasks and stimulus modalities. Examples of such readouts can be observed from ‘tuned cells’ that have normally distributed activity centered around specific target duration(s). These types of neurons can be observed in areas such as the basal ganglia, hippocampus, and the supplementary motor area. A sense of time emerges through the interaction among these cortical and subcortical regions, thereby contributing to working memory, decision-making, and action selection. These oscillatory processes in turn, feed back onto the active dynamics of time perception (e.g., Gu et al., 2015; Matthews & Meck, 2016). This figure is published in color in the online version.

clock analogies, that perhaps involve a circuit(s) with the dedicated purpose of timing. While clock metaphors have been immensely useful for understanding how the brain encodes time it is not the whole story. A recent series of papers by Buonomano and colleagues (e.g., Bueti & Buonomano, 2014; Finnerty et al., 2015; Goel & Buonomano, 2014, 2016; Hardy & Buonomano, 2016) highlight the importance of local-circuit dynamics in temporal processing. Specifically, they show that isolated cortical circuits can learn to time providing further evidence of brain-wide contributions to temporal processing. These intrinsic timers largely focus on the hundreds of milliseconds range and make the dissociation between temporal learning and generalization of a temporal interval.

These papers show temporally precise activity in local circuits. However, it important to consider that as dynamical systems, circuits evolve in a time varying manner with the probability of firing a time T being dependent upon firing at

time $T - 1$. While history dependent firing seems obvious, it means that circuits can develop patterns of activity, that with the correct model, could be used to decode time. That is timing information (Buetti & Buonomano, 2014), among other information (Siegel et al., 2015) has been found across the brain. Widespread encoding of information makes it difficult to determine whether a role is passive or causal in timing. Therefore, it is essential to establish which, and how dynamic information is being used. One approach to understanding the way such time varying signals carry information is to investigate the underlying mechanisms that give rise to this activity. In fact, several main parameters can define the dynamic properties of a recurrent neural-network: the slow synaptic currents (the metabotropic receptor GABA_B), short-term synaptic plasticity (i.e., facilitation or depression), as well as the richness of cell interactions and the complexity of the simulated cortical recurrent networks (Buonomano 2000; Matthews et al., 2014; Merchant et al., 2012).

These dynamics have been further investigated by Goel and Buonomano (2016). They looked at the effect of the interval between the electrical and optogenetic stimulation on the polysynaptic responses of whole-cell recorded pyramidal cells in organotypic cortical slices. A population of these neurons were infected with channelrhodopsin (ChR+) in order to achieve paired electrical and optical activation of specific neurons. The polysynaptic activity changed according to the interval trained between the electrical and light stimuli in the slices. An essential question is whether these changes are due to cell specific or network wide changes. To answer this the authors examined changes in ChR+ and ChR- neurons, finding temporally precise responses in both cell populations, suggesting timing is not mediated through cell specific mechanisms but is the result of indirect activation of neurons due to intrinsic network dynamics of the recurrent cortical networks. These network mechanisms are further supported by the latency of polysynaptic activation profiles increasing as a function of interval, as would be expected from longer neuron chains for larger durations. Interestingly these activation profiles match those observed in neurons in premotor areas in monkeys performing a time production task (Crowe et al., 2014; Merchant et al., 2015), pointing to a potential role for these networks *in vivo*. Finally, these authors measured a shift in the balance of excitation-inhibition specific to the training window that likely allowed for temporal learning. These shifts indicate involvement of multiple types of synapses and network involvement.

One idea is that any type of dynamical activity could be used to keep track of time (Hass & Durstewitz, 2016). The activity could be in the form of ramping (see Knudsen et al., 2014 and Kononowicz et al., in press, which suggest that ramping is primarily involved in motor preparation), state dynamics, oscillators, or delay-line models (e.g., synfire chains). Time related activity in one circuit may then be accumulated as it feeds into other circuits. The functional organization of the brain, including for temporal processing, can be understood in terms of

a hierarchical control system (Yin, 2014a). Dynamics in higher level controllers are useful for precisely timed sensory processing, signal detection or small motor adjustments. For instance, visual (Huertas et al., 2015; Shuler & Bear, 2006), auditory (O'Neill & Suga, 1979), motor (Johansson et al., 2014), or other cortical circuits (Goel & Buonomano, 2016) show shifts in the timing of neural activity that help attend to relevant stimuli. These timed responses can then be sent as error signals to other systems, allowing for adjustments and accumulation of time (i.e., longer durations). Eventually these signals need to end up in an area where temporal processing can be read in a generalized way (e.g., across modality) in order to make decisions. Therefore, in identifying such a 'reader', it is ideal to look for a region that receives multi-modal input, is involved in decision making, and has a 'memory' for comparison. Regions that may fit these requirements include the basal ganglia, hippocampus and premotor cortical system (e.g., Coull et al., 2011; Harrington & Jahanshahi, 2016; Lusk et al., 2016; Mello et al., 2015; Mendoza & Merchant, 2014; Petter et al., in press; Yin, 2014b; Yin et al., 2016).

So while biological evidence suggests that these intrinsic timers (Goel & Buonomano, 2016; Johansson et al., 2014) can learn intervals, there are many questions left open. What is the maximum duration that can be timed by these circuits? How are these intrinsically timed intervals decoded and integrated to make decisions? What areas read the output of intrinsic timers and how do they represent timing information for more general purposes?

2. Cortical Timers

Goel and Buonomano (2016) further elucidate the cortex's ability to time independent of other circuits (Johnson et al., 2010); however, it is unlikely there is a general intrinsic timer across the cortex. In other words, the cortex, among other circuits, cannot accomplish all temporal processing locally. Across neural circuits there are many different types of dynamic activity (e.g., ramping and oscillations — see Kononowicz et al., in press). Even though much of the architecture is conserved across the cortex, primary cortical areas show different timing processing abilities, with the primary auditory cortex mainly focusing on temporal information (Burr et al., 2009; Kanai et al., 2011). These differences are facts that are difficult to reconcile with a hypothesis of a general cortical timer.

Furthermore, these regions may require teaching signals, or feedback from other circuits. While feedback is not required for the hundreds of millisecond intervals in the Goel and Buonomano (2016), it may be the case for longer durations. Adult neurons may also be more dependent upon teaching signals, which can be seen from key differences between *in vitro* and *in vivo* recordings. Generally, the *in vitro* recordings are done with neonate rats, seven-day old animals in this case (Goel & Buonomano, 2016). These younger neurons are often more plastic than adult neurons and may be able to learn intervals more easily. While the slices

in Goel & Buonomano (2016) were cultured around 20 days, which allows for development time, it is still unclear if *in vitro* development converges with that seen *in vivo*. There is limited work in adult slices so it is difficult to truly assess the developmental differences between organotypic and *in vivo* preparations (Humpel, 2015). However, as normal inputs are severed, and certain growth factors and neuromodulators are limited, the circuit dynamics are different than those *in vivo* (Humpel, 2015).

It is important to follow these potential limitations with the idea that recurrent dynamic attractor models (e.g., Hardy & Buonomano, 2016; Laje & Buonomano, 2013) can successfully time intervals on the order of multiple seconds. Such success provides evidence that these circuits can contribute to a perception of time. However, it is reasonable to assume that evolving temporal dynamics of a circuit differ from a cohesive perception of time used to make decisions. Therefore, more research needs to be done on learning these longer intervals in biological systems, and see how these attractor dynamics can then be generalized to other spatial domains (e.g., modalities), or used to coordinate sensory–motor timing.

3. Maximum Duration Encoded by Intrinsic Timers?

It is likely that a neural circuit's ability to time is limited by its temporal dynamics. These dynamics may impose restrictions in accuracy, precision, and most likely duration. While many different regions have been shown to have time related signals (see Bueti & Buonomano, 2014 and Wiener et al., 2010 for reviews) the learned durations of many of these circuits, especially in somewhat isolated cortical preparations (Goel & Buonomano, 2016; Johansson et al., 2014) are extremely limited in nature. Certainly limited durations do not rule out recurrent or feedforward cortical networks that can learn longer durations (see Hardy & Buonomano, 2016 and Laje & Buonomano, 2013 for reviews), but multi-second timing has largely been shown in a few brain regions, the striatum, (Gouvêa et al., 2015; Matell et al., 2003; Mello et al., 2015), hippocampus (MacDonald et al., 2011, 2013, 2014; Pastalkova et al., 2008, but see Xu et al., 2014 for an exception), and premotor cortical system (Coull et al., 2011; Mendoza & Merchant, 2014). What is essential to understand about these multisecond timing experiments is that they have been done *in vivo*, which means the circuits have the full repertoire of input. These intact innervations support the idea that even brain regions that can time longer durations likely depend on larger networks (e.g., cortico-basal ganglia–thalamic) as described by Bartolo et al. (2014) and Merchant et al. (2013a). One of the most important components of *in vivo* timing experiments is the ability to correlate neural activity with timing behavior, which suggests a role for such time varying activity in the perception of time. Further the networks that are involved in timing are not acting with the sole purpose of interval timing (e.g., Bartholomew et al., 2015; Gu et al., 2015).

With their training protocol, Goel and Buonomano (2016) were able to achieve temporal responses to intervals up to 500 ms. It is difficult to speculate what the maximum learned duration that could be achieved by this preparation is. Clearly the variance in light evoked activity increased with the duration of the training interval. As variance increases there will be a point where a downstream system may be incapable of decoding time from this activity. In a decerebrate cerebellar preparation there was limited success in achieving Purkinje cell responses to 800 ms intervals (Johansson et al., 2014). Based on what these circuits can accomplish alone there appears to be a limit to the duration an intrinsic timer can achieve, suggesting the need for integration with other circuits.

4. Temporal Learning and Generalization

As many circuits may be limited in the durations that they can time it is likely that a centralized region(s) is involved in accumulation of time from intrinsic timers. The idea that time can be largely generalized (Buetti & Buonomano, 2014) across these different spatial domains (e.g., modalities, tasks, sensory–motor) further supports the need for a central mechanism. The learning transfer experiments suggest that the temporal processing can be generalized across sensory modalities, stimulation location, and even between time perception and production (Meegan et al., 2000; Nagarajan et al., 1998; Wright et al., 1997). These studies also indicated that this central timing mechanism is interval specific (Bartolo & Merchant, 2009), suggesting the existence of tuned cells, a prediction that was corroborated neurophysiologically a few years later (Bartolo et al., 2014; Merchant et al., 2013b). These learned durations make sense if short durations are learned in higher controllers and sent to a lower central timing mechanism, which will be primed to respond at the time of input.

It is also plausible that this generalization center then sends teaching signals back to other brain regions. A potential avenue for these signals could be in teaching recurrent timing networks outside of the centralized timing mechanism. The need for teaching can be seen from the limitations of these models in unsupervised states (e.g., Finnerty et al., 2015; Liu & Buonomano, 2009; Litwin-Kumar & Doiron, 2012). The basal ganglia may play a role in temporal teaching based upon its proposed role in teaching cortical circuits (Turner & Desmurget, 2010).

To understand the contributions of various circuits to overall temporal perception it is useful to start with well-studied circuits that time relatively short durations. Eyeblink conditioning work in the cerebellum has proven to be an essential model for understanding the mechanisms underlying motor timing. These tasks require precisely timed blinks in response to a conditioned stimulus (e.g., tone) that indicates the arrival of an unconditioned stimulus (e.g., puff of air). Purkinje cells, the sole output of the cerebellar cortex, show pauses in activity that correspond to the blinks and are necessary for successful performance.

Further, activation of Purkinje cells expressing channelrhodopsin can strongly modulate behavior (Heiney et al., 2014). These contributions to temporally precise behavior may prove similar to contributions of learned intervals in primary sensory areas (Chubykin et al., 2013). However, it is unclear what other circuits timed responses are dependent upon and it seems unlikely that these responses reach conscious awareness. A dissociation between timing and temporal perception can be seen from eyeblink conditioning experiments where you can separate conscious awareness of the unconditioned response from task performance (Weidemann et al., 2012), suggesting a more reflexive response. Therefore, temporal responses in the cerebellum and maybe primary cortical areas may be incapable of generating a perception of time on their own. Instead the responses observed by Goel and Buonomano (2016) are likely integrated into a larger timing circuit, perhaps using Bayesian methods based upon the precision of the evidence (e.g., Acerbi et al., 2012; Janssen & Shadlen, 2005; Jazayeri & Shadlen, 2010; Shi et al., 2013).

While evidence from eyeblink conditioning perhaps makes it clear that a perception of time does not always arrive out of appropriately timed behavior, there are still questions about what information can be used for temporal decisions, and what structures are essential for reading off these temporal signals?

5. Future Directions

The full nature of the neural code for temporal processing remains at large. While a primary circuit seems necessary for the generalization of temporal intervals, there are two different hypotheses to how this may arise. One, depends on separate neural substrates for intrinsic timers and generalization mechanisms. This distinction implies that these intrinsic timers are solely responsible for timing all relevant durations and generating decisions based upon the timed intervals. As the interval becomes well learned it is re-localized to a new substrate that allows for generalization of that interval. A second possibility is that these intrinsic timers have some dependency upon a centralized timer mechanism. This dependency could be to accumulate longer durations, to feed into a generalization mechanism which times for all domains with a preference for the initially learned domain, or to make decisions based upon temporal information.

In exploring the second hypothesis, accumulation seems plausible as many models and preparations are limited in the durations they can encode (Merchant et al., 2011). However, it may turn out that all neural circuits can integrate across a wide range of durations (e.g., multiple milliseconds to minutes — see Buhusi & Meck, 2005; Merchant et al., 2013a).

Buetti and Buonomano (2014), highlight the different learning times between generalization and timing. However, this does not ensure that there are separate neural timers. Instead there could just be multi-staged learning in the same neural substrate. Inputs from one region (e.g., visual cortex) that initially learns a timing

task, to a centralized timer, may provide preference for learning the interval in the initial modality but still be dependent upon the core timer. In this way pathways from other modalities (e.g., auditory) may be poor at timing until the interval is well learned, at which point the weak input can still be compared to the timed duration. An alternative from having a central timer is having a central temporal memory. This memory region could compare remembered durations with the currently encoded duration of the intrinsic timer. In this way input from a region where a task was learned (e.g., visual cortex) is more likely to recover the learned duration, whereas unlearned modalities will not be able to recover the memory trace until it is well learned. There is virtually no way that you can make a temporal discrimination without such a stored representation and a comparison rule, thus making a centralized mechanism essential in interval timing and time-based decision-making (Allman et al., 2014; Meck et al., 2012).

However, if there are truly independent timers then there should be a relatively easy way to test this. Inactivate a region that is involved in the generalization of timing. If intrinsic timers are used to form perceptions of time, and independent of any generalization mechanism, then it should be possible to observe modality-specific learning without any generalization. One may argue this has been shown through increasing the difficulty or attentional demands of a task in order to show modality specific learning without generalization. However, increased attentional demands does not rule out a multi-staged learning process within the same neural substrate.

Not including lesion studies which may face problems with degeneracy among others (Petter et al., in press) isolating a generalization region(s) has not been done. However, there is an important complimentary experiment that attempts to assess the role of intrinsic timers. They found that transcranial magnetic stimulation over the visual cortical area V1 only compromised timing of visual based stimuli whereas stimulation over the auditory cortical area A1 impaired temporal processing in both A1 and V1 (Kanai et al., 2011). These different and overlapping (auditory) contributions suggest that there is indeed a region that integrates time and that the auditory cortex plays a larger role in temporal processing.

6. Conclusions

We can no longer view timing as solely a dedicated clock or a local computation performed equally by all circuits. Based on the evidence reviewed, it seems likely that there is interdependency on intrinsic and centralized timers. Decisions, or at least reflexive behaviors (e.g., Heiney et al., 2014) seem to be achievable by intrinsic timers. Perception of these intervals, conscious decision making, and timing of longer intervals seems likely to be dependent upon integration into larger timing circuits in order to guide the full range of actions across multiple time scales (e.g., Meck & Ivry, 2016; Merchant & Yarrow, 2016).

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