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Timing in the visual cortex and its investigation

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While many high-level cortical areas have been implicated in timing, timing activity has also been observed even in the earliest cortical stages of the visual system over the past decade. This activity has been formally modeled as one arising from a reinforcement signal, leading to testable hypotheses with recent experimental support, demonstrating the necessity and sufficiency of that reinforcement signal. As observed in other cortical areas implicated in timing, interval timing activity within the visual cortex abides by the temporal scalar property. Finally, perturbations of the visual cortex during interval timing results in lawful shifts in timing. These and related observations advance the notion that visual cortex is a substrate for learning and expressing visually associated temporal expectations governing behaviourally relevant actions.

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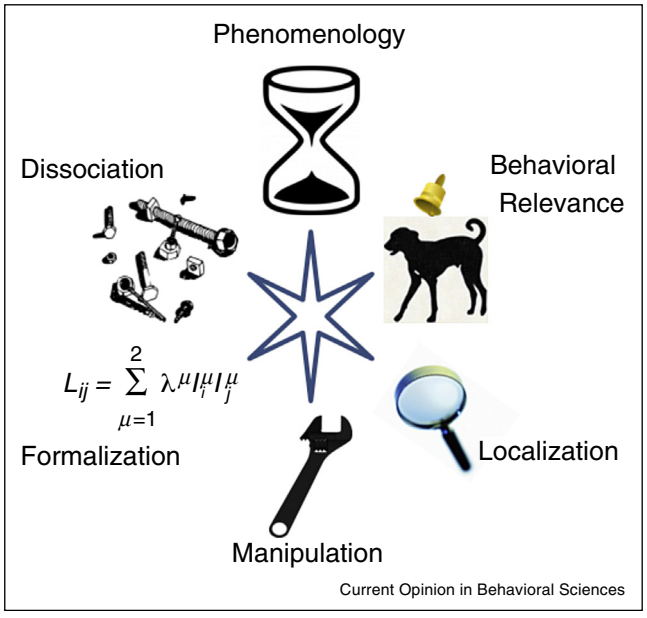
Introduction

An understanding of how the brain apprehends the passage of time, remembers relevant intervals, and produces those intervals to inform appropriately timed actions remains elusive despite much progress toward this goal, as reviewed within this issue, at the experimental, computational, and theoretical levels [1–4]. While it is recognized that any time varying neural process could in principle serve to mark the passage of time [5], one of the fundamental challenges faced by experimenters is in distinguishing between neural activity arising from any ongoing process from that which is truly used as a timing signal. Below we identify a number of qualities observable experimentally that increase the likelihood that a neural pattern of activity in visual cortex — and in cortex generally — is an expression of how the brain apprehends, remembers, and produces temporal intervals; namely, a (1) **phenomenological** description of activity subtending and/or marking the expiry of the interval to be timed, (2) **dissociation** between putative neural-timing activity and behavioral-timing activity, (3) **formalization** of how, in principle, such neural timing may arise, (4) **manipulation** of the biological instantiation of that theorized process, (5) **localization** of that process to the area of interest, (6) generation of neural activity that can give rise to the **temporal scalar property**, and (7) a causal demonstration of the **behavioral relevance** of that neural activity (see Figure 1). Using reports of cued-interval timing in the visual cortex and its mechanistic investigation as a vehicle, we identify general challenges to, and potential approaches for, identifying and understanding the genesis of cortical timing signals.

Phenomenological report of interval timing and dissociation of neural/behavioral activity

Identifying candidate interval timing signals in cortex begins with phenomenological reports of neural activity that modulate predictably in time in response to a cue (such as in reporting a hazard function) or subtends/demarcates the expiry of an interval of interest (such as a delay to reward). Within visual cortical areas, examples of neural activity tracking visually cued hazard functions have been observed in modulations of single unit spiking in monkey V4 [6], gamma oscillations in monkey V1 [7], and BOLD signaling in human V1, 2 & 3 [8]. With respect to reporting the expiry of an interval of interest, such as a delayed reward, is the report of 'reward timing' in V1 of rodents, wherein pairing visual cues with subsequent reward leads to the emergence of cue-evoked neural responses that express the typical delay to reward [9•,10••,11,12]. Trials in which reward is expected but withheld can then be used to assess whether changes in neural activation at the time of expected reward is a consequence of the interval elapsing (as observed in V1), or, more trivially, as a direct response to the acquisition of reward itself. As noted, however, an abiding challenge is in distinguishing between putative timing signals and those that may arise as a consequence of actions [13,14,15••], measured *or not*, that are used during the report of the expiry of the interval. Therefore, the candidacy of a timing signal can be further advanced by assessing whether it can be evoked (as in the case of reward timing [11] even in the absence of producing task-relevant actions (e.g. licking for reward), or otherwise dissociating those actions from neurally encoded intervals [9•,10••,15••]. The identification of candidate timing signals expressing (1) a relation to the interval of interest, (2) an insensitivity to the presence/absence of outcomes, and/or (3) an insensitivity to the actions terminating the interval, then well-motivate a computational investigation into how such neural response profiles may come about.

Figure 1



Six criteria for establishing a brain region's role in informing timing. **(1) Phenomenology**: neural activity within a brain region purported to inform timing should express responses that subtend or demarcate the expiry of the interval of interest. **(2) Dissociation**: while such activity should be able to inform the timing of actions, that activity should be dissociable from the actions taken by the animal to behaviorally report the expiry of the interval. Doing so advances the case that apparent timing activity isn't simply the trivial result of responding, neurally, to those actions themselves. **(3) Formalization**: should the claim be that a brain region generates rather than simple repeats timing activity generated elsewhere, the patterns of activity observed must be formalized into an experimentally testable process that could occur within that brain region. **(4) Manipulation**: essential components of that formal model should then be manipulated to affect the encoding of cue-evoked interval timing, demonstrating their necessity and sufficiency. **(5) Localization**: restricting such manipulations to the target brain region furthers the case that it generates the timing activity observed within it. The case for localization is also furthered by demonstrating that the local circuit, isolated from the rest of its inputs, can yet generate learned temporal intervals. **(6) Behavioral relevance**: finally, lawful shifts in the timing of behavioral actions that result from perturbing neural activity within a brain region during the interval to be timed support causality in informing timed actions.

Formalization and manipulation

Having characterized at the phenomenological level candidate interval timing signals, can their acquisition and expression be successfully **formalized** to capture key features in a parsimonious and biologically plausible way? A family of timing models propose potential solutions to how, in principle, a network could learn and express temporal intervals (see [16], for review). One such model describes the emergence of cued-interval timing activity observed in V1 as resulting from a process of reinforcement learning occurring within V1 itself [15••,17–19,20•]. In it, a signal conveying behavioral outcome permits recently active synapses within V1 to be modified (or, as in [19], the intrinsic excitability of single cells) so as to come to encode the cue-reward delay. Having rationalized, formally, how timing signals may emerge and be expressed in the cortex, the merit of any model can then be challenged by assessing whether its minimal assumptions are satisfied within the area of interest, and, if so, by demonstrating the *necessity* and *sufficiency* of those critical elements.

Since a signal conveying behavioral outcome is an essential provision of the model regarding reward timing in V1, what input may reasonably serve to convey such a signal, and can it be disrupted to show its *necessity* in learning a cued-interval? And, complementary, can such a signal be activated to show its *sufficiency* in establishing, neurally, the cued-interval response? As neuromodulatory systems have been widely implicated in governing synaptic plasticity and responding to behaviorally relevant events [21,22], we conjectured that one or more such systems may convey the acquisition of reward to V1, serving as the hypothesized reinforcement signal. By selectively lesioning cholinergic innervation of V1, we demonstrated that it is indeed necessary for reward timing activity to learn novel cue-reward delays [9•]. We also demonstrated that optogenetically commandeering cholinergic basal forebrain input to V1 is sufficient to condition cued-interval timing activity in V1, mimicking that which is observed following behavioral conditioning [10••]. Together, these observations advance the case that the cholinergic system serves as a reinforcement signal governing the learning in V1 of cue-reward associations and their interceding intervals.

Localization

Manipulations as that above demonstrate how a cortical area can be implicated as generating interval timing by showing how given inputs — themselves not the source of the interval — are critical to the emergence of observing timing activity within that area of interest. That the manipulations of cholinergic innervation were localized to V1 increases the likelihood that interval timing arises from processes occurring within it, rather than simply reflecting timing which might be learned elsewhere, such as described in mPFC [23], LIP [24], medial agranular cortex [25], or striatum [26], amongst others, though this may also occur. Indeed, Makino and Komiyama recently provided evidence in support of retrosplenial cortex sourcing aversively conditioned timing information to V1 [27••]. In general, lesion and/or inactivation, has advanced the case that many cortical areas are involved in timing [28–30], typically by assessing the impact on behavioral reports of timing. Yet definitive evidence that any area expressing timing activity can do so as a consequence of its own internal processes poses a challenge, for how can such a case be made without removing *all* its inputs?