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Time Has Come

The ramp-like rise and fall of activity in neurons of the LIP area of the posterior parietal cortex of alert behavior monkeys performing a duration discrimination task tracks the changing relative likelihoods that the stimulus in their response field will become the target of a saccade.

In this issue of *Neuron*, Leon and Shadlen (2003) open a new chapter in the research on the cellular bases of behavior—determining the neuronal basis for the experience of duration. Given the fundamental role that the experience and control of duration plays in behavior, it is perhaps surprising how little attention has been paid to the neurobiology of interval timing (see, however, Buonomano and Karmarkar, 2002; Gibbon et al., 1997). Perhaps this is because the abstract dimensions of our experience—time, space, and number—are so far removed from the elementary sensations, which, in the empiricist tradition, are the bricks out of which experience is constructed. Be that as it may, the investigation of the cellular neurobiology of the experience of temporal duration is beginning.

Leon and Shadlen recorded from rhesus monkeys while they performed a temporal discrimination task determining if the duration of a test stimulus is shorter or longer than a remembered standard. They observed that neurons in area LIP of the posterior parietal cortex show a ramped response that corresponds approximately to the comparison between a currently elapsing duration and a remembered standard duration. Moreover, they show that the trial-to-trial variability in these firing ramps exhibits a signature of the behaviorally measured interval-timing mechanism: scalar variability (Gibbon, 1977; Killeen and Weiss, 1987). This indicates that the variability grows proportionally with elapsed time. Finally, they show that the neurometric function for ensembles of such neurons—the accuracy with which duration discrimination could be done using those signals—is quantitatively consistent with the psychometric function—the accuracy with which the monkeys do it.

Leon and Shadlen's monkeys judged whether the duration of a test light was shorter or longer than a remembered standard duration. In response to a trigger cue, delivered at a variable delay after the offset of the test light, they indicated their judgment by a saccade to one of two choice targets. The two choice targets were present throughout the trial. On half of the trials, the target that was correct when the test duration was less than the standard was in the response field of the neuron whose activity was recorded. On the other half, it was in the opposite visual field, and the long target was in the response field.

Neurons in LIP respond to a visual stimulus when two conditions are satisfied: (1) it must fall in a certain region of the visual field, and (2) the monkey must intend to make a saccade to it (Colby and Goldberg, 1999). When it is in the requisite location but is not the intended target of a saccade, it does not activate the neuron. For this reason, the region of the visual field where the stimulus must fall is called the *response* field of the neuron, rather than the *receptive* field, which is what it would be called if stimulating that location were alone sufficient to activate the neuron.

In this experiment, the duration of the test light relative to the remembered duration of the standard determined the time course of the neuron's response to a target stimulus in its response field. As time passed during the presentation of the test light, the likelihood that the stimulus in the neuron's response field would become the target of the saccade increased or decreased, depending on whether the target in the response field was the long or the short target.

In alternating blocks of trials, the standard duration was 316 or 800 ms. The significance of a given elapsed time since test light onset varied with the standard duration and so did the extent of the rise or fall in the neuron's firing rate. During the test light, the neuron's rising or falling activity level indicated the elapsed duration relative to the standard, rather than which target would be chosen, as indicated by two critical findings: (1) variations in neural bisection points (estimates of when the critical duration has been attained), based on firing during the test light, do not predict variation in behavioral bisection points (although neural firing in the 100 ms preceding the saccade itself does); (2) the firing rate at the onset of the test light is considerably greater when the short target is in the neuron's response field rather than when the long target is. At that time, the probability of the two choices is the same, but the relative likelihood that the short target will become the target is at its maximum, while the complementary relative likelihood (that the long target will) is at its minimum.

This seminal, methodologically and conceptually sophisticated experiment opens up the second important field of investigation in the neurobiology of time. Thirty years ago, the neurobiology of circadian timing was a mystery. Now, we are well on our way to understanding not only its cellular but also its molecular basis (Morre et al., 2002; Pennartz et al., 2002). The cellular and molecular mechanisms of interval timing, by contrast, remain a mystery, but there is a rich, highly quantitative behavioral literature to motivate and direct the neurobiological inquiry. Some key findings are:

- Duration discriminations are not carrier specific: learned with one stimulus (e.g., a light), they generalize immediately to others (e.g., a noise). It is the duration of the simulus that matters, not what it was that had that duration (Meck and Church, 1982; Roberts, 1982).
- Animals can respond not only to the proportion (ratio) between a currently elapsing interval and a remembered standard, but also to the sum (Barnet et al., 1997; Barnet and Miller, 1996; Roberts and Church, 1978) and difference (Fantino and Goldshmidt, 2000) of two intervals and even to the proportion between

a steadily diminishing difference and a standard (Gibbon and Church, 1981). This is a prime area for investigating the computational capacity of neural tissue.

- Interval timing with scalar variability covers a range from fractions of a second to an hour and perhaps more, although whether the coefficient of variation is constant throughout this range remains to be determined (Gibbon et al., 1997).

On this foundation, investigations of the neural mechanisms for timing and recording in memory the durations of intervals may proceed.

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