and eventually merge close to the bottom of the image. As qualitatively evidenced by the d/dU map of Fig. 4B and quantitatively supported by the line sections plotted at the bottom of this panel, the edge state disappears as soon as the step-step separation decreases below the spatial extent of the edge state (25)—i.e., about 10 nm. We further analyze the response of these edge states to high magnetic fields B. Figure 4C reports a d/dU map (top) and STS data acquired on an odd step edge (bottom) at $B = 11$ T; contrary to the quantum spin Hall state found in HgTe, the 1D TCI state investigated here is robust against time-reversal symmetry breaking perturbations. Finally, Fig. 4D shows that the edge state also persists at elevated temperatures ($T = 80$ K). Despite the reduced intensity evidenced by the STS spectrum, a well-defined 1D channel is still clearly present.

The observation of a distinct type of one-dimensional states at odd step edges of topological crystalline insulators with relatively wide bulk band gaps opens up opportunities for the use of topological materials for sensing and information processing purposes well beyond existing materials (4, 10, 11). Furthermore, the absence of scattering and the high degree of spin polarization observed in tight-binding calculations indicate that the 1D midgap state might be useful for spintronics applications. By patterning the step-and-terrace structure of TCI surfaces, this may allow for the creation of well-separated conductive channels with a width of only about 10 nm. This may lead to interconnections between functional units at ultrahigh packing densities. To fully explore whether the 1D midgap state found at odd TCI step edges display quantum conductance effects, further investigations by, for example, four-probe transport measurements, will be needed.

REFERENCES AND NOTES
20. See supplementary materials on Science Online.

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SUPPLEMENTARY MATERIALS
www.sciencemag.org/content/354/6317/1269/suppl/D1
Materials and Methods
Supplementary Text
Figs. S1 to S7
References (26, 27)

BRAIN RESEARCH

Midbrain dopamine neurons control judgment of time

Sofia Soares,* Bassam V. Atallah,†† Joseph J. Paton‡

Our sense of time is far from constant. For instance, time flies when we are having fun, and it slows to a trickle when we are bored. Midbrain dopamine neurons have been implicated in variable time estimation. However, a direct link between signals carried by dopamine neurons and temporal judgments is lacking. We measured and manipulated the activity of dopamine neurons as mice judged the duration of time intervals. We found that pharmacogenetic suppression of dopamine neurons decreased behavioral sensitivity to time and that dopamine neurons encoded information about trial-to-trial variability in time estimates. Last, we found that transient activation or inhibition of dopamine neurons was sufficient to slow down or speed up time estimation, respectively. Dopamine neuron activity thus reflects and can directly control the judgment of time.

To determine (i) what signals are encoded by midbrain DA neurons during timing behavior and (ii) how DA neurons contribute to variability in temporal judgments, we measured and manipulated the activity of DA neurons in mice as they performed categorical decisions about duration (28). We first trained mice to perform a temporal discrimination task (Fig. 1A, left). Mice initiated trials at a central nose port, immediately triggering the delivery of two identical tones separated by a variable delay. Mice reported the delay between tones as shorter or longer than 1.5 s at one of two lateral nose ports for water reward. Incorrect choices were not rewarded. Performance was nearly perfect for the easiest intervals but more variable for intervals near 1.5 s (the boundary between the “short” and “long” categories) and was well described by a sigmoid psychometric function (Fig. 1A, middle).

We then pharmacogenetically suppressed DAergic neuronal activity and observed impaired temporal judgments on treatment days as compared with adjacent nontreatment days (P < 0.004, n = 3 mice; Fig. 1A, right). We also observed a tendency to perform fewer trials [control group, 177 ± 15 trials; clozapine N-oxide (CNO)–treated group, 115 ± 54 trials; mean ± SD; P = 0.05], suggesting that the animals’ motivation was affected by DAergic suppression. To test whether fluctuations in endogenous DA neuron activity predicted systematic changes in temporal judgments, we used fiber photometry (29) to measure Ca2+ activity in DAergic neurons, targeting the substantia nigra pars compacta (SNC) (Fig. 1, B and C, and figs. S1 and S2).
Fig. 1. Dopaminergic (DAergic) signaling is required and precisely aligned to temporal cues, not movement, during performance of a temporal categorization task. (A) Shown on the left is the task schematic and order of events (circles in the upper panel, nose-ports; gray shading in the lower panel, interval period). A logistic function fit to the daily (gray) and average (black) performance of an example mouse (10 sessions) is shown in the middle. Pharmacogenetic suppression (hM4D) was targeted to midbrain DAergic neurons, and mice were injected with either CNO or saline on adjacent days; shown on the right is mean psychometric performance on days with saline or CNO treatment (black or red, respectively; \(n = 3\) mice). Error bars, SEM. The inset shows the percent of correct trials on days before and after CNO treatment in mice expressing hM4D (filled circles, \(n = 3\); \(*P < 0.005\)) or non–hM4D-expressing controls (open circles, \(n = 4\)). Error bars, SEM. (B) Schematic of the photometry apparatus and viral and surgical procedure. (C) Image of the substantia nigra pars compacta (SNc) histology. (D) On the left, all trials of DA neuronal activity recorded from a single subject are shown, split by interval duration and aligned on trial initiation (first tone delivery; white vertical line). Each row represents a trial, and within each interval, trials are sorted from fast (top) to slow (bottom) response time (RT, time from the second tone to choice; 3759 trials). Shown on the right are mean DAergic neuron responses, split by interval duration (\(n = 5\) mice; intervals are color-coded as throughout). Shading, SEM across mice. (E) Example photometric traces recorded during a single correct and incorrect trial of the 1.74-s interval. (F) Photometric recordings of DA neuronal activity from a single subject, split by outcome (correct choices, top; incorrect choices, bottom) and aligned on choice (white). Within each outcome, trials were sorted by RTs [slow (top) to fast (bottom)]. Red dots mark the time of second-tone presentation (2426 trials). (G) Mean DAergic responses of incorrect trials aligned on the three main task events (first tone, second tone, and choice; \(n = 5\) mice). Shading, SEM across mice.
Fig. 3. Changes in a time-dependent component of choice behavior are predicted by DAergic activity. (A) Trial-by-trial logistic regression (black) that predicts choice from the amplitude of the second-tone DA response (gray), for each of the six time intervals (left to right). The top and bottom histograms illustrate the number of trials, as a function of DA response, in which the subject made long and short choices, respectively (n = 8533 trials, 5 mice). For each session and interval, DA responses are grouped into terciles—high (blue), medium (gray), and low (red)—throughout the figure. (B) Distinct patterns of temporal judgments are expected depending on the nature of the relationship between DA response and choice. (C) Three individual trials illustrating low, medium, and high second-tone DA responses (quantified as the mean response in the gray-shaded box) and grouped by tercile within the entire second-tone response distribution, depicted at right. (D) Average DA response in each tercile for the 1.74-s interval stimulus (n = 8533 trials, 5 mice). Shading, SEM. (E) Psychometric curves constructed using trials from each tercile of DA response judged as long versus short. Each shape represents a different mouse. Black symbols represent responses averaged across all interval stimuli.

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**Fig. 2.** DAergic responses correlate with temporal judgments and are explained by a simple model of reward prediction error (RPE). (A) Linear model (left) including RPE components: expectation of reward P (subject performance, top left) and temporal expectation S (surprise, the inverse of the subjective hazard function; bottom left). w, weight; a.u., arbitrary units. In the middle panel, measured second-tone DAergic response for six time intervals (black traces; n = 5 mice) are compared to predicted DA response (red dots). The graph on the right shows model predictions versus measured DAergic activity (gray symbols, individual mice; mean responses across mice, black filled circles). (B) Average measured DA response for all intervals during correct and incorrect trials. (C) Mean DA response to the second tone when an interval was judged as long versus short. Each shape represents a different mouse. Black symbols represent responses averaged across all interval stimuli.
We observed DAergic responses locked to the three main task events on single trials: the first tone, the second tone, and reward delivery (or omission thereof) (Fig. 1E). Activity increased after reward delivery and decreased when the reward was omitted in the case of incorrect choices (Fig. 1F) (30). DAergic signaling has also been implicated in movement; however, DA neuron activity in this task did not reflect movement per se (Fig. 1, F and G, and fig. S3).

In this task, the second tone marks the end of the interval to be discriminated and is a sensory cue that predicts reward. The amplitude of a RPE at the time of the second tone should be modulated by two factors: the subject’s expectation of reward at tone delivery and their temporal expectation of the second tone itself. First, expectation of reward varies as a function of stimulus difficulty, where the more difficult the stimulus set on each trial, occurrence of the second tone becomes less surprising with time (Fig. 2A). These data suggested that the DA neuron response was systematically related to the horizontal position of the psychometric curve along the time axis and not the vertical position along the choice axis (Fig. 3B). To test this, we split trials into high, medium, and low terciles of the distribution of responses to the second tone [Fig. 3, A (histograms) and C]. While the second-tone response amplitude was used to group trials, the systematic ordering of DA neuron responses emerged toward the beginning of the trial and persisted throughout an interval (Fig. 3, D and F). We next constructed psychometric curves for trials in each tercile and compared a range of models for the psychometric curve. The model that best explained the behavioral data collected from high-, medium-, and low-tercile trials consisted of three sigmoid curves that differed only in their horizontal location along the time axis (Fig. 3E).

We observed a shift toward long choices when DAergic activity was low, and the opposite shift when activity was high. Specifically, as DA activity varied from the lower to the upper tercile, the psychometric threshold shifted by ~340 ms (i.e., ~20% of the 1.5-s category boundary; range, 90 to 620 ms; 6 to 42%; n = 5 mice). The relationship between DAergic response and psychometric shift was observed for recordings in either hemisphere (fig. S6), thus ruling out an explanation based on the laterality of short versus long choices. Instead, these results indicate that higher or lower midbrain DAergic activity is correlated with a change in a time-dependent component of the decision.

How might this correlation between DA neuron activity and the location of the psychometric curve along the time axis relate to our initial finding that temporal expectation contributed to the average second-tone response? The theory of DAergic RPE coding predicts that slower (faster)...
timekeeping, by stretching (contracting) temporal surprise along the time axis, should increase (decrease) DAergic responses to the second tone (fig. S7). We observed a pattern of DAergic response to the second tone that was consistent with this (Fig. 2, B and C, and fig. S7). Furthermore, if DAergic activity reflects RPE continuously throughout a trial, differences in activity associated with slower or faster timekeeping (i.e., the separation between low- and high-activity terciles) should also grow continuously over time, and indeed, this is the case in our data (Fig. 3F and fig. S7). In contrast to the expected impact of variability in the speed of timekeeping on RPE coding, it is not apparent to us how changes in the location of the decision boundary along an animal’s internal notion of time should change RPEs arising at the presentation of the second tone. The most parsimonious explanation of the RPEs arising at the presentation of the second tone is that the location of the decision boundary along an internal notion of time should change with this (Fig. 2, B and C, and fig. S7). Additionally, we found that increasing DAergic activity resulted in a horizontal shift of the decision boundary along an internal notion of time, while decreasing DAergic activity resulted in a lateral shift of the decision boundary along an internal notion of time.

In the speed of internal timekeeping.

tone. The most parsimonious explanation of the RPEs arising at the presentation of the second tone is that the location of the decision boundary along an internal notion of time should change with this (Fig. 2, B and C, and fig. S7). Additionally, we found that increasing DAergic activity resulted in a horizontal shift of the decision boundary along an internal notion of time, while decreasing DAergic activity resulted in a lateral shift of the decision boundary along an internal notion of time.

Although unexpected, the data presented here may explain existing behavioral data. Situations in which DAergic activity is elevated naturally, such as states of high approach motivation (36), response uncertainty (36), or cognitive engagement (37), are associated with underestimation of time (1, 2, 38). Conversely, situations that decrease DAergic activity, such as when fearful or aversive stimuli are presented (39), are associated with overestimation of time (40). These observations, together with our data, suggest that flexibility in time estimation may confer an adaptive advantage on the individual. For example, underestimating duration in better-than-expected situations may lead to longer engagement in those situations, resulting in even greater reward than if time estimation were not flexible. In other words, there may be a normative explanation for why “time flies when we are having fun” underlying our observation that DA neurons, which are so central to reward processing, exert control over time estimation.

REFERENCES AND NOTES

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SUPPLEMENTARY MATERIALS
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RESEARCH REPORTS

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Midbrain dopamine neurons control judgment of time
Sofia Soares, Bassam V. Atallah and Joseph J. Paton (December 8, 2016)
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Editor’s Summary

Time is a subjective experience

Time, like space, is one of the fundamental dimensions of all our experiences. However, organisms do not work like clocks, and our judgment about the passage of time is variable, depending on circumstances. Soares et al. systematically investigated midbrain dopaminergic neurons during timing behavior in mice (see the Perspective by Simen and Matell). When measuring and manipulating mouse activity, the authors observed that dopaminergic neurons controlled temporal judgments on a time scale of seconds.

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