Sensory neural codes using multiplexed temporal scales

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Determining how neuronal activity represents sensory information is central for understanding perception. Recent work shows that neural responses at different timescales can encode different stimulus attributes, resulting in a temporal multiplexing of sensory information. Multiplexing increases the encoding capacity of neural responses, enables disambiguation of stimuli that cannot be discriminated at a single response timescale, and makes sensory representations stable to the presence of variability in the sensory world. Thus, as we discuss here, temporal multiplexing could be a key strategy used by the brain to form an information-rich and stable representation of the environment.

Spatial and temporal dimensions of neural representations

Perception and action are based on neural representations of the external world. Determining the neural code [1–3] (i.e. the smallest set of response patterns capable of encoding relevant stimulus parameters) is therefore a prerequisite for understanding sensory function. The search for the neural code began many decades ago, with the discovery that the number of action potentials elicited by peripheral neurons depends on simple stimulus features [4,5]. It continues today with the exploration of different putative codes, and with systematic comparisons between the information in individual codes and behavioral performance.

Two dimensions of neural representations are important for characterizing a neural code. The first is defined by space: sensory processing is based on spatially distributed populations, ranging from localized groups to populations of neurons spread across brain areas [6,7]. The second dimension is defined by time: neuronal responses evolve over time, and the temporal structure of neural activity can only be neglected at the cost of losing considerable information [8]. Over the past few years, it has become clear that, in analogy to the distribution of information over several spatial scales, the neural code is also distributed along time: sensory information is multiplexed in neural responses at different timescales [9–15].

Here, we focus on the time dimension of neural codes. We discuss how neural activity is patterned on multiple timescales, how the relevance of such patterns can be

Glossary

Complementary information: when the information carried by the combined code is higher than the information carried by either code individually, which means that some information that is not available in one code is provided by the other.

Decoding: the extraction of information about the stimulus from a given neural response. For example, predicting the most probable stimulus that could have elicited an observed response.

Encoding time window: the temporal window containing the response patterns that are considered as the basic information-carrying units of the code.

Encoding: the generation of the set of specific activity patterns that represent the various attributes of external stimuli.

Entrainment: locking of dynamic neuronal activity to a dynamic stimulus.

Latency code: a specific form of temporal code encoding information in the timing of response relative to the encoding window, which is usually defined with respect to stimulus onset.

Local field potential (LFP): a neurophysiological signal (obtained by low-pass filtering extracellular recordings) that reflects the fluctuations in the input and the intracortical processing of the local cortical network, including the overall effect of population synaptic potentials and other types of slow activity, such as spike afterpotentials and voltage-dependent membrane oscillations [36].

Multiplexed code: neural code in which complementary information is represented on different temporal scales. For example, when information is represented by the precise timing of individual spikes on the scale of milliseconds and the slow modulation of the spike count on the scale of hundreds of milliseconds.

Neural code: the smallest set of 'symbols' (neural response features) capable of representing all information that the neuron carries about the considered stimuli.

Oscillation: rhythmic activity pattern of individual or populations of neurons characterized by a dominant frequency. Examples are the theta rhythm (4–8 Hz) or 'gamma' oscillations (usually defined above 40 Hz) seen in field potentials.

Phase of firing code: neural code in which stimulus attributes are encoded by the relative timing of spikes to the phase of a network fluctuation. Phase of firing codes based on fluctuations slow enough so that the phase value is approximately constant in the encoding window can be further distinguished into phase&rate codes (stimulus attributes are encoded by spike count labeled by the phase value) and phase&pattern codes (stimulus attributes are encoded by the temporal spike pattern labeled by the phase value).

Rate code: neural code in which stimulus attributes are encoded by the number of spikes during the encoding window, regardless of their temporal pattern within the window.

Temporal encoding (or encoding by spike patterns): when temporal patterns of action potentials within the encoding window provide information about the stimulus that cannot be obtained from the spike count. In this case, a 'temporal code' is said to be used.

Temporal encoding by interspike intervals: when temporally encoded information is carried by the relative time between spikes (rather than by their absolute time with respect to stimulus onset)

Temporal precision of the code: the coarsest temporal resolution sufficient to extract all information from the code.

Temporal reference frame: the time axis against which the symbols of the code are measured. This can be defined by external events (e.g. stimulus onset) or an internal clock (e.g. oscillations).

Temporal spike pattern: a repeatable sequence of spikes within the encoding window.

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evaluated, and the specific advantages that temporally multiplexed codes offer for sensory representations.

Characterizing neural codes

To characterize a neural code empirically, it is necessary to specify several parameters [16]: the encoding time window, the response patterns that carry sensory information (the symbols of the code), the temporal reference frame against which they are measured, and the temporal precision of the neural code.

Encoding time window

The encoding time window is the first important timescale characterizing a neural code [16]. It is defined as the window containing the particular response patterns that are considered as the basic elements of the code (Figure 1a). Although this window is not known a priori, it is a fundamental parameter defining a code. Its length must be shorter than both the behavioral reaction time of the animal and the timescales on which the relevant stimulus features change [16]. For stimuli characterized by a single timescale, the length of the encoding window can be estimated empirically by considering periods in which the stimulus feature is constant and by determining the shortest window that carries the entire information

provided by the neuron (Box 1). Naturalistic stimuli, by contrast, contain many features that vary independently on several timescales, and often it is unclear which features are represented by the neuron under consideration. Determining the encoding time window is problematic in such situations. However, one can simplify the problem by focusing on the encoding of a specific feature. Alternatively, one can consider a feature-independent approach and compute information about all features using putative encoding windows whose length is varied parametrically, and then characterize the range of encoding window length that maximizes the performance of the code [15,17].

Response patterns defining neural codes

In the most basic example of a neural code (the rate code), the only information-bearing response pattern is the spike count within the encoding window (Figure 1b). The hypothesis of rate coding receives support from the ubiquitous correlation of firing rates with sensory variables [4], and is based on the assumption that trial-to-trial variability in timing and number of spikes can be reduced by temporal summation [18]. Although there are few doubts as to the relevance of this code, it neglects extra information added by the temporal response structure within the encoding
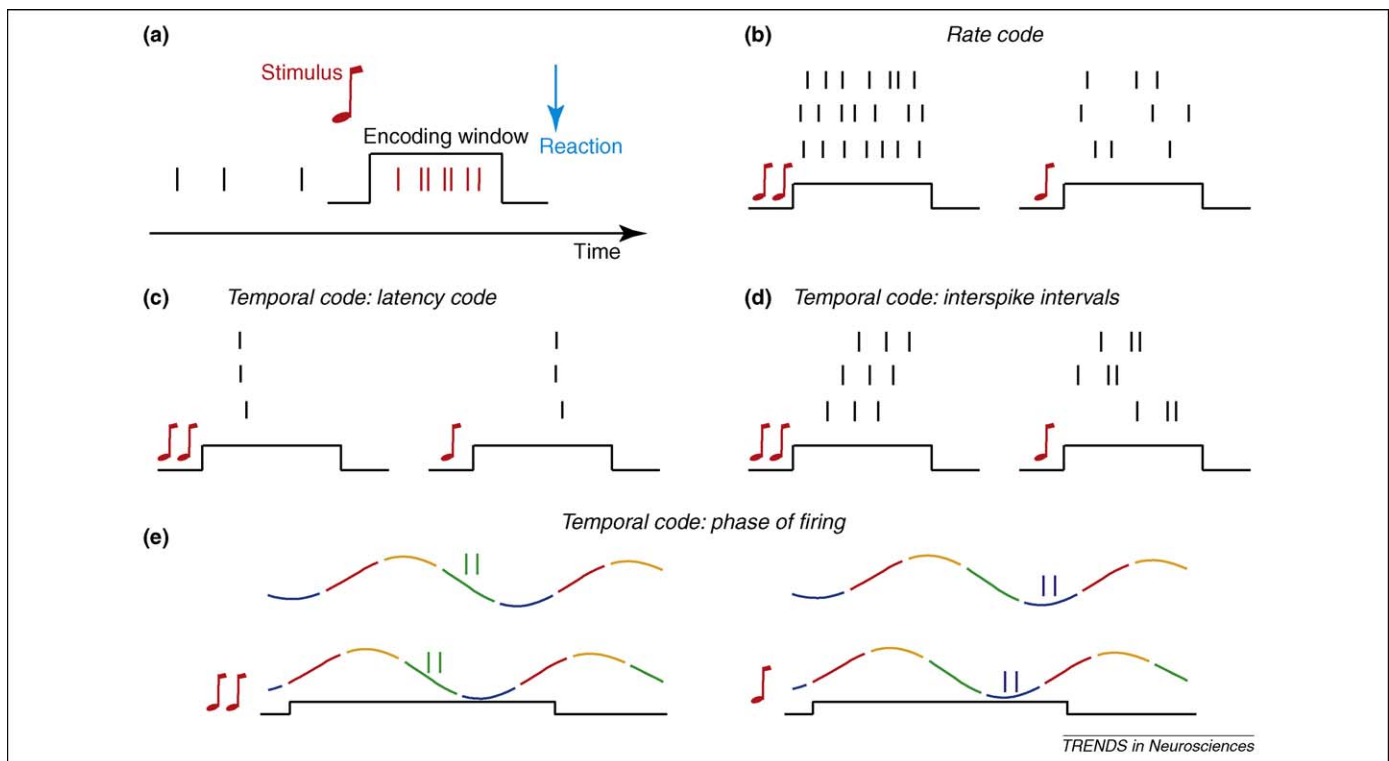

Figure 1. Schematic representation of neural codes. The concepts of encoding time window, spike counts and temporal codes are illustrated using simple examples. In all panels, the x-axis represents post-stimulus time, short vertical lines denote spikes times and each row corresponds to a different trial. In panels (**b–e**), the left and right side, respectively, display responses to two hypothetical stimuli and, in all panels, the thin black line on the bottom denotes the encoding window. (**a**) The encoding time window is the post-stimulus time window containing the stimulus-informative part of the response, here denoted by red spikes. The encoding window must be shorter than the reaction time. (**b**) Rate code. The stimulus is encoded by the number of spikes within the encoding window, and their timing does not add information. (**c**) Temporal encoding by a latency code. The stimulus is encoded by the time of first spike with respect to stimulus onset, which is differentially modulated by the two stimuli. (**d**) Temporal encoding by interspike intervals. The stimulus is encoded by the relative timing of spikes within the encoding window, in this case by the time differences of successive spikes. (**e**) Temporal encoding by the phase of firing. This temporal code carries information in the phase of the LFP oscillations at which spikes are fired. The phase range ($0–2\pi$) of the LFP oscillation has been divided into four equal phase intervals, indicated by different colors. The phase at which spikes were fired can be visualized by coloring the spikes with the color of the concurrent LFP phase. In the example, the two stimuli cannot be distinguished by the firing rate or interspike interval, but by their respective phase of firing (green versus blue).

Box 1. Characterization of temporal codes using information theory

Mutual information (abbreviated 'information') provides a metric to evaluate the performance of candidate neural codes in representing a set of stimuli [21,22]. The information between stimuli and responses is defined as Equation I [86]:

$$I(S;R) = \sum_{s,r} P(s,r) \log_2 \frac{P(s,r)}{P(s)P(r)} \qquad \text{Eqn I}$$

where $P(s,r)$ denotes the joint probability of observing response r together with stimulus s, and $P(s)$, $P(r)$ denote the marginal probabilities of stimuli and responses. Information quantifies the decrease of uncertainty about the stimulus gained by observing a response in a single trial (averaged over all stimuli and responses). Information is expressed in units of bits, with one bit corresponding to a decrease of uncertainty by a factor of two. Information values are always relative to the specific set of stimulus considered. Therefore, one should ideally use stimulus sets comprising features and their variations that are representative of those present in the natural environment of the animal, to ensure that the conclusions obtained based on neural codes generalize to naturalistic situations.

To evaluate temporal codes using information theory, the encoding window T is usually subdivided into smaller time bins (Δt) and the absence or presence of spikes in each bin is represented by a binary sequence [17] (so-called 'spike-word'). The resulting information depends on Δt and the temporal precision required to evaluate the code can be defined as the largest Δt that still provides the full information obtained at finer resolution (i.e. with smaller bins Δt). If this precision equals the encoding window ($\Delta t = T$), the code becomes equivalent to the spike count. If information reached at smaller values of Δt is significantly higher than information obtained from the spike count, we speak of temporal encoding. For stimuli characterized by a single timescale, the encoding window T can be estimated by considering periods in which the stimulus is constant and parametrically varying the 'putative' window T, and defining the encoding window as the one at which the cumulative information estimate starts to saturate (c.f. Figure I).

Multiplexed neural codes can be investigated by constructing higher-dimensional responses containing more than one code; for example, consisting of spike words labeled with the phase of a slow oscillation [15,39].

Information measures suffer from biases when they are computed from small datasets [87]. Such biases can artificially increase the apparent temporal resolution of neural codes and, hence, over-emphasize temporal codes. To eliminate this problem, appropriate statistical procedures should be used [87].
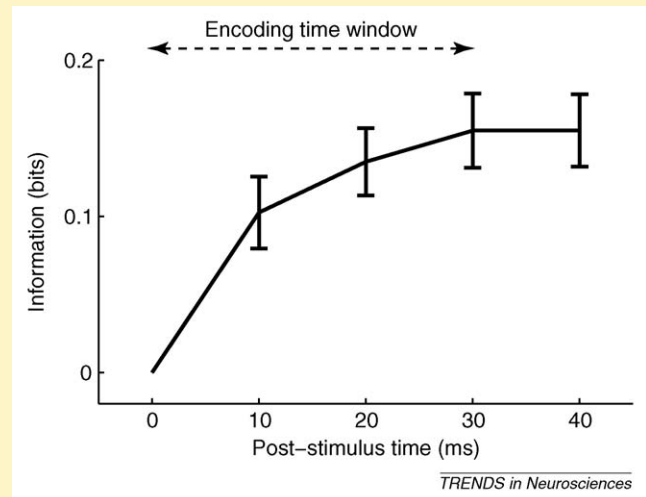

Figure I. Estimating the encoding window using information measures. This illustrates the time course of the stimulus information provided by single neurons in rat barrel cortex regarding the identity of the stimulated whisker (stimulus presented at $t = 0$ ms). Lines represent mean ± SEM over a population of 50 neurons described in Ref. [25], to which we refer readers for full details. The information in spike times (computed with a resolution $\Delta t = 10$ ms) saturates at 30 ms post-stimulus. This suggests that, in this dataset, a value of 30 ms is a sensible empirical choice for the encoding time-window length. Data from Ref. [25].

window, and can be inherently ambiguous in changing environments [19,20].

When the temporal structure of a spike train within the encoding window carries additional information that cannot be obtained from the spike count within the same encoding window, we refer to temporal encoding. This is, for example, the case in which two different stimulus features elicit the same spike count but different temporal spike patterns. Given that the brain usually takes decisions based on single events, the presence of extra information in temporal patterns should be investigated using analysis methods that are capable of quantifying the performance of a code in single trials; for example, using stimulus decoding or Shannon's information (Box 1) [3,21,22].

A simple example of temporal encoding is the latency code, in which information is carried by the latency of the response with respect to the time of stimulus presentation (Figure 1c) [23–25]. Although this code is simple and metabolically efficient, it relies on an external temporal reference frame to define the relevant variable. Measuring response patterns relative to an external reference frame, however, implicitly assumes that the nervous system has access to such external variables; an assumption that might not always hold [26,27].

To avoid the need of precise external reference frames, neural codes could exploit signals intrinsically generated by the nervous system, such as population responses, oscillatory activity, or motor efferent copies [15,28]. A clear advantage of codes relying on internal reference frames is that they can be decoded without detailed knowledge about external stimulus timing. A prominent example is temporal encoding by interspike intervals, whereby information is encoded by the timing of spikes with respect to each other (Figure 1d). In visual and auditory pathways, for example, the relative timing of subsequent spikes exhibits less trial-to-trial variability than does their absolute response latency from stimulus onset, and these interspike intervals provide more information about the stimulus than does the rate code [26,27,29]. Information-bearing interspike intervals can arise from correlations between spike times that cannot be explained by rate modulations; for example, when neurons fire stimulus-dependent bursts, or other instances where neuronal firing cannot be described as a time-dependent Poisson process [30,31].

Another kind of temporal code relying on internal reference frames considers the timing of spikes relative to the timing of ongoing local excitability fluctuations - so-called phase of firing codes (Figure 1e) [10,32–34]. Ongoing excitability fluctuations are reflected in slow rhythmic activity that can be measured by local field potentials (LFPs) [35,36], and the phase of such LFPs reflects the timing of changes in excitability. In the hippocampus, the timing

of spikes relative to the phase of theta (4–8 Hz) oscillations carries information about the position and heading in space of the animal [37,38]. In auditory and visual cortices, the phase of firing with respect to low-frequency (1–8 Hz) LFPs carries a significant amount of information about complex naturalistic stimuli [15,39]. As suggested in Ref. [15], phase of firing codes based on oscillations that are slower than the temporal precision of spikes can be further distinguished into phase&rate and phase&pattern codes. In the latter, the precise temporal spike pattern also adds novel information to that obtained from the number of spikes and the phase at which they were emitted.

Temporal precision of a neural code
Besides the encoding window, a second important temporal scale characterizing a neural code is the temporal precision of the code. This is operationally defined as the coarsest temporal resolution at which spikes need to be measured without losing any of the encoded information (Box 1). Importantly, the timescales of the encoding window and temporal precision are, in principle, distinct concepts, and we speak of genuine temporal coding only when the temporal precision is shorter than the encoding window.

Timescales of neural codes in sensory systems
The temporal precision of neural codes has been systematically investigated in several sensory structures. Peripheral and thalamic neurons in the rat whisker pathway, for

example, encode information about whisker movements at a precision finer than 1 ms [40,41], whereas neurons in somatosensory cortex encode whisker-related information at a precision of a few milliseconds [25,42]. In addition, neurons in auditory cortex carry information on the scale of ∼10 ms [15,22,43,44], and neurons in visual cortex use a coarser precision of ∼20–100 ms [8]. However, as noted above, high temporal precision does not necessarily imply temporal encoding and, in several cases, the high precision of temporal codes can be explained in terms of a rate code operating in short time windows [45]. In other cases, however, high temporal response precision can be attributed to genuine temporal encoding. In fact, such temporal codes often carry information about non-temporal ('what') aspects of the stimulus, such as the orientation or contrast in an image or the identity of a stimulated receptor, and do so over timescales in which the respective feature is constant [8,25,46,47].

For codes relying on internal reference frames, the temporal precision depends on both the scale of the reference frame and on the precision of spikes. For the phase of firing codes in hippocampus or sensory cortex, the phase of the underlying 1–8 Hz reference oscillations has to be determined with a precision of approximately a quarter oscillation cycle [10,39,48], resulting in a temporal scale of 50–250 ms. Phase of firing codes are therefore characterized by a coarser timescale than the above reported spike pattern codes. However, the coarse scale of phase of firing
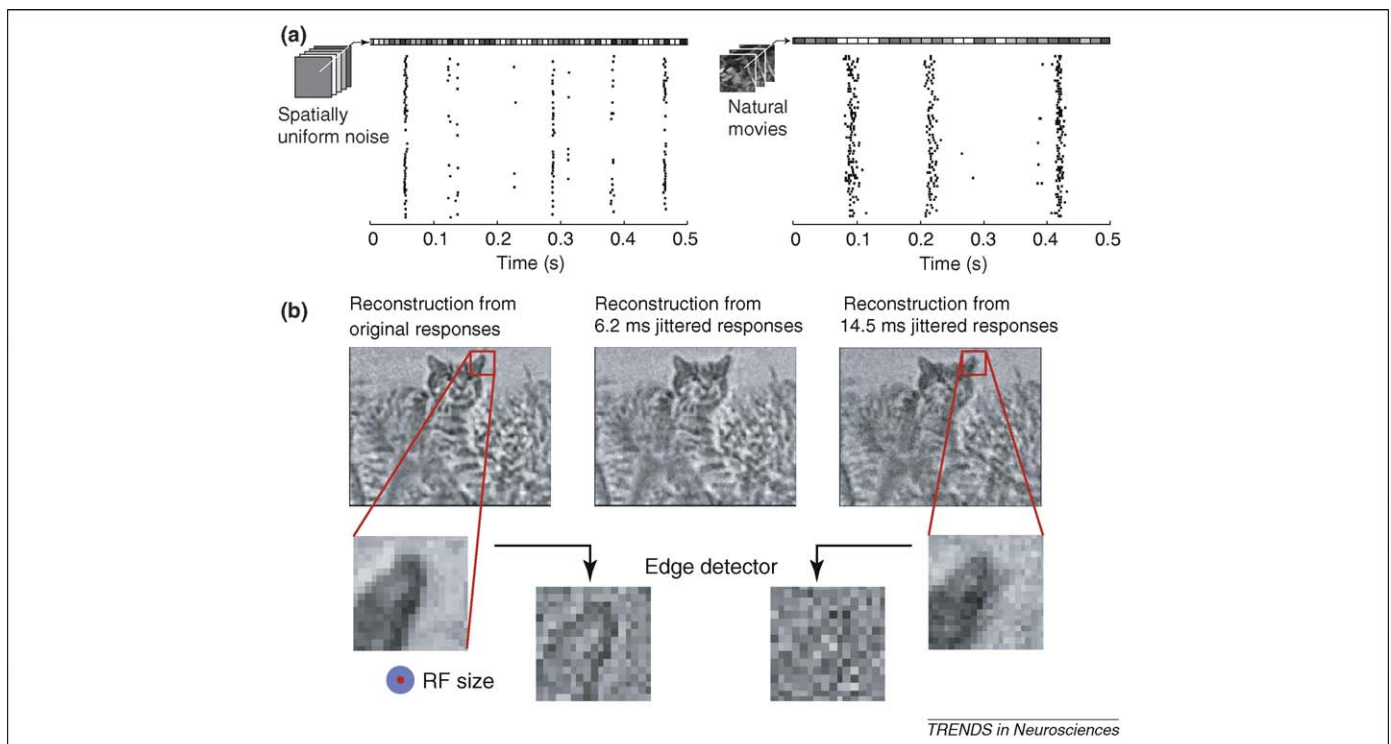

Figure 2. Stimulus timescales influencing the precision of neural responses. Data from recordings in the visual thalamus show that the precision of neuronal responses depends on the prominent timescales of the stimulus; in addition, these data demonstrate that millisecond precision of spike times is required to decode spatial image details [50]. **(a)** Response of one neuron to a spatially uniform 'noise' stimulus whose luminance was randomly refreshed at 120 Hz (left), and a clip taken from a naturalistic movie, whose prominent timescales are slower than those of the noise stimulus (right) [50]. During the noise stimulus, the timing of individual spikes (dots) was repeatable across trial (lines), with trial-to-trial variations in spike times of ∼3 ms. During the natural movie, responses were still repeatable, but spike times exhibit a larger trial-to-trial variability of ∼10 ms. **(b)** Individual frames of the natural movie were reconstructed from an array of model neurons, each with response characteristics similar to that of the recorded neurons and each representing one pixel of the natural movie [50]. Image reconstruction was better from a model based on the original spike trains (left) than from models in which the temporal precision of individual spikes had been reduced; for the middle and right panels, spike times were shifted with an average standard deviation of 6.2 ms and 14.5 ms, respectively. The result demonstrates that the observed response timing precision is required for a temporal code representing fine spatial image details. Adapted, with permission, from Ref. [50] .

codes does not exclude the presence of millisecond-precise codes based on spike times relative to the stimulus. Indeed, the two can coexist, as in the auditory cortex, where spike patterns provide information complementary to that carried by the phase at which these patterns occurred [15].

The precision of neural codes is also influenced by the stimulus dynamics [49,50]. Butts and colleagues [50] demonstrated this by showing that the temporal precision of responses in the visual thalamus differed when neurons were presented either with a full-screen 'noise' stimulus, whose luminance was randomly refreshed at 120 Hz, or with naturalistic movies of much slower dynamics [51] (Figure 2). For both types of stimulus, responses were ∼4.5 times more precise than was the dominant temporal scale of the stimulus. This suggests that neural responses oversample dynamic stimuli with a fixed 'relative precision'. Notably, the increased response precision was important to reconstruct fine spatial details of the stimulus from the responses (Figure 2b).

Natural stimuli also modulate the excitability of local networks on slower timescales. In the visual and auditory cortex, presentation of long sequences of naturalistic stimuli elicits reliable low-frequency (<8 Hz) LFP responses (Figure 3a) [15,52–56], and their phase and power provide information about which stimulus epoch is being presented [14,15,39,52]. Although little is known about the specific features represented by these low-frequency LFPs, it is conceivable that they reflect entrainment to some of the slow variations of sensory features in naturalistic stimuli. In other words, changes in the stimulus might elicit corresponding shifts in network excitability, whose timing is measured by a particular phase value of LFPs. This hypothesis is consistent with the entrainment of low-frequency cortical LFPs to stimuli with strong temporal regularities [55]. It is also consistent with theoretical work showing that the representation of slow stimulus components by entrained oscillations probably constitutes a general property of sensory cortices. Entrained activity might not only serve as an intrinsic frame of reference to interpret spiking activity, but also constitute an independent information channel varying on a slower timescale than do temporal spike patterns [56].

Multiplexed codes: complementary information on different timescales

The finding that neural codes are expressed over a wide range of temporal scales, ranging from rate or interspike interval codes with millisecond precision to much coarser phase of firing codes, suggests the possibility of multiplexed encoding: multiple neural codes operating on different timescales might encode complementary stimulus features [9], and together enhance the coding capacity of the system [9,10,15,33,58].

Early evidence for multiplexed coding comes from research by Victor and colleagues. Studying the encoding of image features in visual cortex, they found that different features were represented by neural responses at different scales (reviewed in Ref. [8]); contrast was represented by latency coding at a temporal precision of ∼10ms (see also Ref. [24]), whereas features such as orientation or spatial
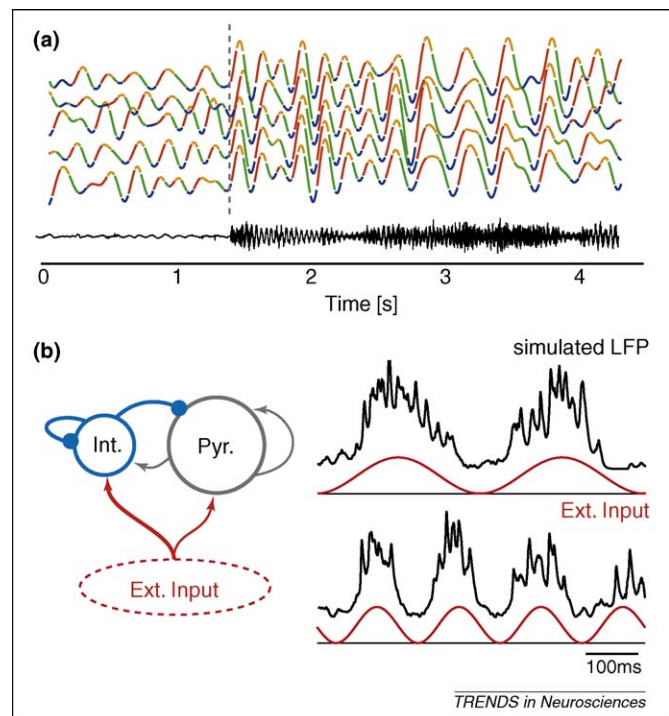

Figure 3. Entrainment of low frequency oscillations by time-varying stimuli. **(a)** Example data illustrating the entrainment of theta-band (4–8 Hz) field potentials in the auditory cortex by the presentation of naturalistic sounds [15]. The colored lines display the instantaneous LFP phase (the phase range 0–2π was divided into four equal phase intervals, as indicated by the color code), the black line displays the sound wave. Although phase values were not aligned across the different trials before stimulus onset (dashed line), they become consistent across trials during stimulus presentation. As a result, the phase can be used to extract information about what part of the sound is being presented. Similar tight relations between low frequency (<8 Hz) oscillations and naturalistic stimuli are also observed in other sensory cortices [14,15,39,57]. The Y-axis is in arbitrary units. **(b)** The phenomenon of entrainment to slow input regularities can be illustrated by simulating recurrent networks of excitatory and inhibitory neurons (schematic structure on the left) receiving time-dependent excitatory external stimulation [57]. When slow periodic external inputs (red lines) are presented, the network develops slow LFP oscillations (black lines) entrained to the external stimulus. When such networks are stimulated with broadband external inputs whose dynamics matches that of thalamic neurons responding to naturalistic stimuli, the LFPs of the simulated network account well for the information carried by the entire LFP frequency range (1–150 Hz) [57]. This suggests that the entrainment to slow inputs characterizing the dynamics of these networks can be used to explain the origin of reliable low frequency LFPs during naturalistic stimulation.

frequency were encoded with coarser temporal precision (30 ms and 100 ms, respectively).

Compelling evidence for multiplexed coding has also been found in the fly visual system and the retina [11,20,59]. In these studies, Fairhall and colleagues considered stimuli whose dynamic range changed over different stimulation epochs. They found that spike rates in 2–10-ms windows encoded stimulus variations scaled proportionally to the current dynamic range, whereas interspike intervals on slightly longer timescales encoded the current dynamic range, and slow modulations of spike counts on the scale of seconds carried information about the stimulus history [11]. This results in a multi-layered coding scheme that enables spike trains to convey stimulus information through several complementary channels, each corresponding to a different aspect of the sensory world and its variations.

Evidence for multiplexed coding was also found in sensory cortices during naturalistic sensory stimulation. In
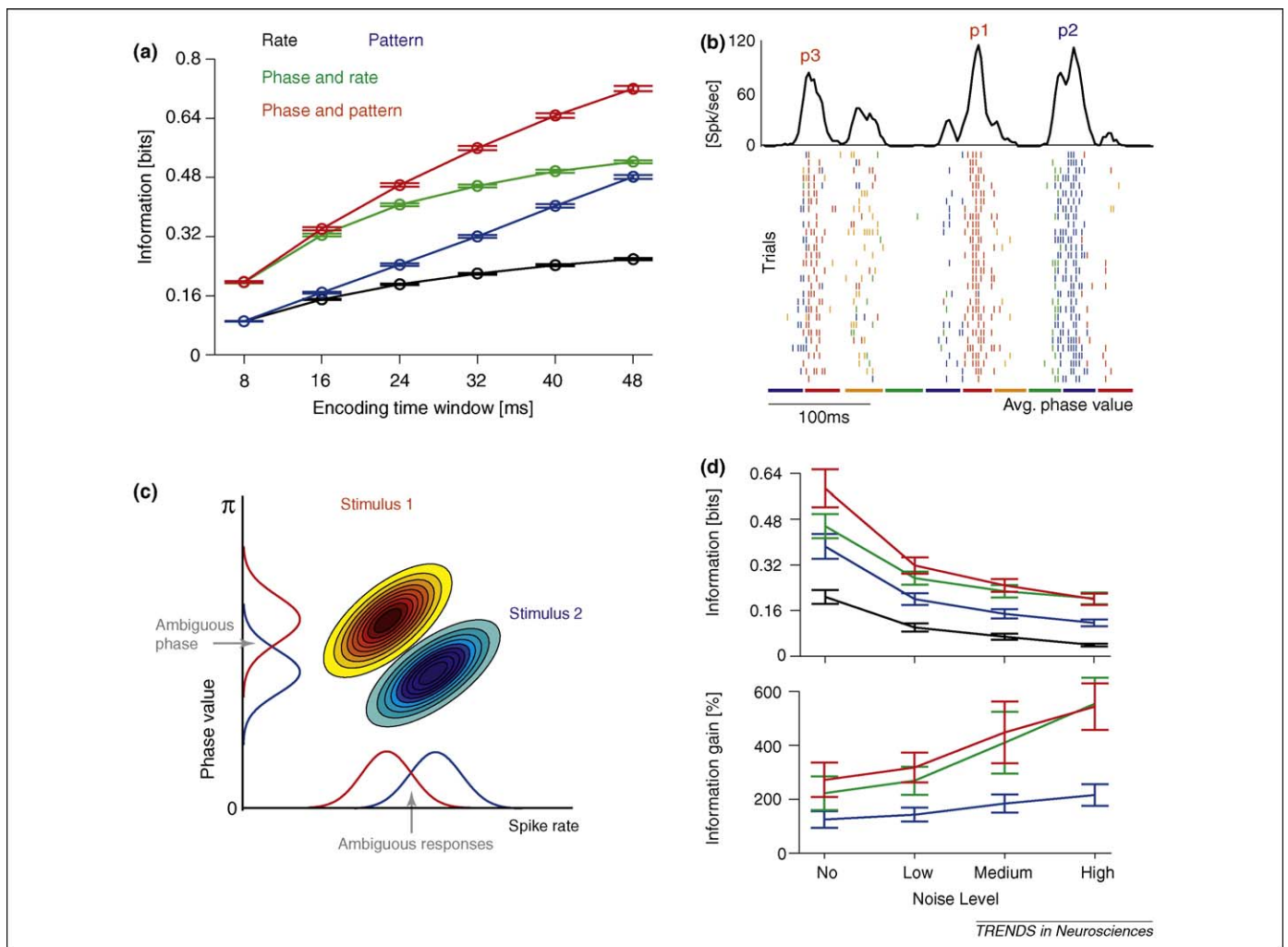
Figure 4. Multiplexed temporal codes enhancing and stabilizing the information about natural sounds. **(a–c)** present data from a study that compared the information about a long sequence of natural sounds and different putative codes derived from the responses of neurons in monkey auditory cortex [15]. (a) Stimulus information for different values of the encoding window (x-axis); lines denote the mean and S.E.M. across different neurons [15]. As well as the rate code, this study investigated spike patterns (considered with 8-ms precision), and two types of phase of firing code, relative to 4–8 Hz LFPs: the phase&rate code, which considers the number of spikes and their phase, and the phase&pattern code, which considers the temporal spike pattern and the phase. Phase of firing codes carried more information than did spike rates and patterns. These results demonstrate that the information in the phase of firing with respect to low-frequency LFPs is complementary to that in spike rates and patterns, and that combining the two codes results in an informative multiplexed code. (b) Example response displaying how the 4–8 Hz LFP phase helps to disambiguate stimuli eliciting the same firing rate [15]. The black line indicates the (trial-averaged) firing rate of one neuron, whereas raster plots display spikes elicited during individual trials. Spikes are color coded with the phase of the 4–8 Hz LFPs at the time of spike (different colors corresponding to quarter cycles, as in Figure 1d). The thick colored lines at the bottom indicate the average (across trials) phase value. Stimuli at time points p1 and p2 elicit the same firing rate, but consistently occur at different phase angles of the oscillations (blue and red). As a result, a rate code could not discriminate these two stimuli, but a phase of firing code could. Stimulus pair p1 and p3, by contrast, consistently occur at the same phase of the oscillation (red), but elicit a different firing rate. Together, these examples illustrate the complementary information between spikes and oscillation phase, and how one code removes ambiguity in the other. (c) Schematic representation of how combined knowledge of spike rate and oscillation phase helps to disambiguate stimuli. The schematic displays the response distributions produced by two hypothetical stimuli, each eliciting a range of spike rates within a particular range of phase values. Although the two distributions of spike rates and phase values overlap, their joint distributions separate in the two-dimensional space. The same principle could also be used to illustrate mutual disambiguation of individual codes in other types of multiplexed code. (d) Data from an experiment determining the robustness of the information in different codes in the presence of acoustic noise [15]. Trial-by-trial variable noise was added to the stimulus sound at four different relative levels (no noise, low, medium and high noise levels). The information in each code (represented by lines color coded as in Panel (a)) decreased with increasing noise level, in concordance with the decreased reliability of the overall stimulus (upper panel). However, information in temporal codes, especially in multiplexed codes based on phase of firing (phase&rate and phase&pattern), was more robust to noise: the information gain relative to the firing rate increased for multiplexed codes with increasing noise level (lower panel), suggesting that multiplexed codes enhance the robustness of cortical information processing to sensory noise. Adapted, with permission, from Ref. [15].

the auditory cortex, information about natural sounds was present in spike times at ~10-ms precision, and was also present at a slower scale in the phase of firing relative to low frequency fluctuations (timescale of tens to hundreds of milliseconds; Figure 4a) [15]. Importantly, information in spike rates and patterns at millisecond timescales was complementary to the information in the phase of firing, as sound periods not discernable from spike rates alone could instead be discriminated by also measuring the phase of firing (Figure 4b). Another study

found that, in the visual cortex, spike rates on 5–10-ms timescales carried information about which epoch of a naturalistic movie was being shown that was largely complementary to that in the phase of firing relative to low-frequency (1–8 Hz) LFPs [39]. Together, these findings suggest that precise spiking activity and slow network fluctuations in sensory cortices constitute largely independent information channels during naturalistic stimulation, which can be combined into highly informative multiplexed codes [14,39,57].

Together, these studies provide accumulating evidence for the hypothesis that temporal multiplexing of sensory information enhances the total information encoded by the responses, and enables disambiguating stimuli that could not be discriminated at a single response timescale (Figure 4c).

Multiplexed codes and stable sensory representations

Under natural conditions, sensory representations are faced with stimuli varying over several orders of magnitude, and need to be robust to environmental distracters. For example, we can understand somebody talking to us despite considerable background noises, or we can recognize objects despite large changes in illumination. Codes using temporal multiplexing might offer an efficient way of dealing with such noisy and variable environments.

How sensory representations deal with environmental distracters remains largely unexplored. Acoustic background noise, for example, not only introduces irrelevant sound features, but also increases signal variability when the same word is repeatedly spoken. To study the impact of stimulus noise on different neural codes, a recent auditory study presented naturalistic sounds either in their original form or mixed with naturalistic environmental noise, which was varied from trial to trial [15]. Although stimulus information decreased with increasing noise for all codes, the information in the phase of firing with respect to slow oscillations (hence a multiplexed code) increased relative to the information in spike counts when increasing noise (Figure 4d). This suggests that using an internal temporal

reference frame, such as slow network oscillations, is central to forming stable sensory representations in unreliable environments [55–58,60].

To deal with changes in sensory environments, such as changes in the dynamic range of stimulus features, neurons adapt their input–output relationship [19,59,61,62]. Adaptation, however, makes responses ambiguous. Responses to the same stimulus value might be different before and after adapting to a particular change in the environment and, thus, could be mistaken for reflecting different stimulus values. Using multiple codes can provide a way to resolve this ambiguity. For example, motion-sensitive cells in the fly visual system adapt to the history of changes in stimulus ensemble, and this adaptation renders the information that these cells provide by spike rates in short (10-ms) time windows ambiguous (Figure 5a–c). However, these neurons overcome this ambiguity by encoding the recent history of the stimulus ensemble using interspike intervals, which provide the necessary information to disambiguate the spike counts (Figure 5d) [11,59].

Mechanisms for decoding multiplexed codes

Decoding multiplexed codes requires the receiving neurons to be sensitive to the different temporal scales of the relevant activity patterns. Sensitivity to temporal spike patterns, for example, can arise by virtue of different synaptic timescales [63,64], and sensitivity to different inter-spike interval sequences might be modulated by synaptic mechanisms, such as short-term depression or
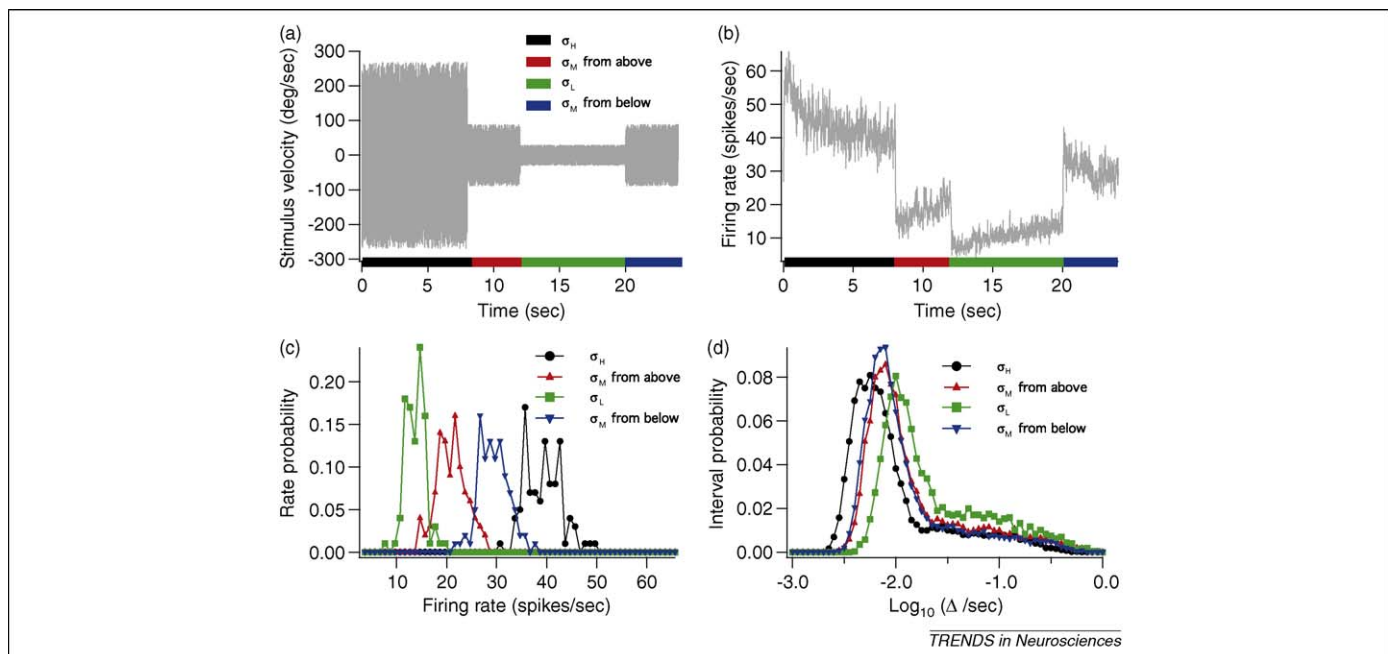

Figure 5. Resolving ambiguity by combining neural codes. Example data from the fly visual system demonstrating how ambiguity in rate codes computed in short windows can be reduced by considering interspike intervals [59]. **(a)** In these experiments, the dynamic range of the visual stimulus was systematically varied over time, and comprised three different standard deviations (SD) of the stimulus velocity (high, medium and low, denoted by σ_H, σ_M and σ_L, respectively). The medium state was reached once from above (i.e. by a decrease in the stimulus SD) and once from below (i.e. by an increase in SD), resulting in four different experimental conditions (color code). **(b)** The time course of the trial-averaged spike rate in sliding 10-ms windows for the three-state switching experiment. In addition to an immediate change in spike rates after changing the stimulus ensemble, spike rates also exhibited response adaptation (here, visible as slow changes over several seconds). **(c)** The distributions over time bins of the trial-averaged rates (computed in 10-ms bins from the last second of each stimulus epoch) for the four experimental conditions. Spike rates for stimuli of intermediate SD different depending on the stimulus history (i.e. on whether the intermediate stimulus value was reached from a larger or a smaller previous value). As a result, the spike rate by itself could not faithfully represent the current stimulus value. **(d)** The distribution of interspike intervals Δ in each stimulus epoch [computed, as for data in (c), from the last second of each epoch]. The interspike interval distributions for both conditions of intermediate stimulus values coincide, suggesting that interspike intervals resolve the ambiguity about stimulus SD that could not be resolved by spike rates. Reprinted, with permission, from Ref. [59].

facilitation [65,66]. As a result, the weighting of particular timescales might be updated by history-dependent learning rules, possibly as a mechanism to adapt neural codes to changing environments [67].

To use the phase of slow oscillatory activity as a reference signal for spiking activity, recipient neurons need to able to combine the timing of afferent spikes with the state of the slow rhythm. Given that low-frequency LFPs reflect changes in neuronal excitability that are spatially coherent over several millimeters [68,69], and given that most synapses are made within local networks [70], pre- and post-synaptic neurons have access to the same slow rhythm for most cortical connections. Hence, at least for local computations within a given sensory cortical area, the same rhythm might serve as frame of reference for the neurons encoding and decoding a given message [33]. Together, these facts suggest that biophysical mechanisms for decoding multiplexed codes exist and are available within the microcircuitry of cortical sensory structures.

Timescales of neural codes and behavior

The observation that information is carried by neural codes at a high temporal precision (rather than by spike rates on long window) does not guarantee that the nervous system makes use of such temporally precise codes. To determine whether this is the case, it is important to establish links between the temporal precision of neural codes and behavior.

One way to link the temporal precision of neural codes and behavior is to compare the behavioral performance of the animal, for example the fraction of correct discriminations as a function of a stimulus parameter, with the stimulus discriminability obtained by decoding single-trial responses [71]. By doing so, a study on the somatosensory cortex obtained better correlations of behavioral performance with spike rates over timescales of several tens of milliseconds than it did with codes of higher temporal precision [72]. This led to the suggestion that spike timing information is not used by the animal in such a task [73]. A study of the auditory cortex, by contrast, reported that the information in temporal codes correlated better with behavior than did information from spike counts [44]. Although reaching different conclusions, both studies suffer from the limitation of undersampling the population of neurons providing the sensory representation of the relevant stimuli.

A recent study [74] aimed to overcome this limitation by comparing the performance of the animal in a visual discrimination task with the performance of neural codes based on the entire population of retinal ganglion cells representing the stimuli. More precisely, the authors compared the performance of mice doing the task with an upper bound on the stimulus discriminability afforded by neural codes at various temporal precisions computed with an optimal decoding procedure from all the relevant retinal neurons recorded *in vitro*. The results were compelling: rate codes over long (hundreds of millisecond) windows codes fell below the behavioral performance, whereas millisecond-precision temporal codes fully accounted for the performance of the animal [74]. This demonstrates that the retinal stimulus representation provided by spike rates over long windows does not provide sufficient information to the animal, which must rely on finely timed temporal response patterns to solve the task.

The ability of the nervous system to exploit neural codes at high temporal precision is also demonstrated by studies manipulating the temporal structure of neural activity and examining how these manipulations cause changes in behavior. In one such study, rats were trained to discriminate activity patterns induced by electrical microstimulation in auditory cortex [75]. Although the only cue available to guide behavior was the relative timing of electrical activity between two stimulation sites, the animals performed above chance even when guided by interstimulation intervals of only 3–5 ms. In another study, bees were trained to discriminate odors while the temporal structure of neural activity in their antennal lobe was manipulated using pharmacological agents [76]. Interestingly, removing prominent oscillatory activity patterns in this structure largely diminished correct odor discrimination, demonstrating that oscillatory temporal patterns of activity is crucial for correct behavioral performance. Hence, mounting experimental data indicate that neural codes with high temporal precision are exploited by the nervous system to guide behavioral choices.

Concluding comments

Evidence is accumulating that multiple neural codes operate simultaneously at different temporal scales, with each code carrying complementary information. Such multiplexed codes could provide several computational advantages, such as reducing the ambiguity inherent to single-scale codes and enhancing robustness of neural representations to environmental noises. Although the existence and the advantages of multiplexed codes are becoming increasingly evident, several challenges remain.

One is to understand the extent to which genuine temporal or multiplexed neural codes are exploited by the brain to cause or guide behavior [44,74,75,77]. To this end, manipulations of neuronal activity will be needed. Such manipulations could either interfere with patterns of neural activity on particular timescales and observe their impact on behavior [76], or could induce novel patterns of activity [75,78] and determine how they affect behavioral reactions and perception. This, however, not only requires clever behavioral paradigms, but also necessitates the continuous fine tuning of techniques to induce or interfere with neural activity.

A second challenge will be to integrate insights into temporal neural codes with other roles assigned to temporal patterns of activity. The temporal structure of activity can have an important role in propagating and routing information through cortical networks [34,63,79]. Mechanisms forming information-rich sensory representations could therefore mediate effective and flexible information transmission simultaneously. In addition, slow network oscillations can dynamically influence the impact of sensory stimuli [77,80]; for example, by mediating attentional enhancement [77,81]. Brain regions controlling cognitive mechanisms, such as attention, could therefore directly influence temporal reference frames for information encoding in lower sensory areas. However, the details about how

sensory representations, attentional selection and information propagation are facilitated by the same neurophysiological mechanisms require further investigation.

A final challenge will be to investigate how temporally structured responses integrate with spatial patterns of activity provided by large populations of neurons [60,82–84]. Although single neurons might be able to drive percepts and elicit responses [85], everyday perception probably results from the coordinated activity provided by larger populations. Much work remains to be done to provide a thorough understanding of how large-scale spatio-temporal population codes achieve those stable and robust representations that are reflected in daily behavior.

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