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Variable Temporal Integration of Stimulus Patterns in the Mouse Barrel Cortex

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Abstract

Making sense of the world requires distinguishing temporal patterns and sequences lasting hundreds of milliseconds or more. How cortical circuits integrate over time to represent specific sensory sequences remains elusive. Here we assessed whether neurons in the barrel cortex (BC) integrate information about temporal patterns of whisker movements. We performed cell-attached recordings in anesthetized mice while delivering whisker deflections at variable intervals and compared the information carried by neurons about the latest interstimulus interval (reflecting sensitivity to instantaneous frequency) and earlier intervals (reflecting integration over timescales up to several hundred milliseconds). Neurons carried more information about the latest interval than earlier ones. The amount of temporal integration varied with neuronal responsiveness and with the cortical depth of the recording site, that is, with laminar location. A subset of neurons in the upper layers displayed the strongest integration. Highly responsive neurons in the deeper layers encoded the latest interval but integrated particularly weakly. Under these conditions, BC neurons act primarily as encoders of current stimulation parameters; however, our results suggest that temporal integration over hundreds of milliseconds can emerge in some neurons within BC.

Key words: cell-attached, in vivo, sensory coding, somatosensory, vibrissae

Introduction

Although the ability to discriminate sensory sequences is central to many aspects of behavior, little is known about the neural sites of temporal integration and sequence representation. For instance, rodents can learn whisker-mediated sensory discrimination tasks that require integrating tactile information over time (Fassihi et al. 2014, 2015; Maravall and Diamond 2014); how individual neurons represent the relevant, temporally extended stimulus properties is unknown. To begin to map cortical signatures of sequence selectivity, we analyzed whether neurons in BC integrate information about sequences of whisker movements over time. We recorded spiking responses from single neurons of anesthetized young adult mice while delivering sequences of irregularly timed whisker deflections and applied information theoretical measures to estimate the correlation between responses and the latest or earlier stimulus intervals.

Materials and Methods

Experimental Subjects and Preparation

All experiments were in accordance with European Union and institutional standards for the care and use of animals in research.

Female mice (ICR; age 4–9 weeks; mean weight 23.6 g, standard deviation 4.8 g) were anesthetized with ketamine/xylazine (100 mg/kg, 10 mg/kg, i.p.) and placed in a stereotaxic instrument (Narishige), with body temperature maintained at 37°C using a homeothermic heating pad (FHC). Animals were regularly checked for hindpaw reflexes and injected with additional doses of anesthetic (20–30% of initial dose) as needed, every 30–60 min.

Recording, Location, and Stimulation

After opening a craniotomy over BC (Lateral 3 mm, Anteroposterior 1.5 mm relative to Bregma) and reflecting the dura, we performed patch clamp recordings in cell-attached mode. Pipettes (resistance 5–7 MΩ) were filled with standard intracellular solution containing (in mM) 130 K-methylsulfonate, 10 Na-phosphocreatine, 10 HEPES, 4 $MgCl_2$, 4 Na_2-ATP, 3 Na-ascorbate, and 0.4 Na_2-GTP; pH 7.33, 287–303 mOsm. Recordings were digitized at 10 kHz (Axon Multiclamp 700B; CED 1401 micro, Spike 2 software, Cambridge Electronic Design); stimulus output voltage was recorded simultaneously with the patch clamp signal. The depth of recorded neurons was controlled through the micromanipulator reading (Sutter MP-225) and ranged between 120 and 1039 µm (mean 574 µm). In a number of recordings, depth was verified by juxtacellular injections of biocytin. Upon perfusion, injected neurons were visualized histologically in 60-µm coronal sections (ABC Kit, Vectastain, and DAB reaction) (Pinault 1996). For the recovered neurons, the depth discrepancy between the manipulator reading and the post hoc measurement was 35 ± 8 µm (mean ± standard error of mean; $n = 16$ neurons, $n = 10$ mice).

For stimulation, 3 glass pipettes were glued to a piezoelectric bender (Physik Instrumente). The pipettes were brought proximal to the whisker pad (distance 1–3 mm) and several (4–5) macrovibrissae introduced into the pipettes. Joint stimulation of whiskers with a common waveform simplified the parameter space, as responses depended only on the temporal structure of the stimulus. Neurons sensitive to correlated whisker motion are readily found in the barrel cortex (Estebanez et al. 2012). The stimulator had a dynamic range of 400 µm and was powered by a purpose-built amplifier (Physik Instrumente).

Stimulus Design

Stimulation consisted of sequences of whisker deflections, each deflection being a stereotypical biphasic waveform: a Gaussian-filtered differential filter (Fig. 1A) (Petersen et al. 2008). Peak-to-peak deflection amplitude was 400 µm. We checked that the piezoelectric wafer followed the deflection waveform by optical monitoring with a custom light-emitting diode–phototransistor circuit. The direction of whisker deflections was manually adjusted at the start of each recording to produce the clearest onset response from the neuron.

Each deflection achieved a maximum speed of approximately 400 mm/s; however, deflection waveforms were such that speed remained close to maximum for just a short time, and median speed was approximately 40 mm/s. Similarly, angular velocity was approximately 7900°/s (maximum), approximately 900°/s (median). These values are at the higher end of those used for passive stimulation or recorded during free whisking in air (Kwegyir-Afful et al. 2008; Khatri et al. 2009), but in the range achieved during natural whisker motion (ca. 1500°/s; (Bagdasarian et al. 2013) and well below the highest values recorded during high-speed exploration (median, 6600°/s; maximum >55 000°/s; Bale et al. 2015). This range of stimulation intensities was appropriate for reliably driving responses, but unlikely to saturate primary afferents.

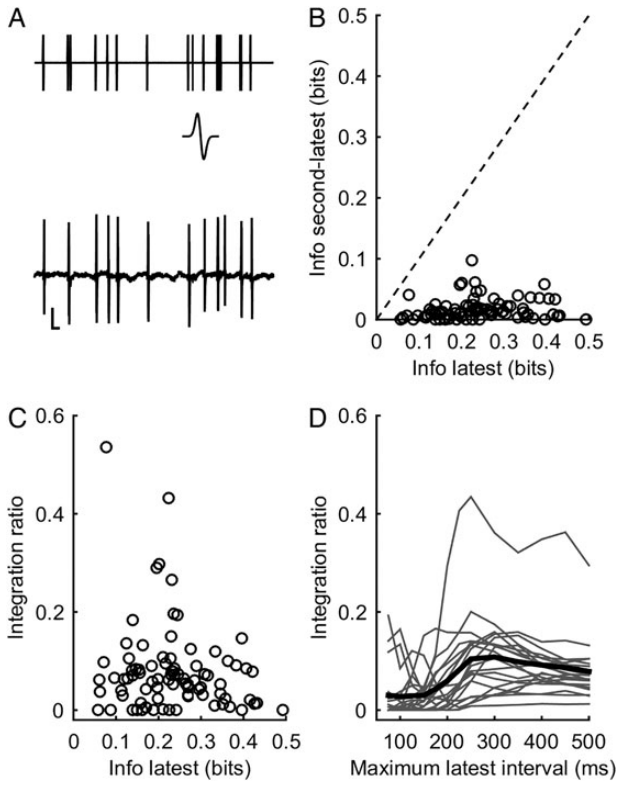

Figure 1. Information carried about the latest and second-latest interval. (*A*) Top, temporally isolated whisker deflections were presented at pseudorandom intervals (range: 40–500 ms). Inset shows a single whisker deflection. Bottom, example cell-attached recording during presentation of stimulus. Neuronal responses (spiking or not spiking) were examined after each deflection. This neuron responded reliably to longer but not shorter intervals and thus conveyed information about interval duration. Scale bars: 100 ms, 2 mV. (*B*) Information contained in the probability of spiking after a whisker deflection about the latest and second-latest interstimulus intervals (each symbol is one neuron, $n = 84$). (*C*) Information integration ratio versus information about latest interval. In general, the strongest integrators were neurons with intermediately strong encoding of the latest interval. (*D*) Effect on integration of limiting the allowed duration of the latest interval. Information about the second-latest interval was computed while restricting the maximum allowed duration of the latest interval ($n = 20$ neurons). Thin gray lines: individual neurons; thick black line: population mean.

Stimulation sequences satisfied the following design criteria: the range of intervals spanned physiologically feasible values, successive intervals were not significantly correlated (i.e., the distribution of values for each interval was drawn independently from that of its neighbor), and the ensemble of interval values permitted unbiased statistical analysis. In the initial design, we implemented the first criterion by basing the sequence on a recording of thalamic spiking responses in vivo (mean interval 217 milliseconds [ms]) (Petersen et al. 2008). We reasoned that the intervals contained in this pattern of thalamic spiking would be characteristic of temporal input patterns relayed to cortical neurons. We then constructed additional stimulus patterns by shuffling (reordering) the initial sequence and by generating Poisson and log-normal distributed ensembles over a similar range of interval values. Stimulation protocols constructed in this way lasted 120 s and included an ensemble of around 400 usable intervals, that is, ca. 400 stimulus presentations.

For the subset of experiments represented in Figure 1D, we constructed an expanded stimulus set that included a larger

(ca. 3000) ensemble of stimulus presentations at independently distributed intervals. These intervals were log-uniformly distributed over the range 40–500 ms (mean 182 ms) to optimize equipopulated sampling (see below). This protocol lasted 586 s. Results on information about the latest interval and on amount of temporal integration did not differ for sets of recordings acquired with different stimulus ensembles but otherwise identical conditions ($P = 0.44$ and $P = 0.31$, respectively, $n = 24$ and $n = 20$ for original and enlarged stimulus set, Kruskal–Wallis test). Thus, findings were robust against variations in sequence design.

Analysis

If a neuron is sensitive to a form of stimulation, its spiking response will correlate with (or "be tuned to") some stimulation parameter and convey information about the value of that parameter. In the present case, the only parameter that varied over the course of a stimulation sequence and could modulate responses was the interdeflection interval. To determine whether responses were modulated by and could discriminate between intervals, we computed the mutual information between spiking response and interval value. Mutual information measures the average decrease in statistical uncertainty about interval duration that an observer would obtain by determining neuronal spiking (Shannon 1948; Cover and Thomas 2006). For an ensemble of possible neuronal responses {resp} and an ensemble of interval values {interv}, mutual information is the difference between the overall entropy (indeterminacy) of the interval distribution and the average entropy of the interval distribution if the neuronal response is known:

$$\begin{aligned} I(\{\text{interv}\},\{\text{resp}\}) &= S[P(\text{interv})] - \langle S[P(\text{interv}|\text{resp})]\rangle_{\{\text{resp}\}} \\ &= -\sum_{\{\text{interv}\}} P(\text{interv})\log_2 P(\text{interv}) \\ &+ \sum_{\{\text{resp}\}} P(\text{resp}) \sum_{\{\text{interv}\}} P(\text{interv}|\text{resp})\log_2 P(\text{interv}|\text{resp}) \end{aligned}$$

Here, P denotes the probability of the response or the stimulus interval taking a certain value, S denotes the entropy of a probability distribution, and summations are taken over the experimental ensembles of values. With base 2 logarithms, I has units of bits: when observation of a response reduces uncertainty by a factor of 2 on average, mutual information is equal to 1 bit. In our calculations, "interv" refers to values of either the latest interval (the one immediately preceding the latest deflection) or the second-latest.

The distributions were determined as follows. After each whisker deflection, neuronal responses were monitored over a 40-ms window, chosen empirically based on the duration of the primary post-stimulus time histogram peak for responsive neurons. The response to each deflection was classified as either spiking or nonspiking: within the 40-ms window, the number of occasions where neurons spiked more than once was negligible, and allowing for extra response categories (2 spikes, 3 spikes, etc.) did not qualitatively affect results. We then computed the distributions of latest intervals or second-latest intervals, conditional on whether the neuron spiked or did not spike after the deflection. These values entered into the second (conditional entropy) term in the equation. This term was subtracted from the entropy calculated from the overall (nonconditional) distribution of stimulus intervals.

Interval values were binned into $n_b = 4$ equipopulated categories, but all qualitative results, particularly the decreased information about second-latest compared with latest intervals, were robust to varying n_b within a reasonable range (2–8). Panzeri–Treves bias correction was applied to correct for possible undersampling (Panzeri and Treves 1996; Panzeri et al. 2007). To test for any qualitative effects of bias, we also carried out information analyses on decimated stimulus ensembles, finding no effects of bias with ensemble sizes down to 50% of the full one. All analyses were computed using Matlab; information estimates used the Information Breakdown Toolbox (ibtb.org) (Magri et al. 2009).

Based on the information analysis, a neuron was classified as responsive to the stimulus if the mutual information between true spiking response and stimulus was substantially greater than resulted from shuffling the correspondence between the latest interval and the spiking response. Shuffling was repeated 100 times and the resulting information averaged; neurons were included in the dataset if information in the true stimulus–response relationship was >2 orders of magnitude greater than this shuffled average. This approach to scoring responsiveness ensured that only neurons representing stimulus intervals were taken into account, while allowing visualization of the full variability in information values across responsive neurons. In addition, a neuron's spiking response had to convey at least 0.05 bits about the value of the latest stimulus interval, consistent with the intuition that cells conveying very small information values are unlikely to participate in stimulus encoding. There were no neurons failing these criteria for inclusion but carrying significant information about earlier intervals. Out of a total of $n = 136$ cell-attached recordings, 84 satisfied these criteria and were included in the final dataset.

In addition to the information-based approach described earlier and in Results section, we also carried out a population decoding analysis based on pooling all neurons recorded under identical stimulation conditions. Linear decoding based on spike count population vectors was used to classify intervals into one of four categories. Classification performance (% correct) for the most recent and earlier intervals revealed that temporal integration as decoded from this method was no greater than with the information-based approach.

Results

We performed cortical cell-attached patch clamp recordings in anesthetized young adult mice during stimulation with sequences of whisker deflections (Fig. 1). To specifically probe neuronal sensitivity to temporal pattern, all individual whisker deflections in a sequence were identical, but were separated by variable interdeflection intervals (Fig. 1A).We tested whether neurons were sensitive to the temporal pattern of whisker deflections by quantifying how much their spiking response after each deflection correlated with the preceding stimulus pattern. To allow for possible nonlinear relationships, we used mutual information as our measure of correlation (Materials and Methods). Neurons were included in the dataset ($n = 84$) if they carried a significant amount of information about the latest interval before a whisker deflection (Fig. 1B).

To determine whether neurons explicitly represent information extending over time, we computed the information conveyed about the latest interval and about several previous intervals. Information about earlier intervals decreased significantly compared with the latest interval (Fig. 1B): information about the second-latest interval was much smaller than that about the latest interval (6.3%, population median; $P < 10^{-28}$, $n = 84$, Wilcoxon rank-sum test), although there was considerable variability around this value (interquartile distance 6.5%). There

was even less information about earlier intervals (data not shown).

Across the dataset, the neurons most informative about the latest interval also tended to carry more information about the second-latest one ($r = 0.25$, $P = 0.021$, $n = 84$, Spearman correlation). However, there was substantial variability around this central tendency: Some neurons that were highly informative about the latest interval did not necessarily convey strong information about earlier ones. This suggested that beyond variability across neurons in overall "informativeness," there was also variability in the amount of temporal integration. To specifically visualize the amount of integration, we computed the ratio of information about the second-latest interval to information about the latest interval, termed the "integration ratio." We plotted integration ratio against information about the latest interval (Fig. 1C). This plot demonstrated that the neurons most informative about the latest interval were not the neurons that integrated the most. Neither was a high integration ratio simply a byproduct of a low level of information about the latest interval (i.e., a small denominator). Instead, the clearest strong integrators were neurons carrying an intermediate level of latest interval information. These strong integrators were capable of achieving integration ratios approximately 0.2 (i.e., 20%) and above.

The above results were obtained considering the full range of presented intervals, 40–500 ms (see Materials and Methods). Responses therefore followed intervals that could be up to 500 ms long: consequently, second-latest intervals could end as early as 500 ms before the neuronal response under consideration. This made it difficult to estimate the true timescale over which neurons were able to integrate information. Consider, for example, a hypothetical neuron carrying information over a timescale of exactly 300 ms. When receiving a stimulus after an interval of 100 ms, such a neuron would be able to discriminate preceding (second-latest) interval values in the range up to 200 ms. However, after a latest interval of 400 ms, the neuron's response would be unable to convey any information about the value of the second-latest interval. Thus, the use of a stimulus set containing the full range of latest intervals up to 500 ms, without controlling the duration of the latest interval, could potentially obscure the ability of neurons to integrate over intermediate times. To address this possibility, we repeated the information analysis above, this time computing information carried about the second-latest interval while limiting the allowed duration of the latest interval. For each maximum allowed size of the latest interval, we calculated information about the second-latest interval taking its full range of variation into account, and divided this by information about the latest interval (also taking its full range into account), to obtain an information ratio. This analysis was performed on a subset of recordings based on an expanded, specifically designed stimulus set (see Materials and Methods). We then plotted information ratio as a function of the maximum allowed latest interval (range: 75–500 ms; Fig. 1D). Restricting the allowed size of the latest interval yielded little increase in temporal integration: the information ratio value for a maximum allowed latest interval of 500 ms (as computed previously) was not significantly different than values for shorter maximum allowed intervals (Fig. 1D; $P = 0.29$, $n = 20$, generalized linear model with Bonferroni correction). Information ratio depended on maximum allowed latest interval mainly in that it dropped sharply when the allowed latest interval was shorter than approximately 200 ms ($P < 10^{-7}$, $n = 20$, generalized linear model with Bonferroni correction). This was attributable to a general absence of neuronal response to latest intervals shorter than approximately 100 ms: This effective refractory period voided any ongoing integration or "memory" about earlier interval values when the latest interval was very short. To summarize this analysis, in neurons where temporal integration was appreciable, it extended over a timescale up to several hundred milliseconds.

Our results suggested that the majority of neurons in the BC represent information principally about the latest stimulus values, although some neurons do integrate appreciably over timescales in the hundreds of milliseconds. We wondered whether this variability in capacity to integrate might be related to differences in neuronal responsiveness. To address this, we plotted the information conveyed by each neuron about the latest interval against its mean firing rate, averaged throughout the duration of stimulation (Fig. 2A). As expected from established results (Borst and Haag 2001; Klampfl et al. 2012; Tripathy et al. 2013), neurons that fired more were more informative about the latest interval ($r = 0.25$, $P = 0.03$, $n = 77$, Spearman correlation). Next, we plotted integration ratio against firing rate (Fig. 2B). This showed that more-active neurons had a tendency towards weaker temporal integration ($r = -0.31$, $P = 0.0053$, $n = 77$, Spearman correlation).

Neurons process information differently according to their location in cortical circuits (Harris and Mrsic-Flogel 2013). We wondered whether the information conveyed by a neuron, and the amount of temporal integration, depended on its depth. Cortical

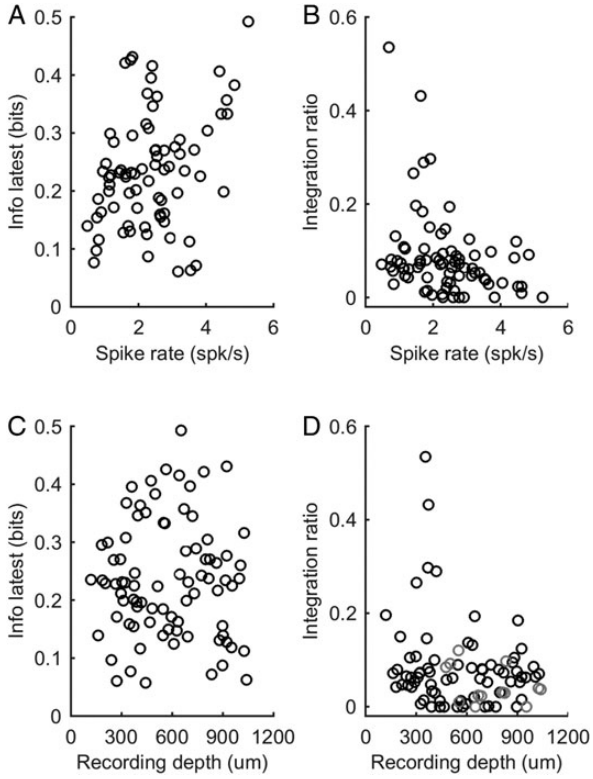

Figure 2. Analysis of information as a function of response spike rate and recording depth. (*A*) Information about latest interval versus mean spike rate over the entire duration of stimulation. More-active neurons conveyed greater information. Each symbol is one neuron ($n = 77$). (*B*) Integration ratio versus mean spike rate. More-active neurons integrated less over time. (*C*) Information about latest interval versus cortical depth. Neurons at all depths could encode significant information ($n = 84$ neurons). (*D*) Integration ratio versus cortical depth. In every layer, most ratios were well under 1, but values varied widely across nearby neurons. A subset of neurons in the upper layers achieved values beyond approximately 0.2. Symbols in gray are the most active neurons from panels A–B (mean rate >3.5 spikes/s), which were located in the deeper layers and had low integration ratio.

depth can be taken as a proxy for laminar location (Lefort et al. 2009). We found that neurons across all recorded depths could encode appreciable information about the latest interval (Fig. 2C). The integration ratio varied even at nearby depths (Fig. 2D).

Across the overall population, the subset of neurons that integrated most strongly had depths suggesting a location in the upper layers (Fig. 2D; 302–468 μm; reading error estimated as ca. 35 μm, see Materials and Methods). Conversely, the most strongly active neurons, which integrated weakly (Fig. 2B), were found at depths consistent with locations in the deeper layers (Fig. 2D, gray symbols) (Lefort et al. 2009). The depth, sensory responsiveness, and weak integration of these neurons are consistent with their receiving direct thalamocortical sensory input. The result is consistent with the notion that temporal integration emerges as a result of intracortical processing.

Discussion

To perform its central roles, the cerebral cortex needs to integrate sensory patterns over time. That single neurons can be sensitive to temporal patterns has been known for decades (Segundo et al. 1963), and mechanisms conferring sequence selectivity at the single-neuron level have been identified (Branco et al. 2010). However, how selectivity to temporally integrated patterns emerges in cortical circuits in vivo remains poorly understood. Here we examined temporal integration in BC, the primary sensory cortical area that processes information corresponding to the rodent whisker system. We found that neurons in mouse BC carry substantially more information about the latest interval in a random stimulation sequence than about earlier intervals. Neurons that are more responsive and informative about the present sensory stimulus integrate less over time. Moreover, neurons located at laminar depths consistent with stronger direct lemniscal thalamocortical input integrate little, while some neurons in the upper layers (Lefort et al. 2009; Feldmeyer et al. 2013) convey appreciable information about earlier intervals over timescales of several hundred milliseconds—i.e., several whisking cycles. Thus, neurons at initial cortical stages of somatosensory processing behave primarily as encoders of current stimulation parameters, but temporal integration can emerge even within BC.

Neurons in BC respond at precise times and can convey stimulus information through response latency and timing as well as response magnitude (Panzeri et al. 2001; Maravall and Diamond 2014; Hires et al. 2015; Zuo et al. 2015). We wondered if considering the full information carried by spike latencies might affect our results. To test this, we parsed responses by whether they occurred at short or long latency, and measured the resulting information about the latest and second-latest stimulus interval. Taking latency into consideration uncovered a slight amount of extra information about the latest but not the second-latest interval, leaving unaffected our qualitative conclusions about information ratios and their variability (data not shown).

Rodents are capable of integrating whisker stimulus parameters and storing them over time to arrive at a sensory discrimination choice (Fassihi et al. 2014, 2015; Guo et al. 2014). A motivation for this study was whether individual neurons in the pathway up to BC can explain this ability. Neurons in the whisker pathway display adaptation and context-dependent sensitivity modulation over timescales on the order of hundreds of milliseconds and even seconds (Maravall et al. 2007; Lundstrom et al. 2010; Wang et al. 2010; Maravall and Diamond 2014; Ollerenshaw et al. 2014). However, a neuron modulates its sensitivity depending on changes in a stimulus parameter need not imply that the neuron can explicitly encode that parameter (Fairhall et al. 2001). Reverse correlation studies of selectivity to stimulus features have consistently shown that the duration of features encoded by BC neurons is short, around tens of milliseconds (Maravall et al. 2007; Estebanez et al. 2012). Moreover, in one study involving rats carrying out a vibrotactile detection task, the animal's behavior was consistent with weak temporal integration of the responses of BC neurons, over timescales limited to approximately 25 ms (Stuttgen and Schwarz 2010). Thus, our findings are consistent with data from other approaches suggesting that most BC neurons report mainly on "instantaneous" stimulus parameters.

Recent work in other primary sensory cortical areas has found responses that correlate not just with current stimulus parameters but with earlier ones as well. In the visual and auditory modalities, compared with the tactile modality, there is a significantly greater number of synaptic processing stages between sensory transduction and primary cortex, potentially creating the scope for greater temporal integration. However, interestingly, timescales for integration (up to a few hundred milliseconds) appear comparable across the different modalities. In cat primary visual cortex, population responses to a sequence of visual stimuli (letters of the alphabet) encode information about letters presented up to several hundred milliseconds before the current one (Nikolic et al. 2009). In ferret primary auditory cortex, responses to presentation of a sequence of tones convey information not just about the current tone but also about the direction of the frequency step from previous to current tone, up to approximately 100 ms after the step occurred (Klampfl et al. 2012).

The present results were obtained for anesthetized naïve mice. In mice trained on an object location discrimination task, BC neurons have access to long-lasting location signals related to past touches of specific whiskers, conveyed by axons that project from primary motor cortex via layer 1 (Petreanu et al. 2012). Thus, pyramidal neurons receiving layer 1 input could potentially respond selectively to sequences of touches with different whiskers, effectively integrating over time. However, this applies to mice trained on a task involving active whisking. In awake animals with no prior training, under passive whisker stimulation in analogous conditions to those reported here, temporal integration in BC neurons is no greater than in anesthetized animals (A Pitas, M Molano, M Bale, and M Maravall personal communication). This suggests that temporal integration in naïve animals occurs only at higher stages of cortical processing. Future studies will need to test temporal integration in animals trained on tasks involving active whisking or passive (receptive) stimulation (Miyashita and Feldman 2013; Fassihi et al. 2014; Maravall and Diamond 2014).

A further important question for future work concerns the mechanisms that generate subsets of neurons with longer integration times. Neurons within a population could become sensitive to stimulus structure over particular timescales by having synaptic inputs with specific dynamical properties: synapses with distinct temporal filtering properties render their postsynaptic targets sensitive to particular features in the stimulus (Buonomano and Maass 2009; Carlson 2009; George et al. 2011; David and Shamma 2013; Diaz-Quesada et al. 2014; Chabrol et al. 2015). In layer 2/3, neurons that project to secondary somatosensory cortex have specific response characteristics favoring temporal integration by their targets, such that their responses summate over time (Yamashita et al. 2013); in assessing the mechanisms shaping temporal integration and sequence selectivity, it will be necessary to parse neurons by identity and projection pattern.

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Notes

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