Variable temporal integration of stimulus patterns in the mouse barrel cortex

Article (Accepted Version)

Cerebral Cortex, doi: 10.1093/cercor/bhw006

Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006

First published 1 February 2016

Variable temporal integration of stimulus patterns in the mouse barrel cortex

Anna Pitas[1,3,*], Ana Lía Albarracín[1,*,†], Manuel Molano-Mazón[1,2,*], and Miguel Maravall[1,3,#]

[1] Instituto de Neurociencias de Alicante, CSIC and Universidad Miguel Hernández, Avda. Ramón y Cajal s/n, Campus de San Juan, 03550 Sant Joan d'Alacant, Spain

[2] Laboratory of Neural Computation, Istituto Italiano di Tecnologia Rovereto, 38068 Rovereto, Italy

[3] Sussex Neuroscience, School of Life Sciences, University of Sussex, Brighton, United Kingdom

* These authors contributed equally.

[†] Present address: Laboratorio de Medios e Interfases, Departamento de Bioingeniería, Universidad Nacional de Tucumán - Consejo Superior de Investigaciones Científicas y Técnicas, Tucumán, Argentina

[#] Corresponding author

Keywords: Cell-attached; In vivo; Sensory coding; Somatosensory; Vibrissae

Running title: Emergent temporal integration in barrel cortex

Number of pages: 17
Number of figures and tables: 2 figures, 0 tables

Word Counts:
Abstract: 182
Introduction: 129
Discussion: 1191
Total (abstract, introduction, materials and methods, results, discussion, references, and figure legends): 5342

Cerebral Cortex, doi: 10.1093/cercor/bhw006

Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006

First published 1 February 2016

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 inter-stimulus 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, i.e. 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.

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; Maravall and Diamond 2014; Fassihi et al. 2015); 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

Cerebral Cortex, doi: 10.1093/cercor/bhw006

Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006

First published 1 February 2016

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, SD 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 37ºC 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 (L 3 mm, AP 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 MgCl2, 4 Na2-ATP, 3 Na-ascorbate, and 0.4 Na2-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

Cerebral Cortex, doi: 10.1093/cercor/bhw006
Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006
First published 1 February 2016

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 ± SEM; n = 16 neurons, n = 10 mice).

For stimulation, three 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 LED-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 ~ 40 mm/s. Similarly, angular velocity was approximately 7900 °/s (maximum), ~ 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 (approx. 1500 °/s; (Bagdasarian et al. 2013) and well below the highest values recorded during high-speed exploration (median, 6600 °/s;

Cerebral Cortex, doi: 10.1093/cercor/bhw006
Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006
First published 1 February 2016

maximum > 55000 °/s; (Bale et al. 2015). This range of stimulation intensities was appropriate for reliably driving responses, but unlikely to saturate primary afferents.

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, i.e. around 400 stimulus presentations.

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

Cerebral Cortex, doi: 10.1093/cercor/bhw006

Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006

First published 1 February 2016

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 inter-deflection 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:

$$I(\{interv\},\{resp\}) = S[P(interv)] - \sum_{\{resp\}} S[P(interv|resp)]$$

$$= -\sum_{\{interv\}} P(interv)\log_2 P(interv)$$

$$+\sum_{\{resp\}} P(resp) \sum_{\{interv\}} P(interv|resp)\log_2 P(interv|resp)$$

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.

Cerebral Cortex, doi: 10.1093/cercor/bhw006

Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006

First published 1 February 2016

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 PSTH peak for responsive neurons. The response to each deflection was classified as either spiking or non-spiking: within the 40 ms window, the number of occasions where neurons spiked more than once was negligible, and allowing for extra response categories (two spikes, three 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 (non-conditional) 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 to 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 data set if information in the true stimulus-response relationship was > 2 orders of magnitude greater than this shuffled average. This approach to scoring responsiveness

Cerebral Cortex, doi: 10.1093/cercor/bhw006
Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006
First published 1 February 2016

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, n = 84 satisfied these criteria and were included in the final data set.

In addition to the information-based approach described above and in Results, 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 inter-deflection 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 & Methods). Neurons were included in the data set (n = 84) if they

Cerebral Cortex, doi: 10.1093/cercor/bhw006

Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006

First published 1 February 2016

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 to 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 data set, 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 ~ 0.2 (i.e. 20%) and above.

Cerebral Cortex, doi: 10.1093/cercor/bhw006

Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006

First published 1 February 2016

The above results were obtained considering the full range of presented intervals, 40-500 ms (see Materials & 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 & 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

Cerebral Cortex, doi: 10.1093/cercor/bhw006

Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006

First published 1 February 2016

shorter than ~ 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 ~ 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 ms.

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 ms. 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 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).

Cerebral Cortex, doi: 10.1093/cercor/bhw006

Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006

First published 1 February 2016

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 ~ 35 µm, see Materials & 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, magenta 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 ms – 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.

Cerebral Cortex, doi: 10.1093/cercor/bhw006
Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006
First published 1 February 2016

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 in order to arrive at a sensory discrimination choice (Fassihi *et al.* 2014; Guo et al. 2014; Fassihi *et al.* 2015). 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 ms and even s (Maravall et al. 2007; Lundstrom et al. 2010; Wang et al. 2010; Maravall and Diamond 2014; Ollerenshaw et al. 2014). However, that 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 ms (Maravall *et al.* 2007; Estebanez *et al.* 2012). Moreover, in one study involving rats carrying out a vibrotactile detection task, the animal's behaviour was consistent with weak temporal integration of the responses of BC neurons, over timescales limited to ~ 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.

Cerebral Cortex, doi: 10.1093/cercor/bhw006
Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006
First published 1 February 2016

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 to 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 ms) 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 ms 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 ~ 100 ms after the step occurred (Klampfl *et al.* 2012).

The present results were obtained for anaesthetized 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 (Pitas, Molano, Bale, and 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).

Cerebral Cortex, doi: 10.1093/cercor/bhw006

Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006

First published 1 February 2016

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.

Funding

This work was supported by the Spanish Ministry of Science and Innovation (BFU2011-23049, co-funded by the European Regional Development Fund), the Valencia Regional Government (ACOMP2010/199 and PROMETEO/2011/086), and the European Commission (FET Project VISUALISE FP7-600954).

Acknowledgements

The authors declare no competing financial interests. We are grateful to Michael Bale and Rasmus Petersen for critical reading of the manuscript.

Address correspondence to Miguel Maravall, School of Life Sciences, University of Sussex, Brighton BN1 9QG, United Kingdom. Email: m.maravall@sussex.ac.uk, phone: +44 7478 510519.

Cerebral Cortex, doi: 10.1093/cercor/bhw006

Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006

First published 1 February 2016

References

Bagdasarian K, Szwed M, Knutsen PM, Deutsch D, Derdikman D, Pietr M, Simony E, Ahissar E. 2013. Pre-neuronal morphological processing of object location by individual whiskers. Nat Neurosci 16:622-631.

Bale MR, Campagner D, Erskine A, Petersen RS. 2015. Microsecond-scale timing precision in rodent trigeminal primary afferents. J Neurosci 35:5935-5940.

Borst A, Haag J. 2001. Effects of mean firing on neural information rate. J Comput Neurosci 10:213-221.

Branco T, Clark BA, Hausser M. 2010. Dendritic discrimination of temporal input sequences in cortical neurons. Science 329:1671-1675.

Buonomano DV, Maass W. 2009. State-dependent computations: spatiotemporal processing in cortical networks. Nat Rev Neurosci 10:113-125.

Carlson BA. 2009. Temporal-pattern recognition by single neurons in a sensory pathway devoted to social communication behavior. J Neurosci 29:9417-9428.

Chabrol FP, Arenz A, Wiechert MT, Margrie TW, DiGregorio DA. 2015. Synaptic diversity enables temporal coding of coincident multisensory inputs in single neurons. Nat Neurosci 18:718-727.

Cover TM, Thomas JA. 2006. Elements of Information Theory, Second Edition: John Wiley & Sons.

David SV, Shamma SA. 2013. Integration over multiple timescales in primary auditory cortex. J Neurosci 33:19154-19166.

Diaz-Quesada M, Martini FJ, Ferrati G, Bureau I, Maravall M. 2014. Diverse thalamocortical short-term plasticity elicited by ongoing stimulation. J Neurosci 34.

Estebanez L, El Boustani S, Destexhe A, Shulz DE. 2012. Correlated input reveals coexisting coding schemes in a sensory cortex. Nat Neurosci 15:1691-1699.

Fairhall AL, Lewen GD, Bialek W, de Ruyter Van Steveninck RR. 2001. Efficiency and ambiguity in an adaptive neural code. Nature 412:787-792.

Fassihi A, Akrami A, Esmaeili V, Diamond ME. 2014. Tactile perception and working memory in rats and humans. Proc Natl Acad Sci U S A 111:2331-2336.

Fassihi A, Akrami A, Schönfelder VH, Diamond ME. 2015. Temporal integration in a vibrotactile delayed comparison task: From sensory coding to decision in humans and rats. In. Society for Neuroscience Meeting. Chicago, IL.

Feldmeyer D, Brecht M, Helmchen F, Petersen CC, Poulet JF, Staiger JF, Luhmann HJ, Schwarz C. 2013. Barrel cortex function. Prog Neurobiol 103:3-27.

George AA, Lyons-Warren AM, Ma X, Carlson BA. 2011. A diversity of synaptic filters are created by temporal summation of excitation and inhibition. J Neurosci 31:14721-14734.

Guo ZV, Li N, Huber D, Ophir E, Gutnisky D, Ting JT, Feng G, Svoboda K. 2014. Flow of cortical activity underlying a tactile decision in mice. Neuron 81:179-194.

Harris KD, Mrsic-Flogel TD. 2013. Cortical connectivity and sensory coding. Nature 503:51-58.

Hires SA, Gutnisky DA, Yu J, O'Connor DH, Svoboda K. 2015. Low-noise encoding of active touch by layer 4 in the somatosensory cortex. Elife 4.

Khatri V, Bermejo R, Brumberg JC, Keller A, Zeigler HP. 2009. Whisking in air: encoding of kinematics by trigeminal ganglion neurons in awake rats. J Neurophysiol 101:1836-1846.

Klampfl S, David SV, Yin P, Shamma SA, Maass W. 2012. A quantitative analysis of information about past and present stimuli encoded by spikes of A1 neurons. J Neurophysiol 108:1366-1380.

Cerebral Cortex, doi: 10.1093/cercor/bhw006

Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006

First published 1 February 2016

Kwegyir-Afful EE, Marella S, Simons DJ. 2008. Response properties of mouse trigeminal ganglion neurons. Somatosens Mot Res 25:209-221.

Lefort S, Tomm C, Floyd Sarria JC, Petersen CC. 2009. The excitatory neuronal network of the C2 barrel column in mouse primary somatosensory cortex. Neuron 61:301-316.

Lundstrom BN, Fairhall AL, Maravall M. 2010. Multiple timescale encoding of slowly varying whisker stimulus envelope in cortical and thalamic neurons in vivo. J Neurosci 30:5071-5077.

Magri C, Whittingstall K, Singh V, Logothetis NK, Panzeri S. 2009. A toolbox for the fast information analysis of multiple-site LFP, EEG and spike train recordings. BMC neuroscience 10:81.

Maravall M, Diamond ME. 2014. Algorithms of whisker-mediated touch perception. Curr Opin Neurobiol 25:176-186.

Maravall M, Petersen RS, Fairhall AL, Arabzadeh E, Diamond ME. 2007. Shifts in coding properties and maintenance of information transmission during adaptation in barrel cortex. PLoS Biol 5:e19.

Miyashita T, Feldman DE. 2013. Behavioral detection of passive whisker stimuli requires somatosensory cortex. Cereb Cortex 23:1655-1662.

Nikolic D, Hausler S, Singer W, Maass W. 2009. Distributed fading memory for stimulus properties in the primary visual cortex. PLoS Biol 7:e1000260.

Ollerenshaw DR, Zheng HJ, Millard DC, Wang Q, Stanley GB. 2014. The adaptive trade-off between detection and discrimination in cortical representations and behavior. Neuron 81:1152-1164.

Panzeri S, Petersen RS, Schultz SR, Lebedev M, Diamond ME. 2001. The role of spike timing in the coding of stimulus location in rat somatosensory cortex. Neuron 29:769-777.

Panzeri S, Senatore R, Montemurro MA, Petersen RS. 2007. Correcting for the sampling bias problem in spike train information measures. J Neurophysiol 98:1064-1072.

Panzeri S, Treves A. 1996. Analytical estimates of limited sampling biases in different information measures. . Network: Computation in Neural Systems 7:87-107.

Petersen RS, Brambilla M, Bale MR, Alenda A, Panzeri S, Montemurro MA, Maravall M. 2008. Diverse and temporally precise kinetic feature selectivity in the VPm thalamic nucleus. Neuron 60:890-903.

Petreanu L, Gutnisky DA, Huber D, Xu NL, O'Connor DH, Tian L, Looger L, Svoboda K. 2012. Activity in motor-sensory projections reveals distributed coding in somatosensation. Nature 489:299-303.

Pinault D. 1996. A novel single-cell staining procedure performed in vivo under electrophysiological control: morpho-functional features of juxtacellularly labeled thalamic cells and other central neurons with biocytin or Neurobiotin. J Neurosci Methods 65:113-136.

Segundo JP, Moore GP, Stensaas LJ, Bullock TH. 1963. Sensitivity of Neurones in Aplysia to Temporal Pattern of Arriving Impulses. The Journal of experimental biology 40:643-667.

Shannon C. 1948. A mathematical theory of communication. Bell Sys Tech J 27:379-423,623-656.

Stuttgen MC, Schwarz C. 2010. Integration of vibrotactile signals for whisker-related perception in rats is governed by short time constants: comparison of neurometric and psychometric detection performance. J Neurosci 30:2060-2069.

Tripathy SJ, Padmanabhan K, Gerkin RC, Urban NN. 2013. Intermediate intrinsic diversity enhances neural population coding. Proc Natl Acad Sci U S A 110:8248-8253.

Wang Q, Webber RM, Stanley GB. 2010. Thalamic synchrony and the adaptive gating of information flow to cortex. Nat Neurosci 13:1534-1541.

Yamashita T, Pala A, Pedrido L, Kremer Y, Welker E, Petersen CC. 2013. Membrane potential dynamics of neocortical projection neurons driving target-specific signals. Neuron 80:1477-1490.

Cerebral Cortex, doi: 10.1093/cercor/bhw006

Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006

First published 1 February 2016

455 Zuo Y, Safaai H, Notaro G, Mazzoni A, Panzeri S, Diamond ME. 2015. Complementary
456 contributions of spike timing and spike rate to perceptual decisions in rat S1 and S2 cortex. Curr
457 Biol 25:357-363.

458

Cerebral Cortex, doi: 10.1093/cercor/bhw006

Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006

First published 1 February 2016

Figures

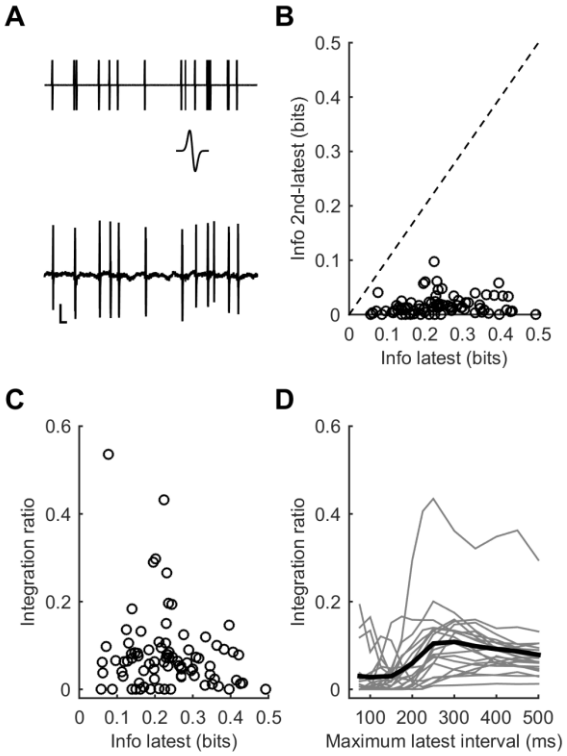

Fig. 1: Information carried about the latest and second-latest interval. A. Top, temporally isolated whisker deflections were presented at pseudorandom intervals (range: 40-500 ms). Inset shows a single whisker deflection. Bottom, example cell-attached recording during presentation of stimulus. Neuronal 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 inter-stimulus 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

Cerebral Cortex, doi: 10.1093/cercor/bhw006

Website for version of record:
http://cercor.oxfordjournals.org/content/early/2016/02/01/cercor.bhw006

First published 1 February 2016

computed while restricting the maximum allowed duration of the latest interval. n = 20 neurons. Thin gray lines: individual neurons; thick black line: population mean.

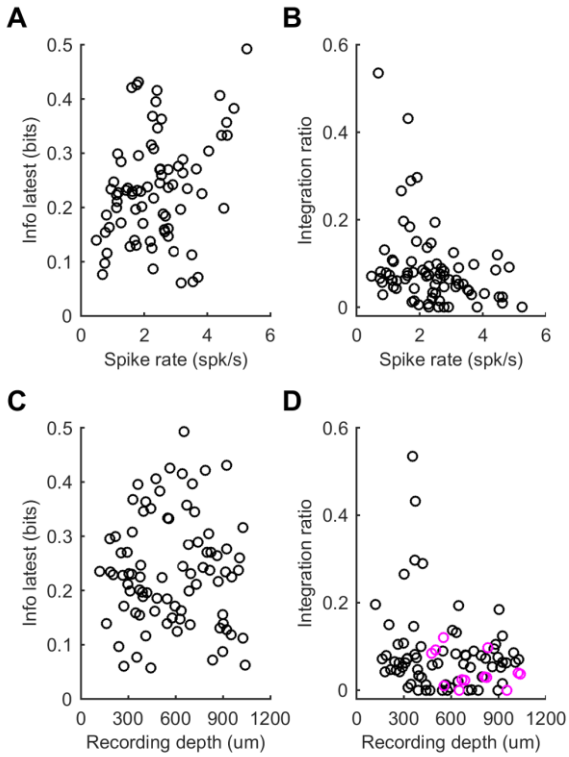

Fig. 2: Analysis of information as a function of response spike rate and recording depth. **A.** Information about latest interval versus mean spike rate over the entire duration of stimulation. More-active neurons conveyed greater information. Each symbol is one neuron, n = 77. **B.** Integration ratio 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 ~ 0.2. Symbols in magenta 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.