Microsecond-Scale Timing Precision in Rodent Trigeminal Primary Afferents

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Communication in the nervous system occurs by spikes: the timing precision with which spikes are fired is a fundamental limit on neural information processing. In sensory systems, spike-timing precision is constrained by first-order neurons. We found that spike-timing precision of trigeminal primary afferents in rats and mice is limited both by stimulus speed and by electrophysiological sampling rate. High-speed video of behaving mice revealed whisker velocities of at least 17,000°/s, so we delivered an ultrafast “ping” (>50,000°/s) to single whiskers and sampled primary afferent activity at 500 kHz. Median spike jitter was 17.4 μ s; 29% of neurons had spike jitter < 10 μ s. These results indicate that the input stage of the trigeminal pathway has extraordinary spike-timing precision and very high potential information capacity. This timing precision ranks among the highest in biology.

Key words: neural coding; trigeminal ganglion; vibrissa; whisker

Introduction

Sensory systems have long been known to convey information by the number of spikes a neuron fires within a time window of order 0.1 s or more (“spike count coding”; Adrian, 1926). However, more recently, it has been established that substantial additional information is available in the timing pattern of spikes (“temporal coding”; Optican and Richmond, 1987; Panzeri et al., 2001; Di Lorenzo and Victor, 2003; Johansson and Birznieks, 2004; Golisch and Meister, 2008; Shusterman et al., 2011). The significance of a timing-dependent code is that it can have a much higher capacity for transmitting information than a spike count code (MacKay and McCulloch, 1952; Petersen, 2013). The capacity is limited by the timing precision with which spikes are fired. This precision is usefully quantified by measuring “jitter”: the trial-to-trial variability in the spike times evoked by a given stimulus. Hence, in any sensory system, it is important to determine the limits of spike-timing jitter.

The original motivation for the present study was, as detailed below, that we discovered that spike-timing precision of trigeminal primary afferents is underestimated under standard experi-

mental conditions. To determine the true limit of spike-timing precision, we recorded the responses of afferents at high sampling rates (100–500 kHz) in response to high-speed whisker deflections, motivated by measurements of whisker speeds in behaving mice. Under our optimized conditions, we found jitter to be in the microsecond range. Our results indicate that the input stage of the trigeminal pathway may permit the trigeminal system to employ exceptionally high-resolution spike-timing codes that may be significant in certain whisker-dependent behaviors.

Materials and Methods

Electrophysiology

All experiments were conducted in accordance with international, UK Home Office, and institutional standards for the care and use of animals in research. Adult male Wistar rats and C57BL/6 mice were anesthetized (two rats with urethane at 1.5 g/kg body weight; one rat and both mice with 1.2–1.5% isoflurane) and prepared for electrophysiological recording as previously reported (Bale and Petersen, 2009; Bale et al., 2013). Briefly, a 2 mm wide square craniotomy was made (in rat, centered 1.5 mm posterior to bregma and 2 mm lateral; in mice, 0 mm posterior and 1.6 mm lateral). The dura was reflected and a tungsten microelectrode inserted vertically through the cerebrium into the trigeminal ganglion. For data recorded at 100–500 kHz, extracellular signals were amplified and bandpass filtered (300–10,000 Hz; NPI), digitized (CED), and continuously stored to hard disk for off-line analysis. Additional data from the study of Bale et al. (2013), recorded at standard sampling rate of 24.4 kHz and bandpass filtered (300–3000 kHz; Tucker-Davis Technologies), are reported for comparison (Fig. 1B–D; *N* = 8 adult male Wistar rats; recording methods otherwise identical).

Whisker stimulation

The presence of a whisker-responsive unit was detected by continual, manual deflection of the whiskers with a hand-held probe, as the microelectrode was lowered. The mean recording site coordinates in rat were 1.5 mm (SD 0.4 mm) posterior to bregma, 2.2 mm (SD 0.3 mm) lateral, and 10.8 mm (SD 0.2 mm) vertically below the pial surface. In mouse, the mean site coordinates were 0.1 mm (SD 0.1 mm) posterior to bregma, 1.5

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mm (SD 0.2 mm) lateral, and 6.6 mm (SD 0.3 mm) vertically below the pial surface. Once a well isolated unit was identified, its principal whisker was determined by manual deflection of individual whiskers. All whiskers were cut to 5 mm from the skin and the principal whisker was inserted into a snugly fitting plastic tube attached to a piezoelectric actuator (P/N PL127.10; Physik Instrumente) 3 mm from the face.

We used two stimulus protocols in this study. The first was a 1–10 s white noise stimulus, low-pass filtered by convolution with a Gaussian (SD 1.6 ms). This stimulus was delivered in both dorsoventral and rostrocaudal directions. We selected the orientation that evoked the most spikes for further analysis. Faithful delivery of the stimulus was confirmed using a phototransistor circuit (Storchi et al., 2012). The aim of the second “ping” protocol was to achieve a transient actuator movement of high velocity. To this end, a 200 ms duration voltage step was delivered to the piezoelectric actuator (without low-pass filtering). This was followed 400 ms later by an identical voltage step in the opposite direction. This stimulus cycle was repeated at least 250 times. We measured the resulting movement of the actuator optically (Fig. 3A). The actuator movement consisted of an initial ramp phase, where the actuator moved rapidly at high velocity (55,700°/s) followed by a complex pattern of motion, due to the high-frequency power in the voltage step driving the resonant modes of the actuator. Here, we focused only on the first spike after the voltage step, evoked by the high-velocity ramp (Fig. 3A, time 0 ms).

Data analysis

Single units were isolated from the extracellular recordings as previously described, by thresholding and clustering in the space of three to five principal components using a mixture model (Bale and Petersen, 2009). Only units exhibiting a clear absolute refractory period were accepted. Spike shapes recorded at different sampling rates were similar.

We defined “spike-time jitter” as the SD of spike times associated with a given stimulus-evoked “event.” The first step in jitter estimation was therefore to parse the neuronal response into events. Our ping protocol evoked a clearly defined event, starting at the onset of the voltage step. Our white noise protocol usually evoked a response consisting of multiple, temporally isolated firing events, the pattern of which was neuron dependent (Fig. 1B–E). Jitter estimation was thus different in the two cases.

Jitter analysis for ping protocol. For a given unit, we calculated the time of the first spike after the voltage step on each trial, and estimated spike-time jitter as the SD of these spike times across trials.

Jitter analysis for white noise protocol. Visual inspection of the rasters confirmed, consistent with previous studies, that jitter was submillisecond (Arabzadeh et al., 2005; Storchi et al., 2012; Bale et al., 2013). We quantified jitter as previously described (Montemurro et al., 2007). For each unit, we computed the peristimulus time histogram (PSTH; binned at the sampling rate) and smoothed it by convolution with a 1.6 ms Gaussian (to match the smoothing timescale of the stimulus). We located the peaks of the smoothed PSTH and, to focus on reliable events, selected those peaks that were at least a fraction ($f = 0.5$) of the highest for that unit. For each such peak, we extracted the spike times, on each trial, in a 1 ms window centered on the peak time. We collated all these peak-relative spike times, for each unit, across peaks and computed their SD (jitter). To check the robustness of our jitter estimates to the smoothing parameter, we repeated the calculation using a smaller Gaussian kernel (0.8 ms). With the original (1.6 ms) kernel, median jitter across units (mice and rats combined) recorded at 100 kHz was 192.3 ms, and with 0.8 ms kernel, jitter was 181.3 ms. Thus a reduction in kernel width of 50% altered jitter by only 5.7%. Our selection of a 1 ms second hard window was verified by inspection of PSTH autocorrelations (Butts et al., 2007).

To test whether there was a relationship between jitter and stimulus velocity/position, we considered units that evoked >3 peaks ($n = 41$). For each such unit, we calculated the jitter for each individual peak (SD across trials) and both the peak absolute value of the stimulus velocity, and the peak absolute value of the stimulus position, τ milliseconds before the peak. We then computed the Pearson correlation coefficient between jitter and prepeak speed/position. This analysis was repeated for τ in the range of 0–2 ms with step size 10 μ s (100 kHz sampling rate) and the correlation coefficient with maximum absolute value retained in each case.

Figure 1. Effect of sampling rate and stimulus velocity/position on spike-timing jitter. **A**, Excerpt of white noise stimulus. **B**, Spike time raster plot, from a rat trigeminal primary afferent unit sampled at 24.4 kHz, evoked by white noise whisker stimulation. **C**, **D**, Expanded view of timing of two firing events (red and blue in **B**), showing discretization of spike times due to the sampling interval (41 μ s). **E**, Raster plot, for an example rat unit, evoked by white noise stimulation, sampled at 100 kHz. **F**, Expanded view of **E** for one firing event, showing spike times sampled at 100 kHz (black small dots) and downsampled to 25 kHz (gray big dots). **G**, Pooled peak PSTH for the example unit in **E** recorded at 100 kHz (black) and downsampled to 25 kHz (gray). **H**, **I**, Scatter plots of spike-timing jitter for rat and mouse units, respectively, recorded at 100 kHz sampling rate (black), compared with that of the same data downsampled to 25 kHz. **J**, Scatter plot of whisker speed versus jitter for an example mouse unit.

Figure 2. Velocity of whisker motion during stick-slip events. **A**, Whisker motion recorded by high-speed video (4800 fps) while a mouse explored a pole before (top), during (middle), and after (bottom) a slip event, with whisker tracker solutions for one whisker overlaid (cyan dots). **B**, Time course of whisker angle for the slip event illustrated in **A** (cyan arrowheads correspond to the frames of **A**). **C**, Time course of whisker speed for the slip event in **A**. **D**, Histogram of peak whisker angular speed in each measured slip event.

Whisking behavior and whisker tracking

Whisking behavior was measured from head-fixed mice according to the method of O'Connor et al. (2010). Mice ($N = 2$, C57BL/6 adult males) were implanted with titanium head posts under isoflurane (1.5–2%) anesthesia. After recovery (7 d), a mouse was put in the behavioral apparatus with its head immobilized by attachment of the head post. The whiskers were illuminated from below using a high-power infrared LED array (940 nm), delivered via a condensing lens and ground glass diffuser, and imaged using a high-speed camera (Mikrotron; 4800 frames/s, 0.21 ms exposure time) through a telecentric lens (Fig. 2A).

We presented a small metal pole (1.6 mm diameter) rapidly into the mouse's whisker field, 5 mm from the face, using a solenoid-controlled pneumatic linear slider. Its anterior–posterior position was controlled by a stepper motor. The apparatus was controlled by custom software running on a real-time processor (Tucker-Davies Technologies). To facilitate tracking, we trimmed all whiskers except rows C and D, to the level of the face fur.

To extract kinematic parameters from whiskers, we developed a custom whisker tracker (WhiskerMan). The tracker differs from existing programs (Perkon et al., 2011; Clack et al., 2012) in that it is designed to extract kinematic parameters of an individual whisker near the whisker base, from mice where multiple rows of whiskers are intact. For this

purpose, it is sufficient to capture the shape of a portion of the whisker near its base. This portion, proximal to the zone of object contact, can be accurately approximated by a quadratic curve (Quist et al., 2011). This significantly facilitates tracking, by limiting the number of free parameters. We parameterized whisker shape using quadratic Bezier plane curves $\mathbf{r}(t, s) = [r_x(t, s), r_y(t, s)]$. Here, x, y are the horizontal and vertical coordinates of the image; $s = [0, \dots, 1]$ parameterizes (x, y) location along the curve; and t is time. For each image frame, the Bezier curve was fitted to the image by a local, gradient-based search. Tracking errors due to whisker crossover events were substantially avoided by using knowledge of whisker shape in previous frames. This was first implemented by setting the initial conditions of the curve, in a given frame, by extrapolation from the solution from the previous frame, assuming constant angular velocity, and second, by constraining frame-to-frame changes in whisker shape/position to be small. The cost function was a sum of two terms. The first term was the line integral of the image over $\mathbf{r}(t, s)$ with respect to s , in the range $s = [0, 1]$. The second (regularizing) term was the Euclidean distance between $\mathbf{r}(t, s)$ and its initial condition for frame t , integrated over s . The location of the base of the whisker was defined as the intersection between $\mathbf{r}(t, s)$ (extrapolated to negative s) and the local contour of the snout. To localize the snout contour in the vicinity of the base of the tracked whisker, we applied to the image frame first a median filter (range 5 pixels) and then convolved with a Gaussian (SD = 6 pixels). The gradient of the filtered image was computed in the direction of the whisker base angle and the local snout contour estimated by computing the minimum of this gradient at each value of x . The whisker angle was measured as the tangent to $\mathbf{r}(t, s)$ at the base.

Results

Limitations of spike-timing jitter estimates

To make accurate measurements of spike-timing jitter, it is essential to apply the exact same stimulus a number of times and to eliminate uncontrolled stimulus variation. To this end, we recorded single-unit activity extracellularly from the trigeminal ganglion of anesthetized rats/mice, in response to mechanical stimulation of the whiskers. We presented 50 repetitions of a 10 s sequence of low-pass filtered white noise (Fig. 1A), identical on every trial, in the rostrocaudal direction (eight rats, 34 single units). Consistent with previous reports (Jones et al., 2004; Arabzadeh et al., 2005; Bale et al., 2013), the neuronal response consisted of temporally isolated episodes of transient, high firing rate (Fig. 1B). Each episode was typically highly repeatable and precisely timed. On inspection of the responses, we observed instances where the trial-to-trial variability in spike timing was so small that the digitizing effect of the 24.4 kHz sampling rate of the data acquisition system appeared to contribute to the jitter (Fig. 1C,D). To test this, we repeated the experiment, using a data acquisition system capable of sampling at 100 kHz (three rats and two mice; rat $n = 31$ single units, mice $n = 15$; Fig. 1E). To quantify spike-timing precision, we then

computed the jitter of the response (SD of trial-to-trial spike-timing differences; see Materials and Methods). This was done both for spikes sampled at 100 kHz and for the same data downsampled to 25 kHz (Fig. 1*F, G*). For the example rat unit of Figure 1*E*, jitter was 107 μ s at 100 kHz, but this increased to 182 μ s at 25 kHz (Fig. 1*G*). At the population level, downsampling significantly increased jitter in both rats and mice (Fig. 1*H, I*). In rats, median jitter increased from 148 μ s [interquartile range (IQR) 108–189 μ s] to 182 μ s (IQR 138–303 μ s; $p = 9 \times 10^{-6}$, signed ranks). In mice, median jitter increased from 217 to 276 μ s ($p = 3 \times 10^{-4}$). Downsampled spike times produced inflated estimates in 40/46 units. These results indicate that standard electrophysiological sampling rates (up to ~ 25 kHz) underestimate the spike-timing precision of trigeminal primary afferents.

A second factor that might limit spike-timing precision is the strength with which a sensory stimulus drives the neuronal response (Bryant and Segundo, 1976; Desbordes et al., 2008). Since first-order neurons in the whisker system are particularly sensitive to whisker speed (Shoykhet et al., 2000; Lottem and Azouz, 2011; Bale et al., 2013), we tested whether higher whisker angular speed correlated with lower spike-timing jitter. Our filtered white noise stimulus contained a range of whisker speeds (IQR 291–1072°/s; 3 mm from the face). We found a significant negative correlation between the jitter of a given response episode and preceding whisker speed, illustrated by the example mouse unit shown in Figure 1*J* (Pearson correlation coefficient $\rho = -0.67$). This was typical (median $\rho = -0.58$). There was a significant, but smaller, correlation with jitter and peak whisker position (median across units, $\rho = -0.32$). Since whisker speeds in behaving rodents are known to reach at least 5000°/s (Ritt et al., 2008; Wolfe et al., 2008; O'Connor et al., 2010), this result indicates that standard, smoothed mechanical stimuli may underestimate the spike-timing precision of trigeminal primary afferents.

Upper limits of whisker speed during object exploration

To find an upper bound on naturally occurring whisker velocities, we made high-speed video recordings (4800 frames/s) of awake, head-fixed mice whisking against a metal pole ($n = 2$; Fig. 2*A*). There were frequent “stick-slip” events where a whisker would first stick against the pole and then slip off at high velocity (Fig. 2*A–C*; Ritt et al., 2008). To determine the speed of these events, whiskers were first tracked using custom software, resulting in time series of whisker angle (azimuth) measurements (Fig. 2*B*; see Materials and Methods). All whisker tracking solutions were verified by human observation. For each slip ($n = 274$: 177 slips for mouse 1 and 97 slips for mouse 2), we computed the peak angular speed at the base of the whisker. An example slip event is illustrated in Figure 2, *A–C*, which had a peak speed of 19,800°/s. Although the median peak speed for all slip-stick events was 6600°/s (Fig. 2*D*), a subset of events was substantially faster: the 95th percentile was 16,800°/s and the fastest 55,600°/s.

Microsecond-scale timing precision of trigeminal primary afferents

The preceding results indicate that, to determine the limit of spike-timing precision for trigeminal primary afferents, it is necessary both to deliver whisker stimuli with high velocity and to sample the electrophysiological signal at a high rate. To this end, we delivered a mechanical whisker ping stimulus whose initial velocity was 55,700°/s at 3 mm from the face (Fig. 3*A*) and recorded the responses of primary afferents, in anesthetized rats and mice, sampled at 500 kHz (Fig. 3*B–E*). Spikes were well discriminated both from a transient stimulus artifact and from

Figure 3. Microsecond spike-timing precision. **A**, Motion of the piezoelectric actuator in response to a voltage step (“ping stimulus”), measured optically: 1000 repetitions overlaid (gray) with the mean (black). **B**, Extracellular potentials evoked by 250 repetitions of the ping stimulus, applied to the principal whisker (PW; in this case, D2) of a typical mouse unit. The stimulus generates a transient artifact ($t = 0$ ms), clearly differentiated from the unit-spiking response, starting at $t = 1$ ms. **C**, Response of the same unit as in **B** to the ping stimulus delivered to an adjacent whisker (AW; E2). Since primary whisker afferents respond only to deflection of a single whisker, this isolates the stimulus artifact from neural activity. **D**, Extracellular potential recorded at 500 kHz sampling rate for a different example mouse unit, following ping stimulus at time 0. The first spike post-stimulus onset on each trial is highlighted by a red dot. **E**, Extracted spike waveforms for the unit in **D**. **F**, Extracellular potential recorded at 500 kHz sampling rate for all trials of the mouse unit in **D**. First spike post-stimulus onset on each trial highlighted by a red dot. **G**, Histogram of spike-time jitter for all 500 kHz single units. Inset shows expanded view for range 0–20 μ s. **H**, Jitter as a function of (downsampled) sampling rate for the six units with lowest jitter (gray) and the median of all units (black).

background noise (Fig. 3*B,C*). For the example unit in Figure 3, *D–F*, the spike-timing jitter of the first spike post-stimulus onset was 14.7 μ s. Such precise responses were common in both rats ($n = 8$; median 15.7 μ s; IQR 10.3–78.4 μ s) and mice ($n = 13$; median 32.5 μ s; IQR 6.3–55.6 μ s). With data from both rats and mice combined, median spike-timing jitter was 17.4 μ s (IQR 8.4–59.6 μ s). Ninety percent (19/21) of primary afferent units had jitter <100 μ s (Fig. 3*G*); 29% (6/21) had jitter < 10 μ s. The most precise units had jitter of 5.1 and 5.3 μ s, in rats and mice, respectively. Finally, to check whether 500 kHz sampling rate was sufficient to accurately estimate jitter, we subsampled the 500 kHz data in the range 10–500 kHz and repeated the jitter analysis at each subsampled rate. We found that the estimated jitter reached its asymptotic value at $\sim$ 100 kHz, with no evidence for residual underestimation of jitter at 500 kHz (Fig. 3*H*).

Discussion

The aim of this study was to determine the limit to spike-timing precision in the whisker system. To this end, we measured the spike-timing jitter of trigeminal primary afferents in both rats and mice. We found that jitter estimates were biased upward both by typical electrophysiological sampling rates (25 kHz) and by temporally smoothed whisker deflections. When mice whisked against a pole, we found that whisker velocities reached 16,800°/s for the 5% of fastest stick-slip events. To determine the true timing precision limit, we delivered ultrafast whisker deflections (55,700°/s) at high sampling rate (500 kHz). Our main result was that, under these optimized conditions, jitter was remarkably low (minimum 5 μ s; median 16 μ s for rats and 33 μ s for mice).

Our results extend previous reports of high spike-timing precision in the whisker system. Depending on which neurons are studied, on how whiskers are stimulated, and on how the timing precision is quantified, measurements of precision vary from 0.1–10 ms (Panzeri et al., 2001; Petersen et al., 2001; Jones et al., 2004; Arabzadeh et al., 2005; Montemurro et al., 2007; Jadhav et al., 2009; Lottem and Azouz, 2011; Bale et al., 2013; O'Connor et al., 2013). Our results show that the true precision is an order of magnitude higher than the highest previous estimates. Under standard experimental conditions (24.4 kHz sampling rate; speed IQR 291–1072°/s), we found jitter values of 0.15 ms in rat, which agrees with previous reports (Jones et al., 2004; Arabzadeh et al., 2005). We attribute microsecond jitter to our combined use of high sampling rates (100–500 kHz) and high whisker stimulation velocity (55,600°/s). It is possible that even higher spike-timing precision might be measured with higher velocities. However, since 55,600°/s was at the extreme end of the slip speeds that we measured behaviorally, and since whisker speeds of freely moving rats and head-fixed rats are in the same range (Khatri et al., 2009), it is unlikely that higher velocities are ecologically relevant.

Spike-timing precision is limited by receptor transduction mechanisms and therefore differs greatly across sensory modalities. Where transduction depends on a chain of biochemical signaling, as in the visual and chemical senses, jitter is relatively high (Vickers et al., 2001; Pillow et al., 2005; Shusterman et al., 2011). Where transduction is a direct consequence of forces acting on the receptor membrane, as in the mechanosensory, including auditory, and electrosensory modalities, jitter can be much lower. In echolocating bats, spike jitter is reported as low as 20–30 μ s (Suga and Schlegel, 1973; Covey and Casseday, 1991). In the barn owl, microsecond phase delays underpin sound localization (Wagner et al., 2005; Carr and Macleod, 2010; Kuokkanen et al., 2013). In weakly electric fish, primary electrosensory afferents can detect the time disparities of interfering electrical organ dis-

charge signals on a microsecond timescale (Bullock et al., 1972; Carr et al., 1986).

What might be the functional benefit of precise spike timing for whisker somatosensation? Although spike count coding is likely to account for some whisker-dependent tasks, there are other tasks where precise spike timing is likely to play a major role (Diamond et al., 2008). Performance in rough–smooth texture discrimination and some types of object localization can be accounted for by spike count codes (von Heimendahl et al., 2007; O'Connor et al., 2013; Safaai et al., 2013). However, “rough–rough” discrimination between similar textures cannot (Arabzadeh et al., 2006; von Heimendahl et al., 2007). Whisker–texture contact evokes sequences of primary afferent spikes whose precise timing is highly reproducible (Arabzadeh et al., 2005) and spike timing conveys more information about the distinction between similar textures than does the spike count (Arabzadeh et al., 2006). Since the time at which whiskers first contact an object is variable, the relative timing between spikes may be key (Ahissar and Knutsen, 2008; Maravall and Diamond, 2014). Spike-timing codes may also be important for tasks that depend on the relative timing of multiple whisker contacts. Knutsen et al. (2006) trained rats to discriminate anterior–posterior offsets in the location of poles presented to the left and right whiskers, and found that rats could discriminate offsets of only 1°. We reanalyzed the whisker-tracking data from this study and found that angular whisker speeds before pole contact are variable with median 0.37°/ms (95th percentile 1.52°/ms), indicating that spike-timing differences in the millisecond range may be informative. In general, the more precise the spike timing (the lower the jitter), the greater the capacity of a sensory system to represent differences between stimuli (Petersen, 2013). The significance of precise spike timing might be that it allows the early whisker system to represent a larger set of distinct environmental events than would be possible by a time-averaged, spike count code.

In conclusion, using high sampling rate electrophysiology and ultrafast whisker deflections that occur in the awake whisking rodent, we have estimated the spike-timing precision of trigeminal primary afferents to be on the microsecond timescale; joining a select class of neurons in the animal kingdom.

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