Parallel coding schemes of whisker velocity in the rat’s somatosensory system

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Lottem E, Gugig E, Azouz R. Parallel coding schemes of whisker velocity in the rat’s somatosensory system. J Neurophysiol 113: 1784–1799, 2015. First published December 31, 2014; doi:10.1152/jn.00485.2014.—The function of rodents’ whisker somatosensory system is to transform tactile cues, in the form of vibrissa vibrations, into neuronal responses. It is well established that rodents can detect numerous tactile stimuli and tell them apart. However, the transformation of tactile stimuli obtained through whisker movements to neuronal responses is not well-understood. Here we examine the role of whisker velocity in tactile information transmission and its coding mechanisms. We show that in anesthetized rats, whisker velocity is related to the radial distance of the object contacted and its own velocity. Whisker velocity is accurately and reliably coded in first-order neurons in parallel, by both the relative time interval between velocity-independent first spike latency of rapidly adapting neurons and velocity-dependent first spike latency of slowly adapting neurons. At the same time, whisker velocity is also coded, although less robustly, by the firing rates of slowly adapting neurons. Comparing first- and second-order neurons, we find similar decoding efficiencies for whisker velocity using either temporal or rate-based methods. Both coding schemes are sufficiently robust and hardly affected by neuronal noise. Our results suggest that whisker kinematic variables are coded by two parallel coding schemes and are disseminated in a similar way through various brain stem nuclei to multiple brain areas.

Our inferences about the brain mechanisms underlying perception rely on the mechanisms that make it possible for the brain to “reconstruct” a stimulus from information contained in the concerted activation of ensembles of neurons. A significant step toward uncovering the general principles underlying this process and its relevance to sensory perception would be made if the correspondence between neural ensemble activity and sensory stimuli could be determined. In the rodent whisker somatosensory system, tactile information is acquired by an array of whiskers on the facial pad. Using their whiskers, rodents can locate and distinguish objects in their immediate sensory environment and reliably detect small differences in surface texture (Diamond 2010; Diamond et al. 2008; Jadhav and Feldman 2010; Kleinfeld and Deschenes 2011; Mehta et al. 2007; Petreanu et al. 2012; Szwed et al. 2003; Xu et al. 2012). While it is well-established that interactions between whiskers and objects generate a complex pattern of whisker vibrations (Adibi and Arabzadeh 2011; Bagdasarian et al. 2013; Lottem and Azouz 2009; Pammel et al. 2013; Quist and Hartmann 2012; Wolfe et al. 2008), it is insufficiently understood which of the physical features of these vibrations are actually encoded, and what is the coding paradigm which serves as a basis for tactile perception.

Several features of whiskers’ vibrations have been proposed, each of which could underlie the perception of object identity, and each involving different kinds of computations. Two of the features, namely average whisker speed and power spectral density of whisker vibration, require the temporal integration of tactile signals, such as mean speed or total power of whisker vibrations (Arabzadeh et al. 2003), or the spectral frequency of whisker vibrations (Hipp et al. 2006). Other, kinematic features, such as whisker location, velocity and acceleration, on the other hand, require information regarding whisker transients (Arabzadeh et al. 2005; Jadhav et al. 2009; Wolfe et al. 2008). Rather than use these features in mutually exclusive ways, it is likely that rodents process several features simultaneously, depending on the complexity of both stimulus and behavioral tasks. Finally, several studies have shown that rodents’ somatosensory system can measure the amplitudes of forces in the sensory follicles dedicated to tactile sensation, to estimate radial object distance (Bagdasarian et al. 2013; Pammel et al. 2013).

Another important question in the field of sensory physiology involves the coding paradigms that serve as the basis for tactile perception. It is hardly disputed that tactile features may be coded by firing rates (Adrian 1926; Romo and Salinas 2003; von Heimendahl et al. 2007). For instance, changes in firing rates have been proposed as the primary way in which somatosensory system neurons represent velocity (Arabzadeh et al. 2003; Gibson and Welker 1983; Pinto et al. 2000; Shoykhet et al. 2000; Zucker and Welker 1969). This, however, does not exclude the possibility that neurons may also represent tactile features by their spike timing. Substantial evidence from trigeminal ganglion (TG) neurons (Bale et al. 2013; Jones et al. 2004; Lottem and Azouz 2011; Shoykhet et al. 2000; Stuttgen et al. 2006), from the somatosensory thalamus (Deschenes et al. 2003; Petersen et al. 2008), and from primary somatosensory cortex neurons (Arabzadeh et al. 2005, 2006; Panzeri et al. 2001; Petersen et al. 2002b; Pinto et al. 2000), have shown that neuronal responses in the somatosensory system are precise and reliable and can follow the fine temporal features of the stimulus (Deschenes et al. 2003; Ewert et al. 2008), suggesting that relevant tactile information may be represented in neuronal temporal patterns.

In the present study, we examine the transformation of tactile features to transient kinematic variables of whisker vibrations and the coding paradigm that is being used as the basis for tactile perception.

We find that both the radial distance of an object and object velocity are transformed into whisker velocity. We show that whisker velocity is encoded in TG neurons primarily by la-
ency coding, whereas in brain stem nuclei these signals are represented by two competing encoding schemes, latency and firing rate encoding. We discuss the implications of these results in the context of transmission of tactile information to various brain areas.

**EXPERIMENTAL PROCEDURES**

**Recording and stimulation**

*Surgical procedures.* Adult male Sprague-Dawley rats (250–350 g) were used. All experiments were conducted in accordance with international and institutional standards for the care and use of animals in research. This study was reviewed and approved by the Ben-Gurion University animal care and use program, which is supervised and fully assured by the Israeli Ministry of Health and operates according to Israel’s Animal Welfare Act 1994 and follows the Guide for Care and Use of Laboratory Animals (NRC 2011). In addition, it is assured by the Office of Laboratory Animal Welfare, USA (OWLA) no. A5060-01, and fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International.

*Surgical anesthesia,* while recording from TG neurons, was induced by urethane (1.5 gm/kg ip) and maintained at a constant level by monitoring forepaw withdrawal and corneal reflex; extra doses (10% of original dose) were administered as necessary. While recording from brain stem neurons, after initial anesthesia with ketamine (100 mg/kg) and xylazine (10%), a tracheotomy was made following local subcutaneous injection of lidocaine. Rats were mounted in a stereotactic device and respirated with a mixture of halothane (0.5–1.5%) and oxygen-enriched air. Atropine methyl nitrate (0.3 mg/kg im) was administered after general anesthesia to avoid respiratory complications. Body temperature was maintained near 37°C using a servo-controlled heating blanket (Harvard, Holliston, MA). After subjects were placed in a stereotactic apparatus (TSE, Bad Homburg, Germany), an opening was made in the skull above the TG, and tungsten microelectrodes (2 MΩ, Nano-Bio Sensors) were lowered according to the known stereotaxic coordinates of the TG [1.5–3 mm mediolateral (ML), 0.5–2.5 mm anteroposterior (AP)] (Shoykhet et al. 2000), principal trigeminal nucleus (PrV) (2.9 mm ML, 0.3 mm posterior to interaural), spinal trigeminal nucleus interpolaris (SpVI) (2.4–2.9 mm ML, 2.8–4.3 posterior to interaural).

To distinguish clearly between cell ensembles in the magnocellular and parvocellular divisions of the SpVII, all recordings were performed in either the rostral (11.8–12.2 mm AP) or caudal part (12.8–13.3 mm AP) of the nucleus. To verify these locations, we used the rostral part of the PrV as a reference point and then moved back ~3.4 mm or ~4 mm. Once a neuron was encountered, its receptive field was mapped. The recorded signals were amplified (~1,000), band-pass filtered (1 Hz–10 kHz), digitized (25 kHz) and stored for offline spike sorting and analysis. The data were then separated to distinguish local field potentials (1–150 Hz) from isolated single-unit activity (0.5–10 kHz).

All neurons could be driven by manual stimulation of one of the whiskers. Spike extraction and sorting was accomplished using a modified version of MClust (by A. D. Redish, available from http://redishlab.neuroscience.umn.edu/MClust/MClust.html), which is a Matlab-based (Mathworks, Natick, MA) spike-sorting software. The extracted and sorted spikes were stored at a 0.2-ms resolution and peristimulus time histograms (PSTHs) were computed. The scale bars of the PSTHs indicate response probability. For each bin, the number of spikes was divided by the number of trials.

*Artificial whisking* (Fig. 1A; Brown and Waite 1974; Szwed et al. 2003) was induced by stimulating the buccolabialis motor branch of the facial nerve (Semba and Egger 1986). The nerve was cut, and its distal end was mounted on bipolar tungsten electrodes and kept moist. Bipolar rectangle electrical pulses (10–20 pulses of 100 µs at 143 Hz for 70–105 ms) were applied through an isolated pulse stimulator (ISO-Flex; A.M.P.I.) to produce whisker protraction, followed by a passive whisker retraction at frequencies in the range of 1 Hz. The stimulation magnitude was adjusted at the beginning of each recording session to the minimal value that reliably generated the maximal possible movement amplitude (50–200 μA).

C3 whisker displacements transmitted to the receptors in the follicle were measured by an infrared photo-sensor (resolution 1 μm; Panasonic CNZ1120) placed 2 mm from the pad. The voltage signals were digitized at 25 kHz and amplified (~500; FLA-01, Cygnus Technology). During “single whisker” experiments, other whiskers were trimmed off. We then converted the whisker movements to arc degrees.

**Histology.** To mark the recording sites in the brain stem, we induced electrolytic lesions by the recording electrodes. These were made by passing direct current (10–30 μA) for 4 s at a depth that corresponded to each recorded area. In some of the rats, brain tissues were also processed for CO histochemistry. The animals were perfused transcardially with 2.5% glutaraldehyde and 0.5% paraformaldehyde, followed by 5% sucrose, all in 0.1 M PBS (phosphate-buffered saline). The animals’ brains were then placed in postfixative solution of 30% sucrose at 4°C overnight. The next day, freezing microtome sections (120 μm) were prepared and incubated in a solution of 0.0015% cytochrome C (sigma), 0.05% dianisobenzidine in PBS for 20–50 min at 37°C. The reaction was terminated by washing the reagent solution with PBS. CO-stained sections were mounted on gelatin-coated slides, air-dried, and coverslipped.

**Whisker stimulation.** Receptive fields were initially determined by manually deflecting individual whiskers. Whiskers evoking detectable responses were then individually attached to a computer-controlled Galvanometer stimulator (model 6210H Galvanometer Scanner, Cambridge Technology). These scanners, once calibrated, have a resonant frequency well above the range of velocities used in the present study. Each stimulus was presented for 1 s and repeated 25–40 times in both the preferred and the null direction. A period of 2 s separated each stimulus. Stimuli were delivered ~3 mm from the mystacial pad. The whisker was attached firmly to the edge of the galvanometer lever. Accordingly, the angle of the whisker was given by: \( \theta = \tan^{-1}(x/s) \), where \( x \) is the whisker’s displacement in millimeters. Furthermore, individual whiskers were deflected by several types of stimuli which were randomly interspersed in time: first, ramp whisker deflections ranging from amplitudes of 100–2,000 μm with a duration of 20 ms, resulting in velocities of 95–1,910°/s; second, step stimuli were 600–1,200 μm. The galvanometer stimulator was calibrated using a calibrated, noncontact optical displacement measuring system (resolution: 1 μm; LD1605-2; Micro-Epsilon, Ortenburg, Germany).

**Data Analysis**

The significance of the differences between measured parameters was evaluated using one-way ANOVA. When significant differences were indicated in the F-ratio test \( P < 0.05 \), the Tukey method for multiple comparisons was used to determine those pairs of measured parameters that differed significantly from each other within a group of parameters \( P < 0.05 \) or \( P < 0.01 \). Below, averaged data are expressed as means ± SE, unless otherwise stated. Error bars in all of the figures indicate the standard error, unless otherwise stated. To avoid cluttering in the graphs, we use single-sided error bars. Neuron classification into the three cell types was described in detail elsewhere (Lottem and Azouz 2011). Briefly, rapidly adapting (RA) neurons respond to step stimuli with a phasic response. They do not show either directional selectivity at higher stimulus intensities, or any dependence of first spike latency on whisker deflection velocity. In contrast, within the slowly adapting (SA) neurons, namely those having phasic-tonic response, we identified two distinct subgroups, distinguished by their velocity thresholds (170°/s; Lottem and Azouz 2011) for firing: SA\(_{h}\) (low threshold) and SA\(_{h}\) (high threshold). These
subtypes differ in other respects as well: 1) SAht neurons display large phasic responses followed by stochastic tonic firing, whereas SAht neurons exhibit slowly decaying periodic responses, followed by stochastic tonic firing, in response to step whisker deflections; 2) SAht neurons respond to low whisker velocities with a larger number of spikes than SAht; 3) SA neurons display a dependence of first spike latency on whisker deflection velocity (100–56,000°/s), which is expressed differentially by the two subtypes. The two SA subtypes are similar, however, in that all SA neurons show directional selectivity, expressed differentially by the two subtypes. The two SA subtypes are...
To calculate the relative timing between RA and SA neuronal discharges, we convolved SA neuron first spike latency distribution with the inverted RA neuron first spike latency distribution (see Fig. 5A). The relative timing was measured on positive and negative differences, i.e., when RA spikes precede or follow SA, respectively.

To classify brain stem neuronal ensembles according to their functionality, we first calculated a first spike latency range (maximum first spike latency to minimum first spike latency) for each neuron. We then established a first spike latency range, in which all of the neurons that had first spike latency range smaller than or equal to an arbitrary latency threshold were considered shorter latency neurons. Neurons with a first spike latency range higher than the threshold as well as having a minimal spike latency later than the earliest onset spike were considered longer latency neurons.

The precision measure (which is based on Mainen and Sejnowski 1995) gives a measure of the temporal “jitter” of spike latency. Briefly, we detected in each PSTH (bin size = 1 ms) peaks which exceed a certain threshold. This threshold was calculated for each neuron. Threshold calculation was based on the mean ± SD of peak values of the PSTH. We then calculated the standard deviation (SD) of the latency of the spike corresponding to each event. Finally, the SD for all the events was averaged. The precision measure, referred to as the “jitter,” corresponds to this average SD, and therefore increases in the jitter (i.e., increased SD) are associated with decreases in the precision of action potential timing measurement.

**Receiver Operating Characteristics Analysis**

We used signal detection theory [receiver operating characteristics (ROC) analysis, Green and Swets 1974], to compute the probability that an ideal observer could accurately determine the differences among whisker velocities based on neuronal activity. For each measured whisker velocity pair, an ROC curve was constructed. The ROC curve is a two-dimensional plot of hit probability on the ordinate against false-alarm probability on the abscissa. To transform raw data into a measure of discriminability, we analyzed the distributions of several neuronal response characteristics across trials. The distributions also included trials in which there were no responses. Each point on an ROC curve shows a pair of hits and false alarms, representing the proportion of trials in which the first velocity response exceeded a criterion level, plotted against the proportion of trials in which the other velocity response exceeded the same criterion (Fig. 3B). The entire ROC curve was calculated by sweeping the criterion from the minimal level to a value greater than the highest level in the two.
distributions. Improved separation between the two whisker velocity response distributions leads to an increased deflection of the ROC away from the diagonal. Green and Swets (1966) showed that the area under the ROC curve (AUC) corresponds to the performance expected of an ideal observer in a two-alternative, forced-choice paradigm, such as the one used in the present analysis. The ROC curve was calculated for four neuronal response characteristics: 1) the firing rate of a single neuron as a function of whisker velocity; 2) first spike latency; 3) first interspike interval; and 4) time interval between RA and SA response.

To assess the discrimination within all velocity pairs across these four neuronal characteristics, we calculated the AUC for all velocity pairs. This is shown in Fig. 3B for first spike latency. Each value in this matrix represents an AUC value for a velocity pair. To reduce the dimensionality of our analysis, we averaged all matrix values that belonged to the same diagonal (average global AUC, or discriminability plot; Fig. 3C), which illustrates the overall discrimination for all velocity differences. It should be noted that this presentation has some limitations, since the number of elements per diagonal decreases as the difference between the velocities increases.

To measure the significance level of $P$ (correct) in the ensemble of TG neurons, we took all possible whisker velocity comparisons $[(20 \times 19)/2]$ for all SA neurons ($n = 37$) and shuffled the trials across the different stimuli. We then repeated this procedure 500 times to have a distribution of $500 \times 190 \times 37$ AUCs. The significance level was set at 90% of this population, namely 0.625 (Fig. 4A). A similar procedure was used for the brain stem nuclei, where we found that the significance level for the PrV was 0.59, and for SpVi was −0.585.

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Fig. 3. First spike latency of RA neurons is dependent on whisker velocity when the stimulus is filtered. A: sample PSTHs in response to three whisker velocities (unfiltered on the left; filtered on the right). B: the effect of whisker velocity under the same conditions.

Fig. 4. Velocity discrimination using receiver operating characteristics (ROC) analysis. A: ROC curve used to discriminate between the two velocities marked by arrows in Fig. 2A (859°/s and 1,050°/s). The different colored curves above the diagonal show the curves corresponding to each of the neuronal features. B: area under the curve (AUC) values, using first spike latency $^{-1}$, for all pairs of velocities (the black square corresponds to the AUC of the first spike latency ROC in B). C: averaging of all diagonals results in a discriminability plot. Δ, Change.
RESULTS

Encoding of whisker velocity in TG neurons plays a major role in rats’ perception of their tactile environment. We employed several stimulus paradigms to examine the role of whisker velocity in the representation of tactile stimuli. 1) We used objects moving at different velocities to touch a whisker at a constant radial distance (approximately in the middle of the whisker; Fig. 1A). The figure shows that whisker velocity changes as a function of object velocity. 2) We examined whether an object moving at a constant velocity (575 mm/s), touching a whisker at different radial distances (Fig. 1B), has an impact on whisker velocity. We used normalized values to indicate distance from the pad to the tip of the whisker (smaller values indicate points closer to the pad). We found that the farther from the pad an object touches the whisker, the slower the whisker moves. 3) Finally, we induced artificial whisking in anesthetized rats by facial motor nerve stimulation and monitored the movement of whiskers against objects located at different radial distances (n = 3). An example of whisker trajectories against objects located at different distances is shown in Fig. 1C. Quantification of the impact of object distance on transient whisker velocity is shown on the right-hand side. Radial object location is translated to whisker velocity. We found that the farthest the object was from the pad, the faster the whisker moved. These stimulus velocity changes occur within a range of ~20 ms (shaded area).

Taken together, our results indicate that transient whisker velocities may serve as one of the physical parameters representing tactile features, and that active object contacts show qualitatively different velocity profiles, compared with passive ones.

To characterize the rules governing the transformation of whisker velocity into spike generation, and the transmission of these signals from primary afferents to brain stem neurons, we employed ramp stimuli of various velocities. We probed neuronal response properties in 56 TG neurons obtained from 14 adult rats, using both step and constant velocity ramp stimuli. An example of the responses of RA (n = 19) and SA (n = 37) neurons to step and ramp stimuli is shown in Fig. 1, D and E. We further divided SA neurons into two distinct subgroups, defined according to their velocity threshold for firing (the distinction between the two subtypes is described thoroughly in section herein): SA_L (low-threshold, n = 26) and SA_H (high-threshold, n = 11).

Despite the simple time course of the stimulus, the PSTHs of the different neuronal types have a complex temporal waveform (Fig. 1E). At least three distinct aspects of the response can be observed: first spike latency, which is defined as the time interval between stimulus onset and the beginning of the neural response; first interspike interval; and firing rate. In SA neurons, the decrease in latency can be observed by examining the column of PSTHs in Fig. 1B and noting that, in these neurons, the onset of responses becomes progressively earlier as velocity increases. This phenomenon has been reported in several studies in rodents and humans (to name but a few, Johansson and Birznieks 2004; Kwergij-Afful et al. 2008; Shoykhet et al. 2000). The same applies also to the first interspike interval, which becomes progressively shorter. Finally, the growing number of PSTHs peaking as velocity goes up indicates an increase in neuronal firing rate, which has also been reported previously (Arabzadeh et al. 2003; Gibson and Welker 1983; Pinto et al. 2000; Shoykhet et al. 2000; Zucker and Welker 1969). An example of these characteristics in SA neurons is shown in Fig. 2A. The shaded areas indicate the borders of our measurements of first spike latencies and first interspike intervals, while colored solid squares on the right-hand side indicate the normalized firing rate of the neuron.

One of the goals of the present study was to juxtapose these three aspects of neuronal response and examine their pros and cons in terms of reliability, robustness, and resilience. We calculated the distribution of firing rates, first spike latencies, and first interspike intervals of TG neurons as a function of whisker velocity. An example of these characteristics in an SA neuron is shown in Fig. 2A. The shaded areas indicate the border of our measurements of first spike latencies and first interspike interval, while colored solid squares on the right-hand side indicate the normalized firing rate of the neuron. Velocity dependence is confirmed by the different scalar measures of the neuronal responses, plotted against velocity. Our results show that increased whisker velocity leads to a decrease in both first spike latency (Fig. 2B) and first interspike interval (Fig. 2I), as well as an increase in discharge rates of SA neurons (Fig. 2F). In contrast, RA neurons do not show any apparent dependence of either first spike latency or firing rate on whisker velocity (Fig. 2, B and F, bottom). The minor velocity-dependent changes in the firing rate of RA neurons are mostly due to an addition of a few spikes within a short period (e.g., the increase of firing rate to 50 Hz was due to an addition of a single spike during the 20-ms interval).

We further examined the impact of whisker velocity on the three neuronal response characteristics in the same cell types. SA_L neurons start responding at lower velocities, and their first spike latencies show a clear yet modest dependence on whisker velocity (Fig. 2C, top). In contrast, SA_H neurons start responding at higher velocities, and their first spike latency shows a strong dependence on whisker velocity. RA neurons are activated at a wide range of velocities, and, once they respond, they hardly show any dependence of first spike latency on whisker velocity (Fig. 2B, bottom).

To quantify the influence of whisker velocity on first spike latency and first interspike interval in a continuous manner, we plotted first spike latency and first interspike interval−1 as a function of whisker velocity. These relations were then fitted to a logistic function, in which “no responses” are set to zero. Figure 2D shows the normalized fits of all neurons in our sample. First spike latency−1 in RA neurons is practically step-like, whereas in the two types of SA neurons, first spike latency−1 varies more smoothly as a function of whisker velocity. Thus single RA neurons are less suited to velocity discrimination than SA neurons. Quantification of firing rates as a function of whisker velocity produces very similar results, in which the firing rates of SA neurons are better suited to velocity coding than single RA neurons (Fig. 2, F−H). The smooth increase in first spike latency−1 and firing rate as a function of velocity in the averaged plots (Fig. 2, C and G) reflects different firing thresholds for each RA neuron, as shown by a shift in the plots.

To determine the velocity threshold for neuronal activation, we examined the proportions of the different cell types activated at each velocity. This analysis revealed that at lower
velocities, SA_{hi} neurons tend to dominate. As whisker velocity increases, more neuronal types become relevant (Fig. 2E). Furthermore, these results indicate that SA_{hi} and RA neurons can represent whisker velocity by the proportion of active neurons within each subpopulation. All in all, our results indicate that single RA neurons convey little information about stimulus properties (i.e., velocity), other than indicating its onset. In contrast, SA neurons may code for stimulus characteristics by their first spike latency, yet they convey ambiguous information about its onset. The difference in the slopes of the two SA subtypes indicates a larger dynamic range for SA_{hi} neurons, i.e., better discriminability between velocities (Fig. 2D).

Our results challenge the observation that RA neurons change their latency as a function of stimulus velocity (Shoykhet et al. 2000). However, in that study a piezoelectric element was used to move the whiskers. Due to a mechanical limitation of the piezo, the stimulus had to be filtered. Not knowing which type of filters these authors used, we chose a conservative low-pass filter (“filtfilt” filter in Matlab; low-pass filter: cut-off = 250 Hz; slope = 2) in three TG neurons. When we compared unfiltered and filtered stimuli, we found that this filter causes a latency dependence on velocity. Thus RA neurons hardly show any velocity-dependent changes in their first spike latency (Fig. 3B).

The Encoding Mechanisms That Underlie Velocity Discrimination

To examine the possible coding mechanisms underlying tactile discrimination, we used ROC analysis (Green and Swets 1974) to assess the discriminative power and robustness of neuronal response features. The ROC curve for the three neuronal characteristics described in Fig. 2A is shown in Fig. 4A. The ROC curve in the panel, which was used to discriminate between two stimuli (859°/s and 1,050°/s; see arrows in Fig. 2A), shows that both first interspike interval and first spike latency are better at discriminating between the two velocities than the firing rate.

An assessment of the predictive performance of each of the response characteristics can be obtained by computing the AUC. The AUC can then be used to assess the discriminatory powers of the various response features. It approaches 0.5 for a chance level discrimination, and equals unity (or zero) for a perfect discrimination. To assess the amount of stimulus-related information conveyed by the different neuronal response characteristics, we calculated AUCs for all velocity pairs. This is shown in Fig. 4B for first spike latency. Each colored patch in this matrix represents an AUC value for a pair of velocities (the black square corresponds to the AUC of the first spike latency ROC curve in panel A of the figure). We then constructed a discriminability plot (Fig. 4C), which illustrates the overall discrimination for all velocity differences; it shows that as change in velocity increases, so does discriminability.

Figure 5A compares the discrimination curves of all SA neurons for all three neuronal features (firing rate, first spike latency and first interspike interval). The panel shows that first interspike interval and first spike latency are better at velocity discrimination than neuronal firing rates. To examine the role of the different neuronal types in velocity discrimination, we created discriminability plots for each of neuronal response features and for each of the three neuronal types. Our results indicate that SA_{hi} neurons are superior to both SA_{lt} and RA neurons in velocity
discrimination for all response features. With respect to firing rate, SA₈ and RA neurons show comparable discriminability, whereas SA₉ neurons’ temporal response properties discriminate various velocities as well (Fig. 5, C and D).

“When” and “What” Signals in TG Neurons

Stimulus identity can be evaluated from SA first spike latency only if stimulus onset time is known. We have shown that first spike latency in single RA neurons does not depend on stimulus velocity and, therefore, may serve as the stimulus onset signal. To determine whether RA and SA neuron responses can serve as “when” and “what” signal, respectively, we examined velocity discrimination using the relative timing between RA and SA neuronal discharges (Fig. 6A, gray area).

To determine the robustness of the “when” signal, we took two approaches: first, we pooled the first spike latencies from an ensemble of RA neurons (n = 19; see EXPERIMENTAL PROCEDURES section). To determine whether a population of RA neurons can provide an accurate and reliable onset signal, we examined the impact of whisker velocity on the mean first spike latency of the 5th (1st), 32nd (6th), and 53rd (10th) percentiles of first spikes across the ensemble (the numbers in parentheses are actual spike numbers). Our results show that these neurons hardly change their latency and can signal stimulus onset for all velocities (Fig. 6B).

Second, we averaged all of the points on the various discriminability plots (using the time interval between RA and SA neuronal discharge) for different RA spike percentiles. The results show that, even if we discard the more reliable half of the RA population, velocity discrimination using relative timing deteriorates just slightly and stays well beyond the significance threshold (Fig. 6C). Thus RA neurons can provide the brain with a robust and reliable onset signal.

We next combined this onset signal (RA first spike latency distribution) with each of the SA neuron’s first spike latency to get a relative timing distribution for each velocity (see the EXPERIMENTAL PROCEDURES section). As in our previous analysis, we created from these distributions ROC curves for all velocity...
pairs and calculated a discriminability plot. Our results indicate that, while relative timing signals carry less information about whisker velocity than first spike latency of SA neurons, both are superior to firing rate (Fig. 6). Although this is true for both types of SA neurons, SAht neurons show superior velocity discrimination in their relative timing (Fig. 6E, right). Brought together, our results show that the relative first impulse timing in an ensemble of TG neurons accurately and reliably reflects whisker velocity. We showed that stimulus onset time can be evaluated using stimulus-independent first spike latency of RA neurons, whereas stimulus identity can be gauged by stimulus-dependent relative timing between RA and SA neuronal discharge.

**Transmission of Velocity Signals Through the Brain Stem**

Tactile signals from TG neurons are transmitted through brain stem nuclei to multiple brain areas through several parallel pathways (Haidarliu et al. 2008; Veinante et al. 2000; Yu et al. 2006). To determine which response features are disseminated through brain stem nuclei, we recorded from neurons in the parallel pathways in the PrV and SpVi obtained from nine adult rats (Fig. 7A). Figure 7, B and C, shows typical responses of PrV neurons to step and ramp stimuli with various velocities. We recorded from 78 PrV neurons, 68 of which were significantly responsive (3 SD above spontaneous activity). Out of these neurons, 55 showed consistent velocity dependence of their first spike latency and firing rate. We grouped these neurons according to their responses to step stimulus to SA ($n =$ 46) and RA ($n = 8$) neurons (Fig. 7B). In contrast to TG neurons, PrV neurons did not show as clear a difference in their responses to various velocities. Both types of neurons exhibit a varying degree of velocity dependence in their first spike latencies (Fig. 7, B, right).
We also recorded from 109 SpVi neurons, 100 of which were significantly responsive. Of these neurons, 83 showed consistent velocity dependence of both first spike latency and firing rate. We found that rostral (SpVi; \( n = 34 \)), intermediate (\( n = 21 \)), and caudal (SpVi; \( n = 28 \)) neurons respond differently to step stimulus as well. In the SpVi, the majority of the neurons were RA (Fig. 7C, RA: \( n = 21 \); SA: \( n = 13 \)), whereas in the SpVi, most neurons were SA (Fig. 7C, RA: \( n = 8 \); SA: \( n = 20 \)) (as reported also by Chiaia et al. 1987). Same as in the PrV, SpVi RA and SA neurons did not show a clear difference in their responses to various velocities. Both types of neurons exhibited a varying degree of velocity dependence in their first spike latency.

To ascertain which signals are transmitted through second-order neurons in brain stem nuclei, we charted a discriminability plot for the three different features for each neuron in the three brain stems. We quantified this jitter by measuring the SD of first spike latency and found that first spike latency jitter increases from first- to second-order neurons. To examine the mechanisms responsible for this deterioration, we measured the jitter in first spike latency in all three brain regions. We quantified this jitter by measuring the SD of first spike latency and found that first spike latency jitter increases from first- to second-order neurons (Fig. 8, A and B), which may underlie the use of temporal coding in velocity discrimination. Moreover, this jitter is dependent on whisker velocity in SA neurons, but not in RA neurons. To eliminate the possibility that this deterioration is due to the nature of our stimulus, we compared first spike latency jitter in response to ramp and complex stimuli in the same neurons. We used filtered white noise stimulus with a velocity equivalent of 900°/s (low-pass filter, 250 Hz); an example of TG and PrV neuronal responses to complex stimuli is shown in Fig. 8, C and D. To compare response jitter between the two brain regions and between the two stimuli, we similarly calculated the first spike latency jitter in response to complex stimuli. We found that the first spike latency jitter in TG neurons is stimulus independent (Fig. 8, E and F, see horizontal lines). In general, however, SA neurons in PrV and SpVi show significantly less deterioration in their first spike latency jitter when responding to complex stimuli, compared with ramp stimuli (Fig. 8E). These results suggest that a temporal jitter in first spike latency may be the main...
cause for the deterioration of velocity discrimination. Moreover, this deterioration is less evident when complex stimuli are used.

In the preceding analysis, the “when” and “what” signals were predefined using the adaptation profile of the studied neurons (RA vs. SA). However, an alternative way to transmit an onset signal would be to divide the neurons functionally according to their velocity dependence. That is, we set a latency range criterion in which neurons with a velocity-dependent latency range that is lower than the criterion are assigned to convey the onset signal. We used a dynamic latency threshold in which we chose a subset of the neurons (“velocity-independent” neurons) with a predefined latency range in each area (the range of first spike latency in response to the full range of whisker velocity). We considered these neurons to be the carriers of onset signal and calculated the relative timing between this subset of neurons and each of the remaining (“velocity-dependent”) neurons. For each latency threshold, we charted the relative timing discriminability plot and compared it to first spike latency and firing rate discriminability plots. An example of discriminability plots for both brain stem areas at a latency range threshold of 4.4 ms is shown in Fig. 9A. The plots indicate that all three features are nearly equally effective in velocity discrimination.

To quantify the transmission of the three signals using our functional classification, we calculated the ratio between relative timing and firing rate discriminability plots for all latency thresholds. Figure 9B shows that, at almost all latency ranges, the ratio is close to one. To see whether these two functionally defined groups of neurons correspond to the previously described RA and SA neurons, we calculated in both areas and at different time ranges the proportions of RA neurons out of the “velocity-independent” neuronal population. We found that, in the PrV region, RA neurons play a minor role, whereas in SpVi, most “velocity-independent” neurons are RA neurons (Fig. 9C). Thus the different brain stem areas may have a different degree of “shuffling” of RA and SA populations (Sakurai et al. 2013). All in all, our results suggest that stimulus onset time can be estimated using velocity-independent first spike latency of a subset of the neurons, while stimulus identity can be gauged by velocity-dependent relative timing between these neurons and stimulus-independent neuronal discharge.

The Impact of Noise on “When” and “What” Signals

One of the major caveats in using the temporal features of the neuronal response to code for whisker velocity is the response’s sensitivity to both intrinsic and extrinsic noise. These types of noise may cause spike time jitters and additions or subtractions of spikes, which could have a detrimental effect on the quality of the temporal code. It is therefore essential to test the noise-sensitivity of “when” and “what” signals. More specifically, spontaneous firing, if high enough, could be detrimental to the coding of an onset signal.

We tested for the impact of noise in both TG and brain stem neurons. In TG neurons, we introduced noise in two different ways: 1) we added noise to the stimulus (Fig. 10A; this could be thought of as emulating naturally occurring small whisker movements caused by the wind, for instance); 2) we superimposed the stimuli on a direct current whisker offset, which resulted in neuronal discharges in SA neurons. The introduction of these two types of noise resulted in spontaneous neuronal discharges (24 ± 1.2 spikes/s; Fig. 10A, bottom). To determine the effect of these two types of noise on the “when” and “what” signals, we repeated the previous analysis (Figs. 5 and 6) to create discriminability plots.

To eliminate the bias which could arise from the fact that stimulus onset was known to us, our trials began 15 ms prior to actual stimulus presentation (Fig. 10A). Under these conditions, some trials had “negative” first spike latencies, signifying that neurons fired before stimulus onset. We saw that, in

Fig. 9. Velocity discrimination in the brain stem with the functional classification of “when” and “what” signals. A: discriminability plot using the different neuronal features in SA neurons in PrV and SpVi areas. The threshold latency range for the “when” neurons was set to 4.4 ms. B: the ratio between the discriminability plot of RT and FR of SA neurons in PrV and SpVi neurons against the latency range threshold. C: the proportion of RA neurons out of functionally classified “when” neurons as a function of threshold and area. Averaged data are expressed as means ± SE.
TG neurons, unlike first spike latencies, relative timing and firing rate signals maintained the level of velocity discrimination in the system (Fig. 10B). This is due to the fact that RA neurons, which relay the onset signal, are much less affected by noise: not firing during both static whisker offset (as their name implies) and low-velocity noise. In brain stem neurons, using lightly anesthetized rats, we chose neurons that discharge spontaneously (PrV: \( n = 46, 72\% \); firing rates = 5.08 ± 0.75 spikes/s; SpVi\(_1\): \( n = 13, 38\% \); firing rates = 1.89 ± 1.0 spikes/s; SpVi\(_2\): \( n = 20, 60\% \); firing rates = 7.53 ± 1.69 spikes/s). We found that, in brain stem neurons, only mild deterioration appeared in relative timing and first spike latency signals, while no degradation was observed in firing rate signal. These results were consistent across all brain stem nuclei (Fig. 10C). Put together, our results indicate that, within the noise limits we tested, relative timing and firing rate signals are transmitted with the same reliability and efficiency through the brain stem.

**DISCUSSION**

The present study shows that, in the rats’ whisker somatosensory system, both the speed and the radial distance of a moving object are translated into changes in whisker velocity during transient movements. Moreover, it has already been shown that, during artificial whisking, the radial distance of a stationary object is translated into variations in whisker velocity (Bagdasarian et al. 2013). These observations, supported as they are by previous studies, suggest that whisker velocity may be used by rats to detect and discriminate isolated, punctate whisker deflections (Ito 1985; Pinto et al. 2000; Simons 1978). Thus rodents can evaluate whisker kinematic variables, as well as the amplitudes of forces in the sensory follicles for tactile sensation. Such multiple variables as bending moment, axial force, lateral force as well as velocity, can reliably represent the coordinates of a contacted object’s position (Knutsen et al. 2008; Pammer et al. 2013).

A range of coding schemes for whisker velocity available at the first- and second-order networks was investigated using passive whisker stimulation in anesthetized rats. The feasibility of these schemes lies at the heart of an ongoing debate about the way the brain represents sensory information and the role of single neurons in this encoding (Averbeck et al. 2006; Meister and Berry 1999; Stanley 2013; Zador 1997). In the present study, we asked whether these neurons transmit tactile information by their firing rate or by the relative timing of their action potentials. The velocity sensitivity of neurons in the whisker somatosensory system has been measured in a number of previous studies (Ito 1985; Pinto et al. 2000; Shoykhet et al. 2000; Simons 1978). Most of the work done in this area has focused on neuronal firing rates in response to fast transient or ramp-and-hold deflections, reporting a monotonic dependence of firing rates on deflection velocity, which is consistent with our present results. However, we showed also that the relative timing of the first spikes in ensembles of first-order sensory neurons contains a wealth of information about the stimulus. Specifically, the relative timing of the first spikes contains reliable information about whisker velocity. In these ensembles, RA neurons apparently convey stimulus onset, whereas SA
neurons seem to transmit stimulus identity. Furthermore, first
spikes code this information more efficiently than firing rate,
which traditionally was thought to represent information in
primary sensory neurons.

As tactile information is transferred from first-order neurons
to various brain stem nuclei, whisker afferent arbors in differ-
ent subnuclei of the same axon tend to have different sizes,
shapes and bouton numbers (Shortland et al. 1996), which
indicates that second-order neurons in each brain stem subnu-
cleus receive a different sensory information. However, we
showed that, while the different subnuclei contain different
proportions of RA and SA neurons (Fig. 7C), the transmission
of whisker velocity information (based on our stimulus)
through the various response features varies only slightly (Fig.
7E). More surprisingly, at the PrV level, the “when” signal,
represented by RA neurons, is reduced by a large amount.
This was indicated by measuring a subensemble of neurons, which
did not show any velocity dependence on the “what” signal
(Fig. 9C). These results argue in favor of a “shuffling” of RA
and SA populations, as was also predicted by anatomy (Sakurai
et al. 2013).

All in all, our results suggest that temporal and firing rate
codes provide the brain with independent information about
whisker velocity. Given that numerous parallel pathways are
used to process tactile information (Haidarliu et al. 2008;
Veinante et al. 2000; Yu et al. 2006), it is conceivable that
these encoding paradigms are used by the rest of the brain for
different processes and at different time scales, depending on
context and conditions. Each of these codes provides signif-
ificant information about whisker velocity and thus, in principle,
may guide sensory perception in behaving rodents.

In many situations, the rodents actively move their whiskers,
thereby setting whisker speed. The resulting neuronal re-
sponses can serve as both representations of the tactile envi-
ronment and feedback signals that may convey the actual
whisker velocity to the system, during either whisking in the
air or contact with an object. These conjectures are consistent
with studies which suggest that somatosensory cortex re-
sponses are transient and are the most sensitive to whisker
velocity (Pinto et al. 2000), and that spiking on the ascending
pathway is precise and carries information about detailed
features of the trajectory (Hipp et al. 2006; Jones et al. 2004;
Petersen et al. 2008).

Our findings support the notion that the whisker somato-
sensory system is able to extract transient kinematic events,
in addition to the total power and spectral frequency of whisker
vibrations (Abazadzeh et al. 2003; Hipp et al. 2006). These
findings fit well with several papers by both the Schwarz group
(Gerdjikov et al. 2010; Schwarz et al. 2010; Stuttgart et al.
2006; Waiblinger et al. 2013), and Adibi et al. (2012), which
linked a high level of psychophysical performance in rodents to
the presence of transient kinematic signals.

Methodological Considerations

To explore the transformation of tactile features into tran-
sient kinematic variables of whisker vibrations, we used arti-
ficial whisking, which generates whisking-like movement of
the vibrissae. However, it should be borne in mind that the
actual displacement generated by electrical whisking is not the
same as naturally occurring whisking (Berg and Kleinfeld
2003). Yet, although whisking movements during artificial and
natural conditions may differ in detail, artificial whisking does
induce mechanical interactions between whiskers and objects
which are within similar ranges under both conditions, as well
as in head-fixed untrained rats (Bagdasarian et al. 2013; Lottem
and Azouz 2009; Ritt et al. 2008). More importantly, several
studies have shown that the somatosensory system of rodents
can use the amplitudes of forces in the sensory follicles for
tactile sensation to estimate radial object distance (Bagdasarian
et al. 2013; Pammer et al. 2013). Therefore, it is possible that
whisker velocity may be one of several variables used to sense
the environment.

Our study relied on a set of applied stimuli (brief, individual
deflections with different velocities), whereas, in many situa-
tions, the system operates with continuous dynamic whisker
stimulation or self-induced whisker movements. We suggest,
however, that the results of the present study are applicable to
numerous situations in which discrimination of whisker velo-
city is required (Fig. 1).

Other studies have reached very different conclusions re-
garding the roles of RA and SA neurons, when more complex
stimuli were used. For example, Jones et al. (2004) have shown
that RA neurons are as efficient in encoding velocity as SA
neurons when stimulated with naturalistic noise waveforms. In
contrast, RA neurons were shown to be less suited to velocity
discrimination than SA neurons in response to constant stimuli
since, as their name implies, they emit so few spikes in
response to such stimuli.

Finally, we used anesthetized animals. This procedure has its
advantages, besides several disadvantages. While the magni-
tudes and correlations of cortical neuronal activity are signif-
cantly different from behaving animals, certain characteristics
cortical sensory processing, such as texture encoding, are
consistent across various brain states, including anesthesia
(Albaziadzh et al. 2005). Moreover, it has been shown that the
transmission of tactile information in anesthetized rodents can
be very reliable in response to varying stimuli (see multiple
references in the Introduction and DISCUSSION sections). Hence,
we believe that anesthesia does not play a major role in brain
stem neuronal fidelity.

Latency Encoding

The study reported herein is one of several studies that show
a clear correspondence between cellular functionality and tac-
tile information transmission. Specifically, RA neurons convey
stimulus onset times, and SA neurons communicate stimulus
identity. First spike latency has been shown to transmit infor-
mation in a variety of sensory modalities, including the audi-
tory (Furukawa and Middlebrooks 2002), visual (Gawne et al.
1996; Reich et al. 2001), somatosensory (Johansson and Bir-
ziens 2004; Panzeri et al. 2001), and olfactory (Junek et al.
2010) systems.

However, it is still unclear whether the different sensory
modalities can actually acquire an accurate measure of first
spike latencies, since latency determination requires an estima-
tion of stimulus onset from which to extract latency. Thus a
major feature of the temporal encoding scheme in general, and
latency encoding in particular, is the requirement that, to obtain
stimulus identity (“what”) from the neural responses, stimulus
onset times (“when”) must be used (Abazadzh et al. 2006;
Gawne et al. 1996; Meister and Berry 1999; Panzeri et al. 2001; Reich et al. 2001; VanRullen et al. 2005). However, with the exception of one clear instance (Johansson and Birznieks 2004), an internal neural representation of the onset time remains unclear, a fact considered by many to be a major drawback of the temporal coding strategy (Arabzadeh et al. 2006; Chase and Young 2007; Phillips 1998; VanRullen et al. 2005). To overcome this obstacle, a number of possible mechanisms have been proposed, in which first spike latency information could be achieved by comparing the response times of a subensemble of neurons to the mean response times of the entire population (Zohar et al. 2011). Other studies have used relative spike latencies or rank order codes to estimate the time of stimulus onset (Furukawa and Middlebrooks 2002; Gollisch and Meister 2008).

Neuronal Noise and Temporal Encoding

Our results suggest that a population code based on spike latencies can be a powerful mechanism for the rapid and reliable transmission of tactile information. Neurons responsible for early sensory processing have been shown to evoke reliable and temporally precise patterns of spikes (Buracas and Albright 1999; Petersen et al. 2002a). These first-order spikes are transmitted through highly efficient synapses to the thalamus and the cortex (Deschesnes et al. 2003). Thus our results mesh well with the literature and suggest that temporal response properties of the various neuronal subtypes can be utilized to code for whisker velocity.

However, as we have shown, “when” and “what” signals may be prone to errors. Onset estimation in RA neurons may deteriorate because of several factors. 1) First is detection errors. As whisker velocity decreases, the proportion of activated RA neurons decreases as well and eventually may fail to signal the presence of a stimulus (Fig. 1E). We have shown that, even at the lowest velocity examined, a significant proportion of RA neurons still discharge (Fig. 2E). 2) Second is the temporal fidelity of the estimation. The onset signal has to be independent of stimulus identity. We have shown, using the slope of the plot of RA first spike latency dependence on velocity, that first spike latency in most TG RA neurons is independent of whisker velocity (Figs. 1E and 2D), while first spike latency estimation in brain stem nuclei is noisier (Fig. 7). However, by using a population of RA neurons or velocity-independent neurons in first- and second-order neurons, we were able to reduce the small jitter in the onset signal. The introduction of low-level noise did not result in TG and brain stem RA neuronal firing, showing them to be robust and reliable onset detectors. In contrast to the onset signal, the deterioration in velocity discrimination is mostly influenced by the increase in the “jitter” of first spike latency signals of SA neurons (Fig. 7), which defines the basic temporal encoding strategy.

A major finding of this study is that a large deterioration of velocity discrimination occurs at the second stage, both for relative timing and firing rate signals, making them coequal candidates for velocity discrimination (Fig. 7). This large deterioration in relative timing signal contradicts previous studies, which have shown that the neuronal responses in the somatosensory system are precise and reliable throughout and can faithfully follow the temporal structure of the stimulus (Deschesnes et al. 2003; Petersen et al. 2008). To resolve this discrepancy, we compared the responses to both stimuli and found that the deterioration of temporal encoding is dependent on whisker velocity in SA neurons (Fig. 8A). The transmission between first- to second-order neurons plays a critical role in this deterioration (Fig. 8B). Using naturalistic noise stimuli significantly reduced first spike latency jitters, indicating that temporal encoding is stimulus dependent and therefore more suited for the representation of continuous whisker signals (Buracas and Albright 1999; Petersen et al. 2002a). The mechanisms underlying these differences lie beyond the scope of the present study. However, several findings in the literature suggest that inhibitory interneurons may play a role in reducing spike jitter (Gabernet et al. 2005; Pouille and Scanzianini 2001; Wilent and Contreras 2004), and that this inhibitory control may be stimulus dependent.

Readout Mechanisms

Several decoding mechanisms that rely on determining precise relative timing of first spikes may require the integration of “when” and “what” signals. One of them involves neurons that can be “tuned” to respond to a wide range of specific durations (Hooper et al. 2002). Through this mechanism, the temporal sum of the synaptic inputs of such a neuron corresponds to its firing rate (Loewenstein and Sompolinsky 2003). Within this framework, neurons can also integrate the two signals through mechanisms of coincidence detection. Owing to both their intrinsic and synaptic characteristics, such neurons could be sensitive to particular temporal patterns in their inputs (for example, the time interval between two afferent inputs), thereby converting a temporal representation of the stimulus into a firing-rate-based one (Azouz and Gray 2003; Polsky et al. 2004).

A second class of mechanisms that can recognize specific temporal firing patterns may be implanted through supervised learning rules in which a neuron is able to distinguish between different temporal input patterns. This is accomplished through the “tempotron” learning rule, which adjusts the synaptic efficacy of the different inputs. Through such learning rules, neurons can “learn” to categorize a broad range of input classes, as characterized by the latencies of single spikes (Gutig and Sompolinsky 2006).

Where does this integration occur? Based on Fig. 7 it seems likely that PrV neurons code mostly SA signals (i.e., velocity), and that SpVi neurons contain both RA and SA signals. If so, the integration is likely to occur downstream to these neurons. Several findings in the literature and our own observations show that TG neurons are sensitive to stimulus kinematics such as velocity, position, and acceleration (Bale et al. 2013; Petersen et al. 2008), and that these neurons correspond to SAth, SAar, and RA neurons, respectively (unpublished observations). These channels remain mostly separated in the thalamus (Petersen et al. 2008), suggesting that the signals were generally kept separate up to the thalamus. We conjecture that, upon arrival at the cortex, these channels converge, since numerous barrel cortical neurons are sensitive to a combination of multiple kinetic features (Maravall et al. 2007). An alternative approach was shown by Chagas et al. (2013), in which each TG neuron contains a combination of several kinetic features, suggesting that this integration may occur at earlier stages.
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DISCLOSURES

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AUTHOR CONTRIBUTIONS

Author contributions: E.L., E.G., and R.A. conception and design of research; E.L. and E.G. performed experiments; E.L. and E.G. analyzed data; E.L., E.G. and R.A. wrote the manuscript; R.A. prepared figures; R.A. edited and revised manuscript; R.A. approved final version of manuscript.

REFERENCES


