Populations of striatal medium spiny neurons encode vibrotactile frequency in rats: modulation by slow wave oscillations

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Hawking TG, Gerdjikov TV. Populations of striatal medium spiny neurons encode vibrotactile frequency in rats: modulation by slow wave oscillations. J Neurophysiol 109: 315–320, 2013. First published October 31, 2012; doi:10.1152/jn.00489.2012.—Dorsolateral striatum (DLS) is implicated in tactile perception and receives strong projections from somatosensory cortex. However, the sensory representations encoded by striatal projection neurons are not well understood. Here we characterized the contribution of DLS to the encoding of vibrotactile information in rats by assessing striatal responses to precise frequency stimuli delivered to a single vibrissa. We applied stimuli in a frequency range (45–90 Hz) that evokes discriminable percepts and carries most of the power of vibrissa vibration elicited by a range of complex fine textures. Both medium spiny neurons and evoked potentials showed tactile responses that were modulated by slow wave oscillations. Furthermore, medium spiny neuron population responses represented stimulus frequency on par with previously reported behavioral benchmarks. Our results suggest that striatum encodes frequency information of vibrotactile stimuli which is dynamically modulated by ongoing brain state.

dorsolateral striatum; medium spiny neurons; somatosensory; vibrotactile

METHODS

Surgery was carried out under institutional ethics approval and a project license granted by the UK Home Office under the Animals (Scientific Procedures) Act 1986.

Animals and surgery. Experiments were performed under urethane anesthesia in eight male Wistar rats (Charles River Laboratories, Wilmington, MA) weighing between 350 and 500 g. Rats were injected with an initial dose of m/kg urethane, which was supplemented with a second 0.25-mg/kg injection 20 min later. Pinch and corneal reflexes were monitored throughout the experiment, and the rat received 0.15-mg/kg top-ups if necessary to maintain anesthesia. This dosing regimen is similar to what was used previously to assess tactile encoding in rat barrel cortex (Arzabadeh et al. 2006; Hirata and Castro-Alamancos 2011). A similar regimen has also been used to study cortical contributions to UP and DOWN states in medium spiny neurons (Kasanetz et al. 2006). Thus the current approach provides results that are directly comparable with these studies. Body temperature was monitored rectally and maintained at 37°C using a homeothermic pad (Harvard Apparatus, Boston, MA). For fluid replacement, 5% glucose was continuously administered via an infusion pump (3 ml/h; Instech, K. D. Scientific, Holliston, MA). Glycopyrronium bromide (40 μl/kg im; Anpharm, Warsaw, Poland) was given to reduce respiratory tract secretions. Animals were fixed to a stereotaxic frame, and the head was adjusted so that lambda and bregma were on the same horizontal plane. A left-side craniotomy was performed under institutional ethics approval and a project license granted by the UK Home Office under the Animals (Scientific Procedures) Act 1986.

Tactile stimulation. The whisker stimulation was constructed from a glass capillary (1 mm o.d.) glued to a piezo bender (Physik Instrumente, Karlsruhe, Germany). The tip of the capillary was further thinned through heating until a whisker hair could rest snugly inside the tip opening. Voltage commands were programmed in Matlab (Mathworks, Natick, MA) and delivered using custom-written LabVIEW software (National Instruments, Austin, TX). The stimuli consisted of brief pulsatile deflections (single-period cosine wave, 100 Hz, duration 10 ms) presented to
the right C1 whisker for 1 s at interpulse intervals of 22, 17, 13, and 11 ms corresponding to frequencies of 45, 60, 75, and 90 Hz (amplitude 12°, i.e., 5-mm distance from the whisker base) (Fig. 1, A and B). The length of the glass capillary and point of attachment of the piezo element were optimized to remove ringing of the stimulator. Calibration with a phototransistor (HLC1395; Honeywell, Morristown, NJ) showed that differences in amplitude and peak velocity between frequencies were smaller than 3%. The capillary tip was positioned 5 mm away from the skin and tilted at an angle of 155°–175° against the whisker such that the vibrissa rested against the inside wall of the capillary, ensuring that the stimulator engaged the whisker immediately.

Electrophysiological recordings and analysis. Wideband signals were acquired continuously via an op-amp-based headstage amplifier (HST/8o50-G1-GR, 1 kHz gain; Plexon, Dallas, TX), passed through a preamplifier (PBX2/16wb, 1,000 kHz gain; Plexon), and digitized at 40 kHz. Recording electrodes consisted of quartz glass-coated platinum/tungsten wires pulled and ground to custom shapes in our laboratory (shank diameter 80 μm; diameter of the metal core 23 μm; free tip length ~8 μm; impedance 1–3 MΩ; Thomas Recording, Giessen, Germany). DLS recording electrodes pierced dura and were advanced into DLS using established coordinates, covering DLS areas receiving extensive barrel cortex input and known to respond to air puffs delivered to the whisker (Hoffer and Alloway 2001; Syed et al. 2011). DLS penetrations were located AP 0.8 to 1.5 mm, ML 2–5 mm, DV 4–7 mm (Fig. 1C). All data processing was done offline. For spike sorting, the raw signal was band-pass filtered 300–3,000 Hz, and spikes were sorted using the Matlab-based Wave_clus software to yield single-unit spike trains (Quiroga et al. 2004). Wave_clus performs unsupervised spike detection and sorting using wavelets and super-paramagnetic clustering. All automatic detection thresholds and...
sorting solutions were examined individually and adjusted if needed. Field potentials were recorded from the same electrode and were downsampled to 5,000 Hz and evoked responses extracted from the raw data using a 200 Hz low-pass Butterworth filter. Responses were averaged over 20 trials. Single unit tactile responses were calculated by adding spikes in a 500-ms window after stimulus onset and subtracting the baseline firing rate calculated over 100 ms. To investigate the effect of DLS slow oscillations on tactile responses, local field potentials (LFPs) were low-pass filtered <5 Hz using a second order Butterworth filter, and a Hilbert transform was applied to obtain the instantaneous phase angle (Saleem et al. 2010). Mean phase angle and resultant vector length were calculated using the Matlab Circular Statistics Toolbox (Behrens 2010; Fisher 1993). Analyses were calculated using Neuroexplorer (Nex Technologies, Littleton, MA) and custom-written Matlab routines. ANOVA were performed using SPSS (IBM SPSS, Somers, NY).

RESULTS

DLS tactile-evoked potentials are modulated by slow oscillations. Vibrotactile stimuli elicited evoked field potential responses in DLS (Fig. 2A). Studies done in cortex show a strong relationship between the phase of low-frequency LFP of deep cortical layers and intracellularly recorded neuronal UP/DOWN states (Saleem et al. 2010). We low-pass filtered field potential traces <5 Hz and used a Hilbert transformation (Fig. 2, B and C) to derive the instantaneous phase of spontaneous striatal LFP. Instantaneous LFP phase at stimulus onset calculated in this manner was evenly distributed across the 0–360° waveform cycle as would be expected with random stimulus presentations (mean resultant vector length of the phases at onset = 0.06, P = 0.3). We next calculated the slope of the evoked potential curve between 0 and 200 ms after stimulus onset and plotted it against the phase of the slow oscillations assessed at stimulus onset on a trial by trial basis (compare Wyble et al. 2000). The magnitude of the tactile response showed a clear modulation by oscillation phase (Fig. 2D). The response was strongest during the 0–180° portion of the slow wave oscillation corresponding to a DOWN state, and it was virtually absent at 270° corresponding to the UP state oscillation. Evoked potentials, however, did not appear to be modulated by stimulus frequency, even when controlling for slow oscillation phase.

A  MSN spike phase, neuron 1

B  MSN spike phase, neuron 2

C  Population spike phase angles

Fig. 3. Spontaneous medium spiny neuron (MSN) activity related systematically to the phase of the ongoing LFP oscillations that were used to infer UP and DOWN states (see text). A and B: representative single unit activity. From left to right: spike waveforms and averages; time stamps of spiking activity relative to the ongoing LFP oscillations recorded simultaneously from the same electrode; angle histograms of instantaneous LFP phase at the time of spike occurrence. r is the length of the mean phase angle vector and represents the strength of directionality. ** <0.001 (Rayleigh’s test). C: average LFP phase angles at the time of spike occurrence for all 35 medium spiny neurons recorded in this study. Average phase angles are represented by the angle of the resultant vectors, whereas resultant vector length represents the magnitude of the directionality effect.
Populations of MSNs encode vibrotactile stimulus frequency during DOWN/UP transitions. Medium spiny projection neurons (MSNs) represent more than 90% of rat striatal neurons, and unlike DLS interneurons are characterized by a relatively low firing rate (Berke et al. 2004; Rymar et al. 2004). To ensure only this cell type entered our data set, we recorded units with low baseline activity (<5 Hz), and the firing rates we observed (1.37 spikes/s ± 1.25, means ± SD) are consistent with previous studies (Barnes et al. 2005; Berke et al. 2004; Mowery et al. 2011; Schmitzer-Torbert and Redish 2008; Sharott et al. 2009). Furthermore, we noted that the spike waveforms of the recorded units showed peak to valley intervals (means ± SE) of 735 ± 57 μs and peak widths of 372 ± 15 μs, which are in agreement with previously reported MSN extracellular waveform characteristics (Wiltschko et al. 2010).

We recorded from 35 neurons. Consistent with previous work showing subthreshold responses to tactile stimuli in intracellular recordings but a weak spike response when single pulses were used (Pidoux et al. 2011), here with the delivery of high frequency stimuli only a small percentage of cells responded to a 45-Hz stimulus. Seven out of the 35 recorded units (20%) showed a significant change in firing rate during the 500 ms after stimulus onset (P < 0.05; Wilcoxon signed-rank test). In all cases, the response was a small increase in firing (0.53 spikes/s ± 0.18). When stimulating at 60 Hz, we obtained 23% responsive units (0.52 spikes/s ± 0.14), at 75 Hz 23% (0.54 spikes/s ± 0.49), and at 90 Hz 11% (0.70 spikes/s ± 0.34). Thus tactile responses of individual MSNs to stimuli at different frequencies were sparse, similar to responses to pulses (Pidoux et al. 2011). To investigate a possible contribution of UP/DOWN state transitions, instantaneous LFP phase was used to construct phase histograms of MSN spike times (Fig. 3, A and B) (Saleem et al. 2010). Spontaneous MSN firing was highest during the negative component of the LFP wave, consistent with recent combined intracellular and LFP recordings in cortex showing a mean phase distribution of the low-pass filtered LFP trace of 200–225° during UP states (Fig. 3C) (Saleem et al. 2010). Thus our DLS results are consistent with the previously observed phase relationship between cortical membrane states and slow oscillation phase.

We next tested if slow oscillation phase affects DLS tactile responses. To do this, we extracted the instantaneous phase of striatal LFP at the onset of each stimulus. Within each unit (i.e., individual trials serving as replications), phase did not appear to modulate the relationship between stimulus frequency and firing rate (ps > 0.10 for the phase × stimulus interaction term in individual unit multiple regressions). However, in the population (i.e., individual cell averages serving as replications), the tactile response was related to LFP phase at stimulus onset (Fig. 4). This was supported by a phase (4 quadrants) × stimulus (4 frequencies) repeated measures ANOVA [main effect of phase, F(3, 102) = 10.31, P < 0.01; interaction, F(9, 306) = 1.86, P = 0.056]. We tested different amplitude (2–12°) × frequency (45–90 Hz) combinations on a subset of cells (n = 17). This did not reveal any amplitude effects, but confirmed the phase × frequency interaction [F(9, 27) = 2.34, P = 0.017]. The interaction was followed up with simple one-way ANOVAs at each phase interval, which showed a clear frequency response for stimuli arriving between instantaneous phases of 90 and 180° [F(3, 102) = 3.24, P = 0.025].

In previous work, cortical DOWN states showed a mean phase distribution of 290–320° (compared with 110–135° during UP states; here 0° corresponds to the positive peak in the slow oscillation, cf. Fig. 1C); thus the 90–180° quadrant roughly corresponds to the transition from DOWN to UP states. Specifically, firing rate was significantly higher for 45 Hz compared with 75 and 90 Hz and for 60 Hz compared with 90 Hz (pairwise comparisons, P < 0.05). The effect of frequency was not significant in other phase intervals. We conclude that tactile responding is sparse and shows no stimulus frequency modulation at the level of individual MSNs. However, firing rate was related to stimulus frequency in the population, and this effect was dynamically modulated by slow oscillation phase: vibroacoustic frequency was encoded during the transition from DOWN to UP states.

Spike-phase coding refers to the encoding of information in the relative timing of neuronal activity to slow background rhythms (Kayser et al. 2009). To assess whether the timing of spikes relative to the ongoing slow oscillation is related to stimulation frequency, we calculated the average LFP slow oscillation phase of all recorded neurons in a 2-s window prior to stimulus presentation (cf. Fig. 1C). The interaction between instantaneous stimulation frequency and slow oscillation phase was compared with 75 and 90 Hz and for 60 Hz compared with 90 Hz (pairwise comparisons, P < 0.05). The effect of frequency was not significant in other phase intervals. We conclude that tactile responding is sparse and shows no stimulus frequency modulation at the level of individual MSNs. However, firing rate was related to stimulus frequency in the population, and this effect was dynamically modulated by slow oscillation phase: vibroacoustic frequency was encoded during the transition from DOWN to UP states.

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to tactile stimulation as well as during the 1 s of tactile stimulation separately for each of the four stimulation frequencies. However, a \(4 \times 2\) (frequency \(\times\) window) within-subjects ANOVA across neurons showed no effect of frequency or analysis window \((p > 0.5)\). Thus we found no evidence for spike-phase coding of frequency information in this system.

**DISCUSSION**

Striatum is increasingly being recognized as contributing to sensory processing in addition to its traditional role as a motor structure (Sathian et al. 1997; Schneider et al. 1987; Zia et al. 2003). Here we characterized the encoding of vibrotactile information in rat DLS assessing striatal responses to frequency stimuli applied to a single vibrissa. Our results suggest that populations of striatal neurons are in principle able to represent vibrotactile frequency in this system. This property of MSNs is modulated by slow wave oscillations likely originating in cortex or thalamocortical loops.

We found that field potentials obtained within the DLS projection field of the barrel cortex show robust responses to tactile vibrations but carry no information about stimulus parameters. LFP reflects neural activity summed over some distance from the recording location, which may, to some extent, explain the loss of stimulus detail observed here (Kajikawa and Schroeder 2011). To address this, we characterized the tactile response of individual MSNs recorded within the DLS to higher frequency stimuli (45–90 Hz) that were shown to elicit discriminable percepts in head-fixed rats. We found that the MN tactile response to this stimulus set was sparse. This observation is consistent with recent intracellular work showing superior tactile responses in subthreshold cellular activity and only weak action potential generation (Pidoux et al. 2011). However, we also demonstrate that stimulus parameters of tactile vibrations in the higher frequency range are well represented in the population response. It is also noteworthy that these population results fit quite closely the behavioral discrimination performance observed in head-fixed rats in earlier work (Gerdjikov et al. 2010). This is compatible with some forms of sensory encoding carried out in DLS to support its role in automatic stimulus-response behaviors observed in lesion studies (Ding et al. 2010; Yin et al. 2008). However, we acknowledge that this is correlational evidence, and further work is necessary to elucidate the possible role of DLS medium spiny neurons in tactile perception.

During slow wave sleep, quiet wakefulness, and some forms of anesthesia, brain states are characterized by low-frequency, large-amplitude membrane potential changes (Petersen et al. 2003; Steriade et al. 1993). These so-called UP and DOWN states are an attractive model for understanding how internally generated states may impact the neural representation of sensory stimuli (Haslinger et al. 2006; Watson et al. 2008). We found that both tactile-evoked potential and MSN responses are dynamically modulated by brain state, and that the optimal representation is achieved during LFP phases consistent with DOWN to UP transitions \((0–180^\circ)\). This result is consistent with tactile responses obtained in cortex, where multiunit responses are a smooth function of prestimulus LFP that peaks between 90 and 180\(^\circ\) and is mostly flat between 270 and 360\(^\circ\) (Haslinger et al. 2006). Previously reported findings that cortical responses to sensory input are modulated by UP/DOWN state transitions suggesting that these oscillations play a role in information processing or gating (Civильico and Contreras 2012; Hasenstaub et al. 2007; Petersen et al. 2003). In the current study, we show that a similar gating mechanism operates at the level of striatum. The gain adjustment of DLS sensory input observed here may relate to specific sensory tasks or arousal states, which also affect brain state (Castro-Alamancos 2004; West 1998).

This is the first report of striatal responses to precise vibrotactile stimuli in behaviorally relevant frequency ranges in the rat whisker system. These stimuli evoke discriminable percepts in behavioral tasks and carry most of the power of vibrissa vibration elicited by a range of complex fine textures. We found that the striatal representation of specific stimulus parameters was sparse and that population responses in striatum appear to well represent stimulus parameters. The tactile stimulus representation obtained in DLS parallels previously reported behavioral benchmarks. DLS slow oscillations appear to play a permissive role in these tactile representations.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**

T.G.H. performed experiments; T.G.H. analyzed data; T.G.H. approved final version of manuscript; T.V.G. conception and design of research; T.V.G. drafted manuscript; T.V.G. edited and revised manuscript.

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