Coding of self and environment by Pacinian neurons in freely moving animals

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SUMMARY

Pacinian corpuscle neurons are specialized low-threshold mechanoreceptors (LTMRs) that are exquisitely tuned to high-frequency vibration (~40-1000 Hz)[1–5]. Although much is known about their tuning properties, it is unclear how Pacinians encode naturalistic behavior. Here, we developed a technique to record from Pacinian neurons and other LTMRs in awake, freely moving mice. We find that Pacinian LTMRs can robustly respond to self-generated vibrations caused by movement alone. Pacinians are highly active during a wide variety of natural behaviors, including grooming, digging, and climbing. Pacinians in the hindlimb are sensitive enough to be activated by forelimb- or upper-body-dominant behaviors. Strikingly, Pacinians can uniquely and reliably encode subtle vibrations of surfaces encountered by the animal, including low-amplitude vibrations initiated over two meters away. Finally, as a population, there is a broad range of Pacinian responses during natural behaviors and environmental vibrations, and an individual Pacinian's responsiveness is strongly dependent on its distinct sensitivity and frequency tuning. Thus, Pacinian corpuscle LTMRs, with their varying sensitivities, frequency tuning, and body distributions, collectively encode a wealth of vibro-tactile features of self-initiated movements and the environment.

MAIN TEXT

Touch is encoded by combined activation of sensory neurons that respond to distinct features of mechanical stimuli[6]. The tuning of sensory neurons is generated by their innervation of specialized end organs in the skin and deep tissue[4,5,7–11]. Conserved from humans to mice, sensory neurons innervating Pacinian corpuscles can phase-lock their firing to mechanical vibrations at frequencies up to 1000 Hz and are most sensitive between ~200-600 Hz[1–5,12–19]. Despite their exceptional ability to detect vibration, it is unclear as to what extent vibrations are encountered and how Pacinians are activated during naturalistic behaviors or conditions that involve the entire body, as existing recording techniques are performed in anesthetized animals[17,18,20] or restrained subjects[19,21]. To answer these questions, we have developed a strategy to record from single dorsal root ganglion (DRG) neurons, including Pacinian neurons, in awake freely moving mice (**Fig. 1a-b, Extended Data Fig. 1)**. These recordings allowed us to measure how a variety of Aβ sensory neurons encoded stimuli as animals explored their environment, reacted to external stimuli, and performed active movements using full body motions.

We obtained high signal-to-noise single-unit recordings from individual low-threshold mechanoreceptors (LTMRs), including Pacinian corpuscle neurons (Aβ RA2-LTMRs), and proprioceptors that innervated the hindlimb (**Fig. 1a**). Electrodes were then implanted, and animals were awoken and allowed to recover. The identified unit could be recorded as animals moved freely, carrying only a light-weight implant (< 1.5 grams; **Fig. 1b-c**, **Extended Data Fig. 1**). Animals were alert and fully mobile after only a few hours of recovery, performing typical behaviors such as grooming, burrowing, eating food, and running, and recordings remained stable for hours even during the most physically demanding tasks.

In humans and primates, Pacinian corpuscles are found in the deep dermis and subcutaneous tissue[22,23]. However, in mice and other small mammals, Pacinian corpuscles are found in the periosteum membrane surrounding bones of the limbs[24–28], far from where the animal makes contact with the ground. Given this distance between Pacinians and the skin, we first asked whether they were activated during movement. Pacinian neurons were robustly activated as animals explored their environment and some were almost constantly active (**Fig. 1d, j, k, i**). To our surprise, Pacinians were some of the most active neurons during running, firing on average at hundreds of Hz and often with brief bursts at very high instantaneous frequencies, up to 900 Hz

57 (**Extended Data Fig. 2**). The firing rate of Pacinians was often higher than any other cell type,
58 including proprioceptors, which are known to be strongly activated by movement. Other LTMRs
59 innervating hindlimb hairy and glabrous skin had lower firing rates, and their cutaneous
60 receptive fields had to be directly contacted to evoke firing.

61 To understand how Pacinians and other sensory neurons are activated during behavior, we
62 focused on locomotion, which can be broken into several components of the step cycle. We
63 performed high-speed imaging at 200 frames/second to analyze the relationship between firing
64 and body movement (**Fig. 1d-i**). Pacinians were consistently most active when the foot contacted
65 the ground at the end of a step. However, some Pacinians were also broadly active at all step
66 cycles, even during stance when the hindlimb was not in motion. The profile of Pacinian firing
67 also depended on the type of surface making contact with the foot. Soft, crumbly bedding
68 generated large bursts when the foot made contact (**Fig. 1d, f**), whereas hard surfaces, such as
69 acrylic, generated a brief burst followed by a brief suppression of firing (**Fig. 1e, f**).
70 Proprioceptors and LTMRs varied in changes to their activity during running (**Supplemental**
71 **video 1**). Whereas most neurons increased their firing when the foot made contact with the
72 ground, some proprioceptors transiently decreased their firing during the step cycle (**Fig. 1g, j-l**).
73 The timing of LTMR and proprioceptor firing also varied, with some activated before the foot
74 contacted the ground (**Fig. g-l**). The nature of LTMR and proprioceptor firing was related to the
75 cutaneous receptive field or muscle they innervated, as previously described for proprioceptors[29–
76 31].

77 The firing of Pacinians across the step cycle led us to ask how mechanical stimuli move through
78 the body. In the hindlimb, Pacinians are most often found at the base of the fibula[9,32], suggesting
79 that vibration propagates through the bone and tissue of the ankle to activate Pacinians. Could
80 footfalls from the contralateral foot propagate through the body's skeletal system to activate
81 Pacinians? We found that during locomotion Pacinians fired in response to footfalls of the
82 ipsilateral hindlimb, but not the contralateral hindlimb (**Extended Data Fig. 3**). Thus, activity
83 during locomotion is likely generated by vibration of the ipsilateral limb.

84 In addition to firing during all parts of the step cycle, we observed that Pacinians were often
85 activated by subtle movements. These subtle movements did not activate other LTMRs. Most
86 Pacinians became completely silent when no movements were visible (7/9), but some continued

87 to fire (2/9). We hypothesized that very small movements not detectable in videos could be
88 sufficient to activate Pacinians. This led us to ask whether Pacinians respond to vibrations that
89 are generated by micromovement of the skin along surfaces, or whether Pacinians are activated
90 by movement of the body alone in the absence of contact with external surfaces. To test these
91 possibilities, we removed all external stimuli from the hindlimb and body by lifting animals by
92 the tail or recording tether to suspend them in the air (**Fig. 2a, Supplemental video 2**). When
93 airborne, animals often moved their limbs, presumably to balance themselves or find a nearby
94 structure. During these movements a majority of Pacinians (5/9) fired even though there was no
95 contact between the limbs and any surfaces or foot collisions with the body (**Fig. 2b-c**). Thus,
96 Pacinians can be activated by movement of the body itself, even in the absence of external
97 stimuli. We found that other LTMRs did not fire when animals were airborne, unless the
98 receptive field was in an area where hair was deflected by movement of the limb, especially near
99 joints.

100 During natural behavior, we observed that many movements activated Pacinians. Interestingly,
101 Pacinians in the hindlimb could be activated during behaviors that primarily involved the upper
102 body. When mice were placed in an arena filled with sand, they instinctively burrowed[33], using
103 their forelimbs to dig and push sand behind them through their legs (**Fig. 2d-e, Supplemental**
104 **video 3**). Pacinians were activated by digging motions despite little detectable movement in the
105 hindlimbs (**Fig. 2f-g**). The time course of activation matched the duration of pushing sand with
106 the forelimbs. While digging, animals accumulated sand or bedding within their fur. In order to
107 remove foreign objects from their hair, they often cleaned themselves by vigorously shaking
108 their upper body in a highly stereotyped behavior known as the 'wet dog shake' that is performed
109 by many different animals[34] (**Fig. 2h, Supplemental video 3**). During wet dog shakes, the
110 hindlimb remained firmly in place, but Pacinians fired during the rotation of the head and upper
111 body (**Fig. i-j**). Thus, Pacinians could be activated during behaviors involving the upper body
112 that required some degree of balance and postural support by the hindlimbs.

113 Animals were also placed on sloped structures to determine how Pacinians were activated by
114 climbing. As animals scaled obstacles, they occasionally slipped on the smooth metal surface of
115 the climbing structure (**Fig. 2k-l**). We found that Pacinians were robustly activated when animals
116 slipped (**Fig. 2m-o**). Firing of Pacinians during slip was especially obvious when slips were

preceded by a period of still posture on the sloped surface (**Fig. 2m, Supplemental video 4**). Thus, movement of the hindlimb across a smooth surface with the animal's weight applied was sufficient to activate Pacinians.

The remarkable responsivity of Pacinians during self-motion prompted us to ask whether Pacinian LTMRs are also activated by vibrations generated by distant sources, external to the mouse. We placed animals on different materials and vibrations were generated by running the experimenter's finger or a metal tool across the material with slight pressure (**Fig. 3a**). Movement of the finger across the surface generated vibrations that could be simultaneously measured with an accelerometer, with the amplitude of vibrations expressed as the root mean square amplitude in units of g-force (g_{RMS}, **Fig. 3b**). These vibrations ranged in amplitude depending on the surface and vigor of movement, but were smaller in amplitude than those generated by a cell phone (0.5 g_{RMS}, 150 Hz). These externally generated stimuli were often sufficient to activate Pacinian neurons (**Fig. 3b, Supplemental video 5**). For example, running a metal tool across sandpaper generated strong vibrations in the sandpaper, and robustly activated Pacinians as mice stood on the surface many centimeters away (**Fig. 3c-d**). Running a finger across sound insulation foam or cardboard generated more subtle vibrations of different frequencies compared to sandpaper, and these distant surface vibrations also strongly activated Pacinians. Materials that generated vibrations outside of the detectable range of Pacinians, such as a smooth acrylic surface did not activate Pacinians. Interestingly, the amplitude of vibrations alone was insufficient to explain Pacinian firing - movement over cardboard generated vibrations that were larger in amplitude compared to that of foam, but generated responses that were of smaller or equal magnitude (**Fig. 3e, f**), possibly due to the different frequencies generated by each stimulus. The responses to external vibrations were also unique to Pacinians, as other LTMRs and proprioceptors did not respond to floor surface vibrations (**Fig. 3f**, **Extended Data Fig. 4, Supplemental video 6**).

How do external vibrations propagate through the mouse to activate Pacinians? Given their sensitivity to both internally generated movement and upper body movements, we asked whether hindlimb Pacinians could also detect vibrations that propagate from either the contralateral hindlimb or the forelimbs. We examined moments when animals were on a vibration source, but had lifted their ipsilateral hindlimb off the surface, such as during the swing phase of walking.

Pacinians fired robustly to vibrations, but they paused their firing to near baseline levels of activity when the ipsilateral hindlimb was not making contact with the surface (**Extended Data Fig. 5**). These findings suggest that Pacinians are likely detecting external vibrations primarily propagated up the ipsilateral hindlimb.

The sensitivity of Pacinians to vibrations of manufactured surfaces like foam, cardboard and sandpaper led us to ask whether they can respond to external vibrations propagating across surfaces naturally encountered by mice in the wild. We noted that vibrations can be detected most effectively when mechanical waves are propagated in rigid but low-density materials such as cardboard or wood. We therefore placed animals at the end of a long tree branch, a structure on forest floors likely to be explored by wild mice **(Fig. 3g-h**). A probe was used to deliver mechanical stimuli to the opposite end of the tree branch, and vibration frequency and amplitude were measured using an accelerometer placed near the mouse. Tree branches effectively transmitted weak mechanical stimuli such as taps or gentle movement of the probe along the surface of the wood (**Fig. 3i**). These distant stimuli could be robustly detected and encoded by Pacinians when animals were still. Remarkably, these stimuli could be as far as 2.5 meters away from the animal (the furthest distance tested) and still activate the Pacinian (**Fig. 3i, Supplemental video 7**). The magnitude of firing scaled with the intensity of vibration, with more vigorous vibrations generating higher firing rates (**Fig. 3j**). Some Pacinians could detect vibrations as low as 0.027 g_{RMS}, corresponding to a displacement amplitude of approximately 100 nm for a 500 Hz sinusoidal vibration (see methods). Taps to the branch could activate Pacinians in less time than it takes to trigger a motor response (<5 ms, **Extended Data Fig. 6**). These mechanical stimuli failed to activate proprioceptors and cutaneous LTMRs, including LTMRs innervating small hairs on the ventral surface of the hindlimb (**Extended Data Fig. 6**). Pacinians could also detect gentle mechanical stimuli delivered far away (1 m) on long stretches of cardboard, likely to be encountered by wild mice in an urban environment (**Extended Data Fig. 6**). Thus, vibrations and mechanical stimuli can be uniquely detected by Pacinians over large distances when vibrations propagate through materials that are likely encountered by wild mice.

When recording from Pacinians, we found that they varied in their tuning and sensitivity. When animals were anesthetized, we measured full vibration threshold tuning curves and their

sensitivity to static indentation of the skin. Most Pacinians were highly sensitive to vibration, with thresholds less than 5 mN for frequencies ranging from 300-500 Hz, and to static indentation. However, some Pacinians (4/9) were less sensitive to both vibration and indentation (**Fig. 4a, b, g**). These less sensitive units (>5 mN indentation threshold) responded differently during behavior in awake animals (**Fig. 4c-f**). Less sensitive units had lower firing rates during movement. During locomotion, these units responded more selectively to footfalls, and remained silent during other phases of leg movement (**Fig. 4c, d, j, Supplemental video 8**). They were also less responsive to externally generated vibrations, responding to large amplitude vibrations generated in sandpaper, but not to smaller amplitude vibrations generated by rubbing foam or cardboard (**Fig. 4e, f, k, Supplemental video 9**). These Pacinians were not activated as animals were removed from external stimuli (**Fig. 4i**), suggesting they were less responsive to self-generated movement. Moreover, the firing rate of Pacinians in response to various behaviors fell as a function of their threshold to indentation and vibration (**Fig. 4g-k**). Thus, across the population, Pacinians exhibit a broad spectrum of sensitivities and responsiveness, with some able to detect very small amplitude vibrations and others responding only to coarse mechanical stimuli such as collision of the limb with surfaces.

DISCUSSION

Pacinian corpuscles are specialized end organs tuned to detect high frequency mechanical vibration[1–4,12–19]. Prior work in anesthetized animals, restrained subjects, and modeling work has proposed a limited set of behaviorally relevant stimuli that may be encoded by Pacinian LTMRs[5,17,20,35–37], but the role of the Pacinian's unique vibration tuning during freely moving behavior has remained unknown. Here we show that Pacinian neurons in awake, freely moving animals can be very active, sensing vibrations generated during self-movement and vibrations encountered in the environment. They are also activated during a wide variety of behaviors, including many that do not involve obvious direct vibration of the skin. Many of these behaviors primarily involve parts of the body not associated with the Pacinian itself. Remarkably, some Pacinians were extremely sensitive to externally generated vibrations despite that the end organ itself was located in deep tissue surrounding the fibula. These sensitive Pacinians located far up the leg of the animal could detect weak vibrations from 2.5 meters away, the furthest distance tested. Our findings indicate that low-amplitude vibrations of mouse hind paws contacting a

vibrating surface propagate through hindlimb bone and tissue to activate Pacinians within the periosteum of the fibula.

The most sensitive Pacinians in the hindlimb were often activated not just by external vibrations, but also by movement, including behaviors involving the upper body and forelimbs. These behaviors likely involve postural changes and movement of the hindlimb that were not detectable by video, but are sufficient to activate Pacinians. We found that a subset of Pacinians are so sensitive that they could respond during movements of different regions of the body and detect external vibrations as small as 100 nm in amplitude. Pacinians that were less sensitive to external vibrations were not activated by body movement alone. Thus, responses to self-generated movement may be a consequence of sensitivity to any sub-micron amplitude vibrations.

Pacinians exhibited a range of sensitivities that were correlated with their responsiveness during behavior. This diversity in tuning is well suited for generating a population code for mechanical stimuli. For example, whereas the most sensitive Pacinians were saturated during vigorous movements, input from less sensitive Pacinians could be informative for discriminating internally and externally generated vibration. Animals also have Pacinians located in each of their limbs, and our results suggest that Pacinians primarily detect stimuli within the limb that they innervate. Thus, animals are equipped with vibration sensors of varying sensitivity across all limbs, providing a rich array of information about both movement and the environment. Future experiments in downstream spinal cord and brainstem regions will be required to understand how self-initiated and environmental high-frequency vibrations are processed and utilized for guiding behavior.

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FIGURES AND LEGENDS

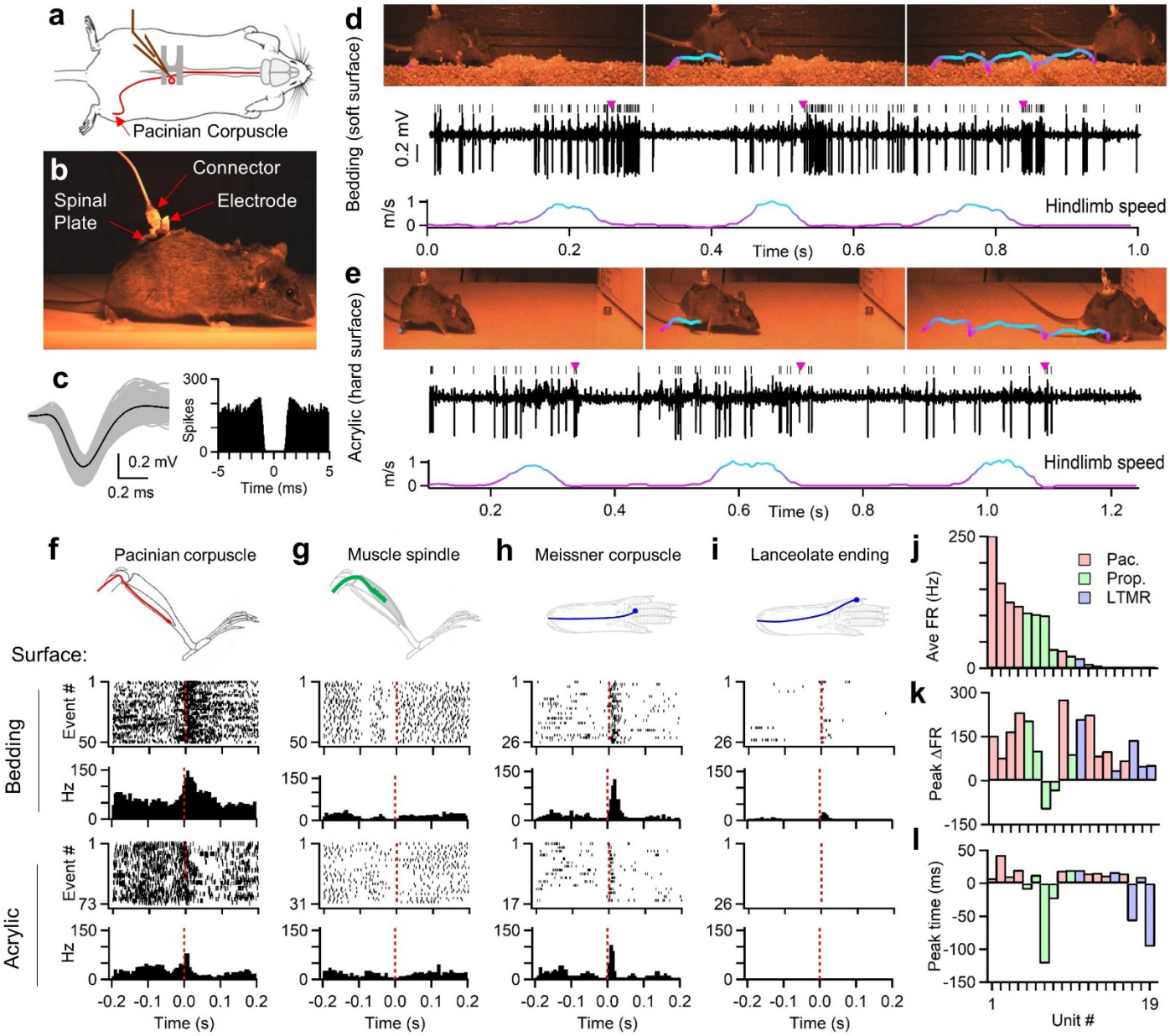


Figure 1: Activation of sensory neurons during locomotion

a. Recording setup: glass electrodes were implanted into L4 DRG for single unit recordings.

b. Video frame of mouse post-implant.

c. Example Pacinian LTMR spike waveforms (left) and autocorrelogram (right).

d. Example video frames of animal during walking on bedding (top), firing of Pacinian LTMR (middle), and hindlimb movement speed (bottom). Trace color indicates hindlimb movement speed. Purple ticks indicate ipsilateral hindlimb touchdown.

e. Same Pacinian as in d, but recorded during walking on a hard acrylic surface.

f. Location of a recorded Pacinian corpuscle LTMR (top). Raster and PSTH when the ipsilateral hindlimb landed (t = 0) at the end of swing cycle during locomotion on bedding (middle) or on an acrylic surface (bottom).

g. Same as f, but for a muscle spindle afferent.

h. Same as f, but for an Aβ RA1-LTMR (Meissner corpuscle) located on a pedal pad.

i. Same as f, but for an Aβ RA-LTMR lanceolate ending neuron innervating digit hairs.

j. Average firing rate (Ave. FR) during any locomotion for each recorded unit. Color indicates unit type: Pacinian (Pac.), proprioceptor (Prop.), or cutaneous LTMR (LTMR).

k. Peak change in firing rate (Peak ΔFR) during or after a hindlimb touchdown.

l. Time of peak change in firing rate during a hindlimb step cycle relative to a foot landing (t = 0; n = 19 units, N = 19 animals).

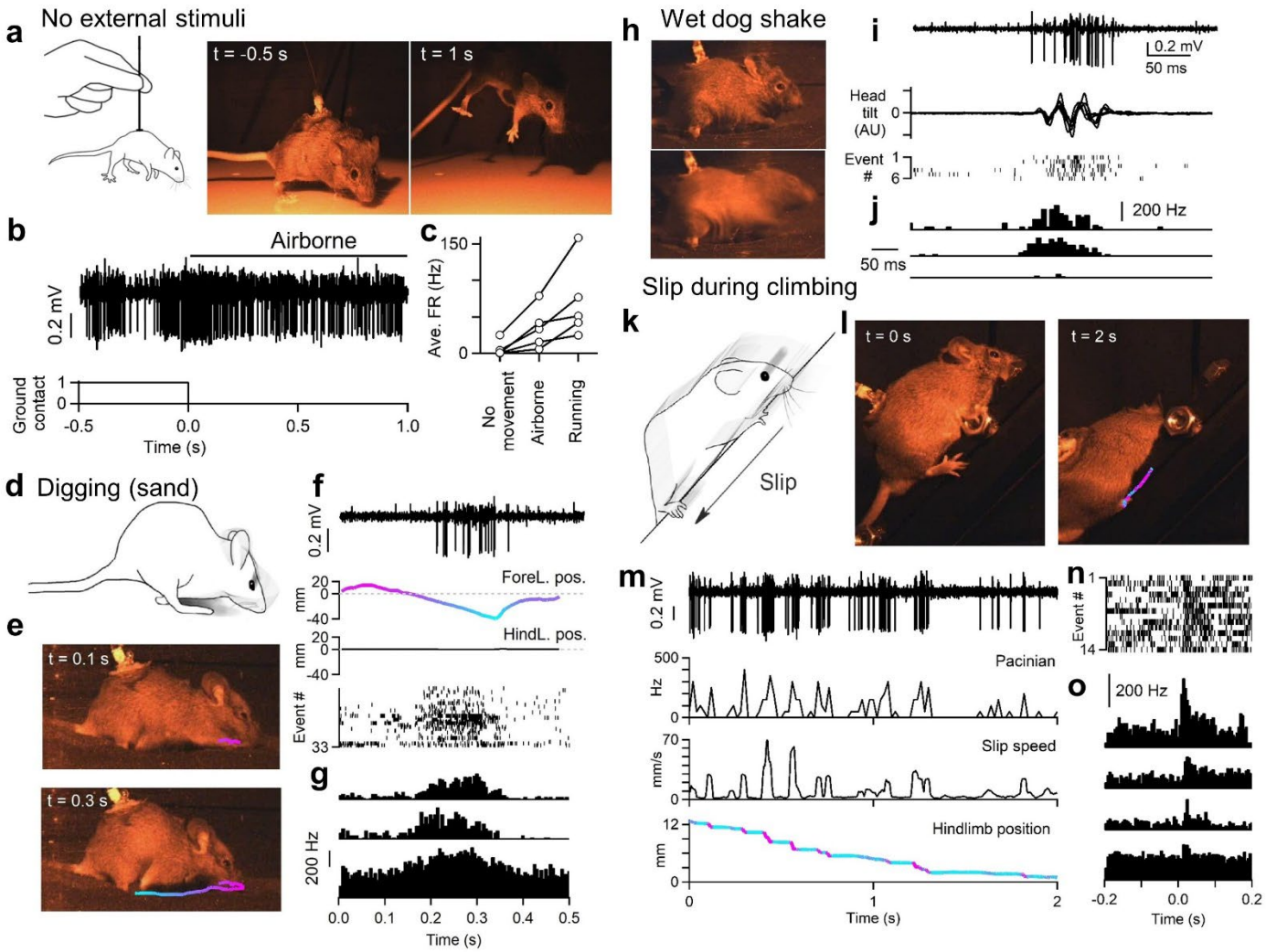


Figure 2: Pacinians are activated during movement and self-generated vibrations

a. Animals were picked up by the recording tether or by the tail (left). Video frames of animal on (middle) or lifted off (right) walking surface.

b. Example hindlimb Pacinian firing when animal was lifted from walking surface.

c. Average Pacinian firing rate when animals were completely still, airborne, or running (n = 30 lifts, N = 5 animals).

d. Animals placed in sand burrowed using forelimbs.

e. Example video frames of animal burrowing with forelimb tracking. Color indicates forelimb position relative to the start of burrowing behavior.

f. Example hindlimb Pacinian recording during burrowing from top to bottom: raw trace, forelimb position (ForeL. pos.), hindlimb position (HindL. pos.), raster of spiking for all events.

g. PSTH of three different hindlimb Pacinians during burrowing. t = 0 is time of burrowing motion start (n = 98 digs, N = 3 animals).

h. Video frames of before (top) and during (bottom) a wet dog shake.

i. Example hindlimb Pacinian recording during wet dog shake from top to bottom: raw recording, relative head tilt measured by LFP during recording, raster of spiking for all wet dog shakes

j. PSTHs of three different hindlimb Pacinians during wet dog shake (n = 27 shakes, N = 3 animals).

k. Animals climbed a smooth metal rail, slipping along the surface.

l. Video frames of animal slipping, with hindlimb tracking. Color indicates speed of movement.

m. Example Pacinian recording during slip from top to bottom: raw recording, firing rate, slip speed, tracked foot position along rail.

n. Raster of spiking for all slips in m, slip start is t = 0.

o. PSTHs of four different Pacinians during climbing slips (n = 77 slips, N = 4 animals).

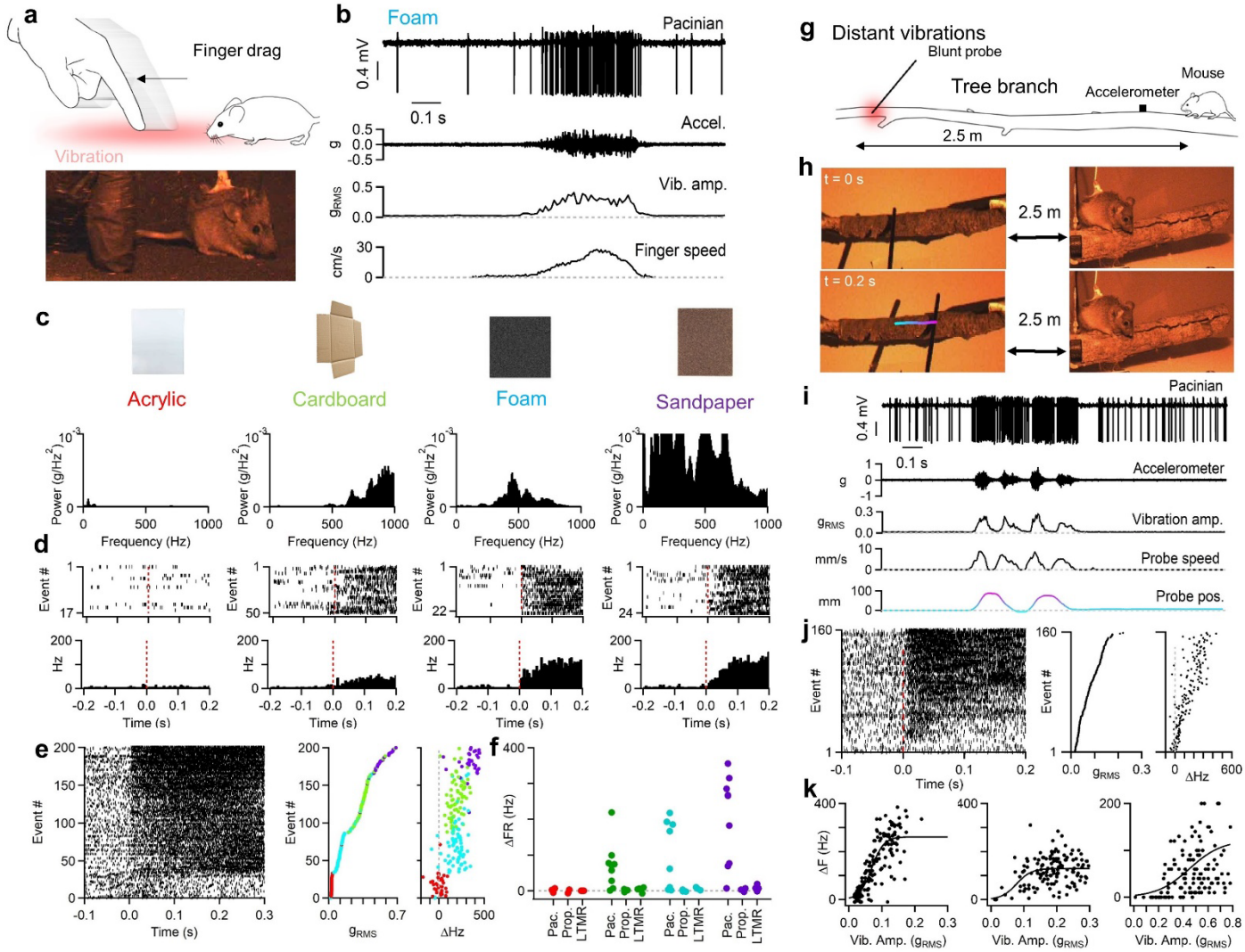


Figure 3: Pacinians are exquisitely sensitive to external surface vibrations

a. Animals stood on surfaces of different materials and the experimenter's finger or a tool was dragged across the surface, creating vibrations (top). Still frame of mouse sitting on foam as the experimenter's finger was moved across the surface (bottom).

b. Example Pacinian recording during surface vibrations. From top to bottom: raw recording, raw accelerometer data, root-mean-square of accelerometer data (vibration amplitude, vib. amp.), speed of probe (finger) movement across surface.

c. Surface material tested (top) and power spectrum of vibrations detected by accelerometer (bottom) for each surface.

d. Example single Pacinian response for vibration of each surface with rasters (top) and histograms (bottom). t = 0 is start time of probe or finger movement across surface.

e. Raster of spiking for all vibrating surface events for an example Pacinian sorted by amplitude of vibration (left). For same example Pacinian, amplitude of vibration for each event color coded by surface type (middle), and change in firing rate for each event (right). Each marker is one event for the unit. Color corresponds to materials in c. Pacinians in d and e are different units.

f. Average change in firing rate for each surface for Pacinians (Pac.), Proprioceptors (Prop.), and cutaneous LTMRs. Each marker is one unit (n = 9 Pacinians, 5 proprioceptors, 4 LTMRs, N = 18 animals). Color corresponds to materials in c.

g. Animals were placed on a tree branch (2.6 m length, 2-6 cm diameter). A probe was used to generate vibrations on the distal end.

h. Example video frames of a mouse on a tree branch (right) and probe movement (left). Color corresponds to probe displacement (see i).

i. Example Pacinian recording. From top to bottom: raw recording, raw accelerometer data, vibration amplitude (root-mean-square accelerometer data), speed of probe movement, probe displacement.

j. For unit in i, raster of spiking for all events aligned to start of probe movement for a single Pacinian (left) sorted by vibration amplitude. Amplitude of vibrations generated by probe movement (middle). Change in firing rate for events (right).

k. For three Pacinians, change in firing rate vs. vibration amplitude during distal probe movement on the far end of the tree branch. Each marker is one event for the unit (n = 3 Pacinians, N = 3 animals).

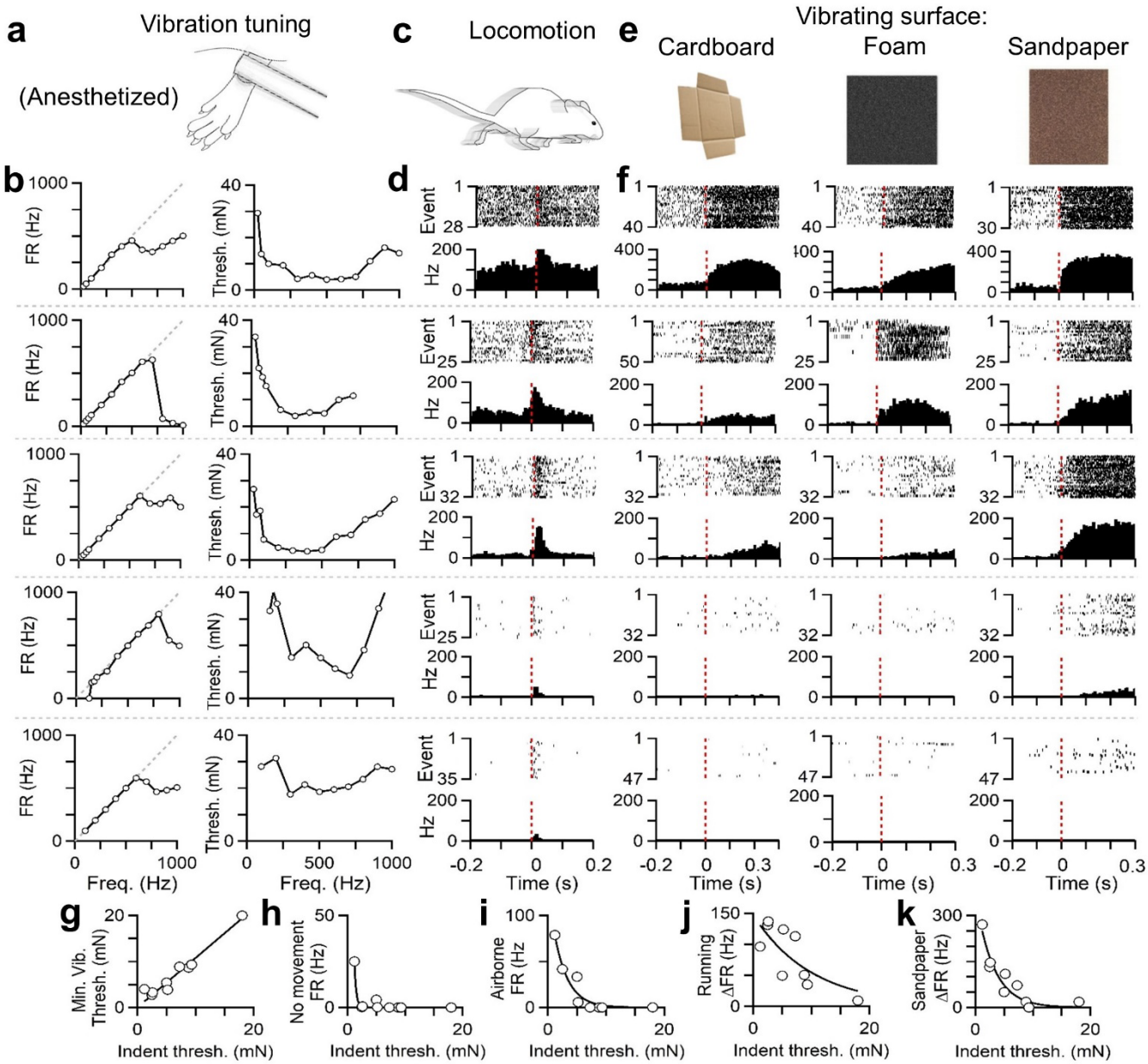


Figure 4: Variable tuning of Pacinians enables broad sensory coding

a. Vibration was delivered to the heel in anesthetized animals during unit characterization.

b. Firing rate vs. vibration frequency (left) and vibration threshold vs. vibration frequency (right, 50% entrainment) for five different Pacinians. Each row is one Pacinian.

c. Firing evoked when the ipsilateral foot landed during locomotion.

d. Same Pacinians in b., but during locomotion in freely moving animals showing rasters (top) and PSTH (bottom) each row. t = 0 is time of ipsilateral foot contacting ground

e. Firing evoked by vibration of surfaces as in Fig. 3.

f. Responses to vibration of cardboard (left), foam (middle) or sandpaper (right) for same Pacinians in b, d. t = 0 is time of vibration onset.

g. Vibration threshold (at most sensitive frequency) vs. indentation threshold for all Pacinians.

h. Firing rate when animal was not visibly moving vs. indentation threshold for all Pacinians.

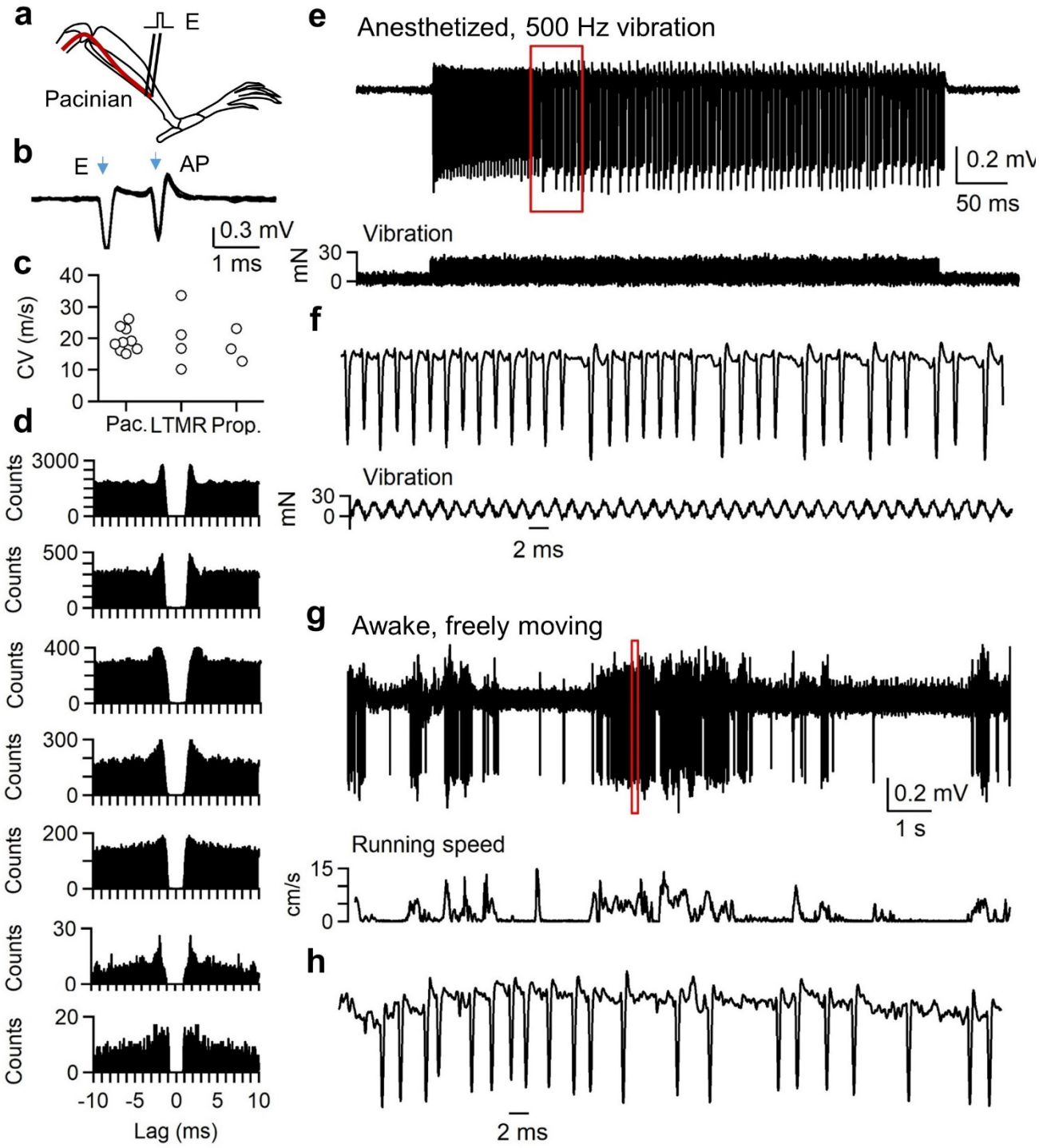
i. Firing rate when animals are not touching any surfaces vs. indentation threshold for all Pacinians.

j. Peak change in firing rate during running vs. indentation threshold for all Pacinians

k. Firing rate evoked by vibrating sandpaper vs. indentation threshold for all Pacinians.

Linear (g) or exponential fits (h-k). Each marker is one unit for g-k (n = 9 Pacinians, N = 9 animals).

410 **EXTENDED DATA FIGURES AND LEGENDS**



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Extended Data Figure 1: Isolation of single units in awake freely moving animals

a. Schematic of electrical stimulation of Pacinian corpuscles. Following behavioral experiments, animals were anesthetized and the leg was dissected to expose the Pacinian. Electrical stimulation was used to confirm the end organ location along the fibula.

b. Example of electrical artifact (E) and evoked spike (action potential, AP) from a recorded Pacinian neuron.

c. Measured conduction velocities of afferents following behavioral experiments.

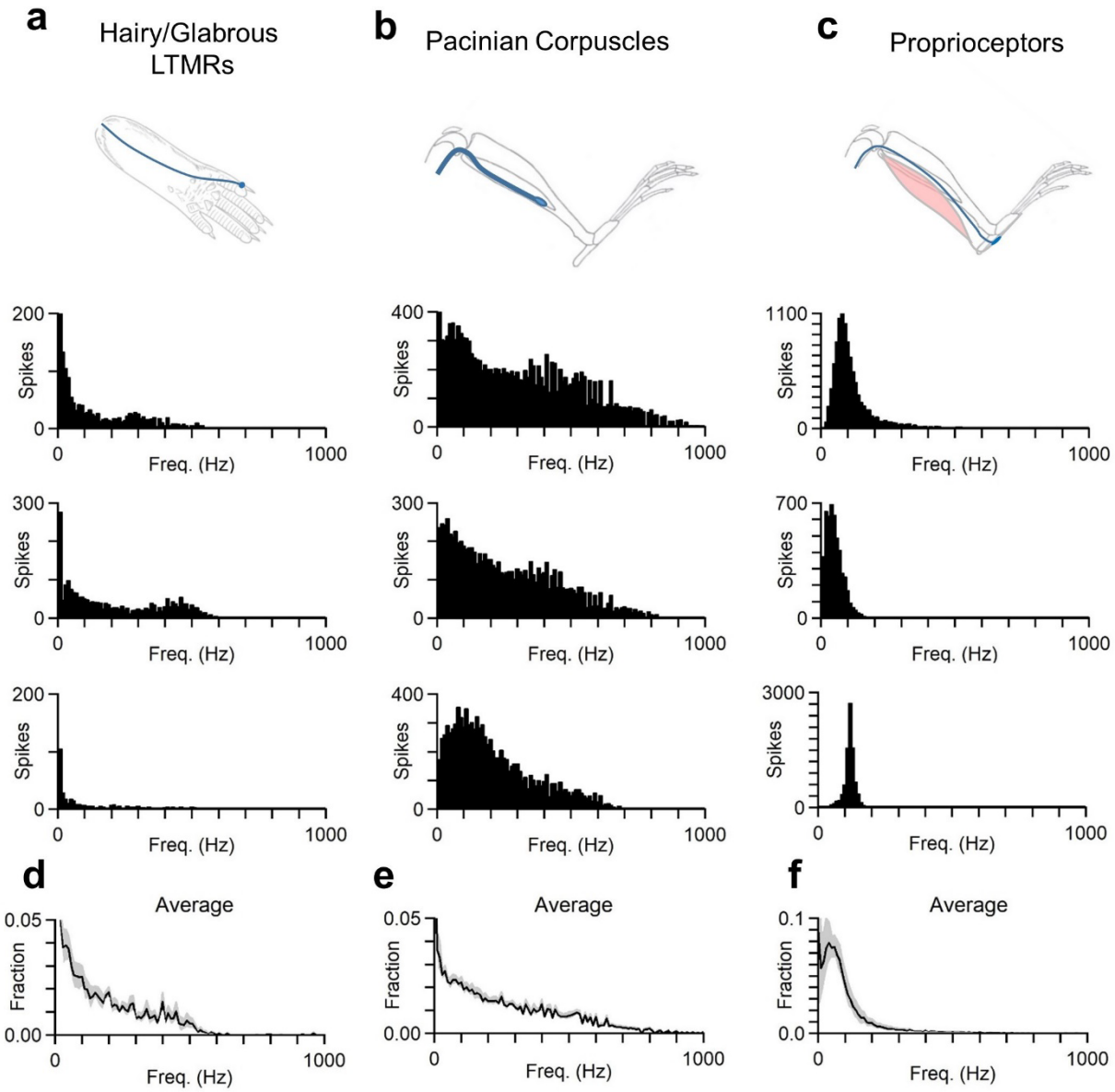
d. Autocorrelograms for firing of seven Pacinians during behavior.

e. Example unit response to 500 Hz vibration under anesthesia prior to recovery.

f. Inset of experiment shown in e. showing use-dependent changes in amplitude and waveform.

g. Same unit as in e-f, but in an awake animal exploring a platform. Raw traces (top) and speed of animal movement (bottom).

h. Inset from g. showing use-dependent changes in amplitude and waveform as in anesthetized recordings.



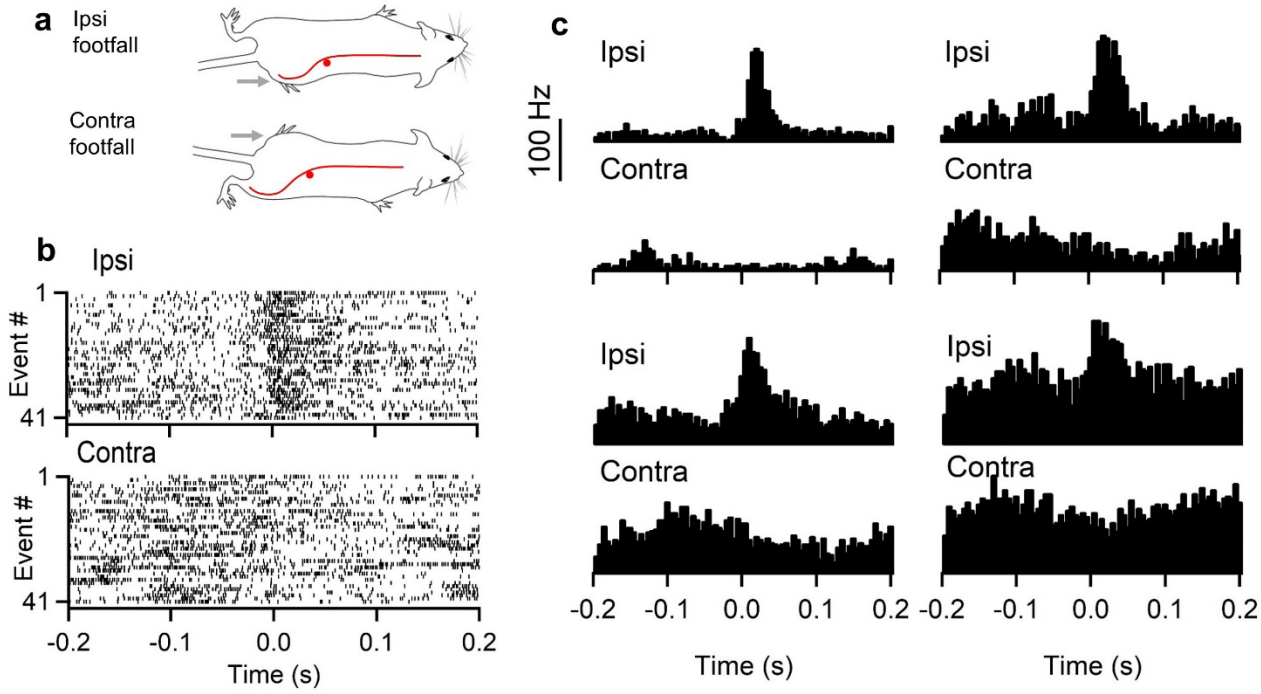
Extended Data Figure 2: Instantaneous firing rates of sensory neurons during locomotion

a. Instantaneous firing rate for three example LTMRs for animals walking across mouse bedding.

b. Same as in a, but for three of the most sensitive Pacinian corpuscles.

c. Same as in a, but for three example proprioceptors.

d-f. Average histogram of instantaneous firing rate for all cutaneous LTMRs (d, n = 4; N = 4), Pacinians (e, n = 9; N = 9), and proprioceptors (f, n = 5; N = 5).

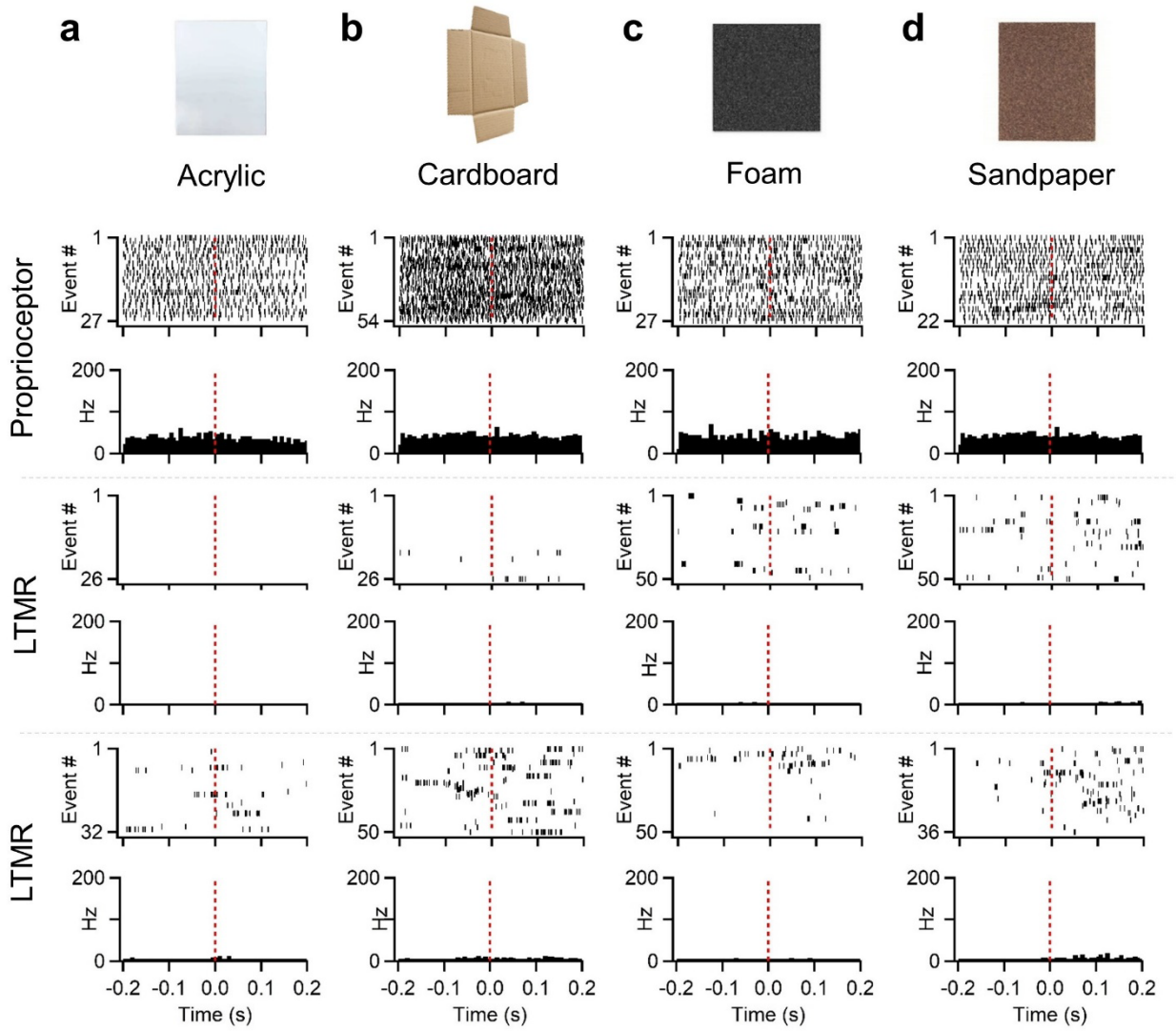


Extended Data Figure 3: Pacinians are activated by the ipsilateral limb during locomotion

a. Footfalls during locomotion of either the ipsilateral (top) or contralateral (bottom) hindlimb were analyzed. The ending of the recorded Pacinian neuron is in the periosteum of the fibula of the ipsilateral hindlimb. Animals ran in home cage bedding.

b. Example raster for a single Pacinian during footfalls of either the ipsilateral (top) or contralateral hindlimb (bottom). t = 0 is the time of foot contact with bedding.

c. Histograms for four different Pacinians for ipsilateral (top) or contralateral (bottom) hindlimb footfalls. n = 4 Pacinians, N = 4 animals.



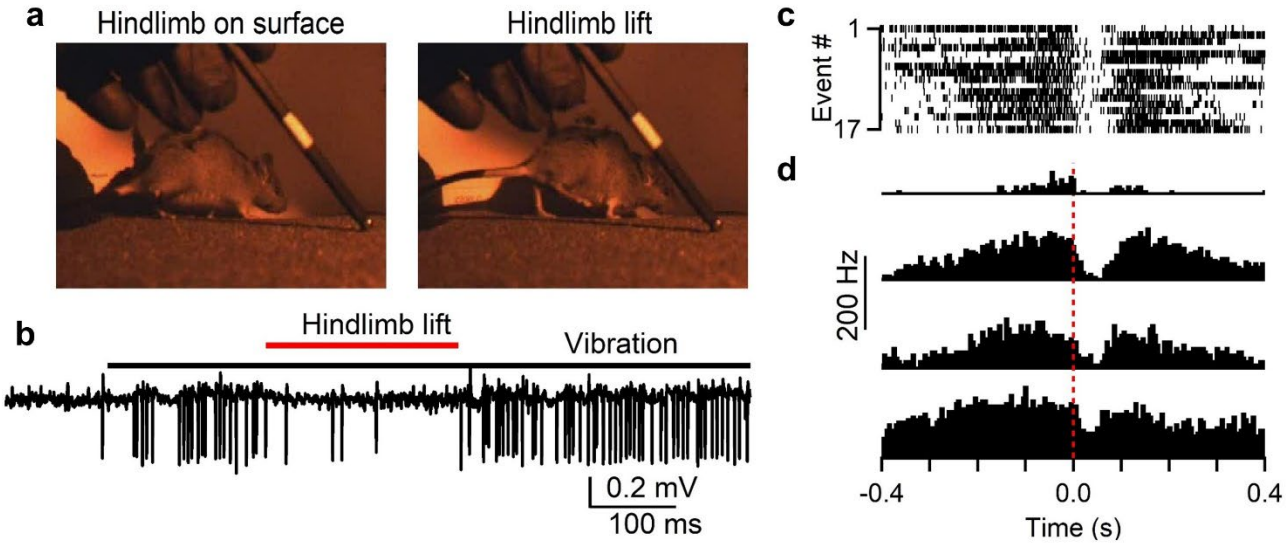
Extended Data Figure 4: Proprioceptors and cutaneous LTMRs do not respond to surface vibrations.

a. Responses of three sensory neurons to movement of a finger across acrylic. Each row is a different unit. Rasters and histograms for a proprioceptor (top), an LTMR innervating the toe (middle), and an RA1-LTMR (Meissner corpuscle) innervating a glabrous pad (bottom).

b. Same as in a, but for cardboard.

c. Same as in a, but for sound insulation foam.

d. Same as in a, but for sandpaper.



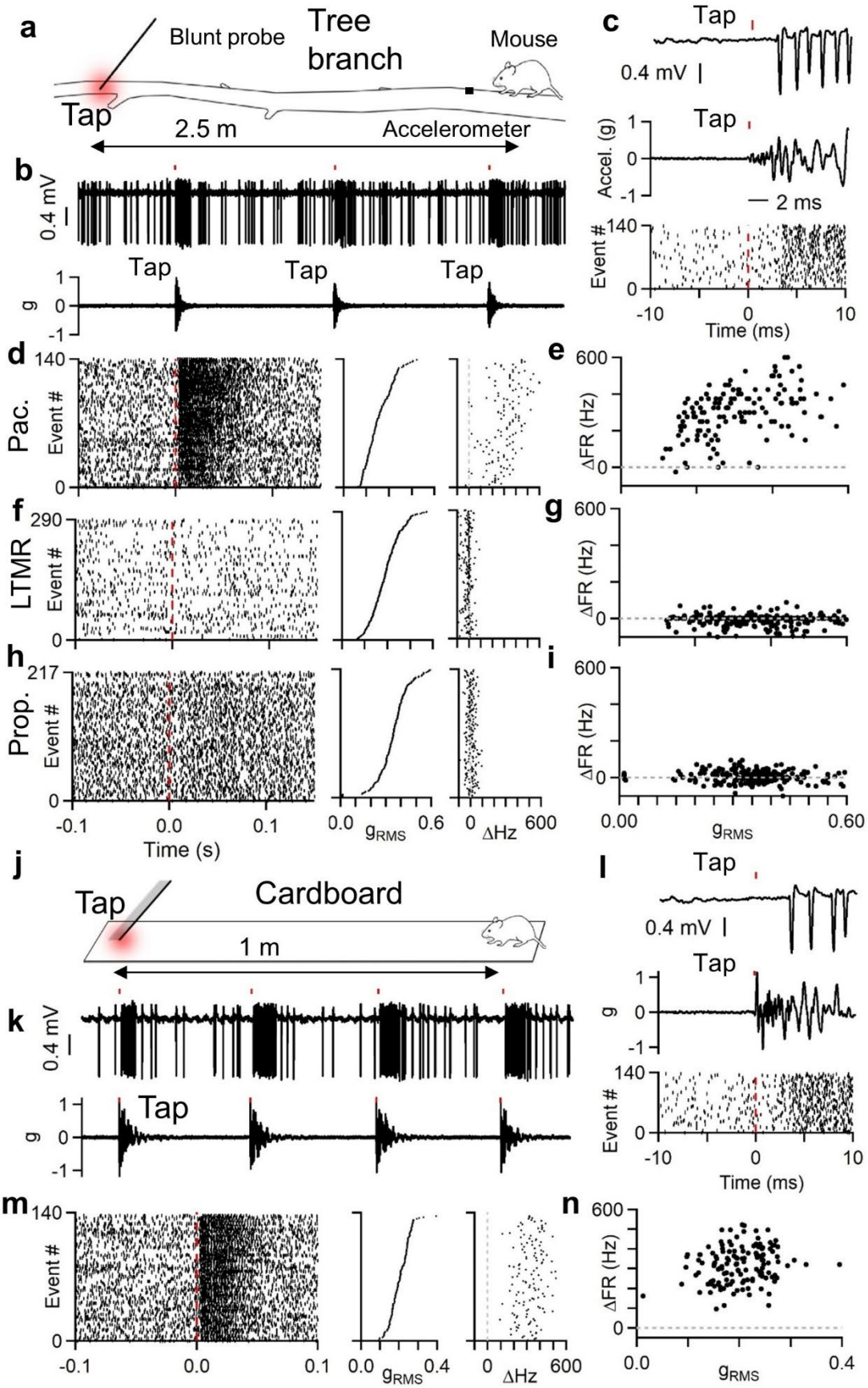
Extended Data Figure 5: Activation of Pacinians by vibration requires ipsilateral hindlimb contact with vibrating surface

a. A probe was moved across sandpaper to generate vibrations. During vibrations, animals typically did not move, leaving the ipsilateral hindlimb in contact with the vibrating surface (left). In some instances, animals walked and lifted their ipsilateral hindlimb from the surface while keeping the other 3 limbs in contact. These moments were analyzed.

b. Example trace of Pacinian during vibration and time when the ipsilateral hindlimb was lifted off the sandpaper.

c. Raster of spiking for all hindlimb lift events for single unit shown in b. t = 0 is when the hindlimb lost contact with the surface.

d. Histograms from four different Pacinians during vibration in which the hindlimb was lifted from the surface (n = 4 Pacinians, N = 4 animals).


a
Blunt probe
Tree branch
Mouse
Tap
2.5 m
Accelerometer
b
0.4 mV
Tap
Tap
Tap
g
c
Tap
0.4 mV
Tap
Accel. (g)
2 ms
Event #
Time (ms)
d
Pac.
Event #
e
ΔFR (Hz)
f
LTMR
Event #
g
ΔFR (Hz)
h
Prop.
Event #
i
ΔFR (Hz)
Time (s)
g_{RMS}
ΔHz
g_{RMS}
j
Tap
Cardboard
1 m
k
0.4 mV
Tap
g
l
Tap
0.4 mV
Tap
g
Event #
Time (ms)
m
Event #
g_{RMS}
ΔHz
n
ΔFR (Hz)
g_{RMS}

506

Extended Data Figure 6: Mechanical stimuli from great distances can activate Pacinians, but not other sensory neurons, within 5 milliseconds

a. Experimental setup. During recording, animals were placed on the end of a tree branch (2.6 m length). A blunt probe was used to tap the opposite end. An accelerometer near the mouse detected the stimulus.

b. Example trace of raw Pacinian firing (top) and accelerometer (bottom) when tapping the distal end of the branch.

c. Inset of tap event from b with raw trace of Pacinian firing (top) and accelerometer (middle), and raster of spiking for all events (bottom). Taps evoked firing in the Pacinian within 5 ms.

d. Firing of all tap events sorted by stimulus intensity for a Pacinian neuron, with raster (left), strength of tap events in units of root mean square gravitational acceleration (g_{RMS}, middle), and change in firing rate evoked by tap (right).

e. Change in firing rate as a function of tap intensity for Pacinian shown in b-d. Data shown for single Pacinian, experiment was replicated in n = 3 Pacinians in N = 3 animals.

f-g. Same as in d-e, but for a cutaneous LTMR. This unit innervated hairs between two digits on the hindlimb, and was extremely sensitive to hair deflection. Experiment was performed in n = 1 LTMR, N = 1 animal.

h-i. Same as in d-e, but for a proprioceptor. This unit innervated a knee flexor. Data shown for single proprioceptor, experiment was replicated in n = 2 proprioceptors in N = 2 animals.

j. Similar experiment to a, but using a long (1 meter) length of cardboard.

k. Example trace of raw Pacinian firing (top) and accelerometer (bottom) when tapping the distal end of the cardboard.

l. Inset of tap event from k with raw trace of Pacinian firing (top) and accelerometer (middle), and raster of spiking for all events (bottom). Taps evoked firing in the Pacinian within 5 ms.

m. Firing of all tap events sorted by stimulus intensity for a Pacinian corpuscle, with raster (left), strength of tap events in units of root mean square gravitational acceleration (g_{RMS}, middle), and change in firing rate evoked by tap (right).

n. Change in firing rate as a function of tap intensity for Pacinian shown in j-l. Experiment was replicated in n = 3 Pacinians, N = 3 animals.

538 **SUPPLEMENTAL VIDEO**

539 Supplemental video and accompanying information may be found online at this link.

540

541 **METHODS**

542 **Animals**

543 All experimental procedures were approved by the Harvard Medical School Institutional Care
544 and Use Committee and were performed in compliance with the Guide for Animal Care and Use
545 of Laboratory Animals. Animals were housed in a temperature-controlled and humidity-
546 controlled facility and were maintained on a 12–12 h reverse light-dark cycle. All experiments
547 were performed on adult animals (aged >5 weeks, <10 weeks) of both sexes. Animals were
548 maintained on mixed C57Bl/J6 and CD1 backgrounds.

549 Experiments were not blinded or randomized because no treatments were performed. Sample
550 sizes were not predetermined.

551 **Implantation and electrophysiology**

552 Experiments were performed within a single day. Animals were habituated to the behavior room
553 for one hour prior to implantation. Animals were then placed under isoflurane anesthesia on a
554 heating pad kept at 37°C. The hair on the back and neck was clipped and sanitized. Animals
555 were administered Buprenorphine SR (1 mg/kg) subcutaneously between the shoulder blades.
556 Bupivacaine (0.16%) was administered subcutaneously to the lower back. After 5 minutes, an
557 incision was made, and more Bupivacaine was applied to the musculature surrounding the L3-L5
558 vertebrae. After another 5 minutes, the muscle was removed surrounding the dorsal and lateral
559 aspects of the L3-L5 vertebrae. The bone overlying the right L4 DRG was removed just to
560 expose the dorsal surface of the DRG and a small area (~1 mm^2) of neighboring spinal cord. The
561 DRG and spinal cord were covered with moistened gel foam. The exposed tissue surrounding the
562 vertebrae was then covered with lens paper. This left only bone and gel foam covering the DRG
563 exposed, and was allowed to dry. The L3 and L5 vertebrae were then fit with Michel clips
564 (Jorgenson) that were untightened. A steel rod was fit through the left loops of the Michel clips.
565 The area was then flooded with dental cement (Parkell). The cement was allowed to set for 20

566 minutes. A custom 3D printed fitting was placed on top of the cement, consisting of an adapter
567 connected to two 35-gauge steel wires, and a clamp for holding the spine was put in place. This
568 fitting was cemented to the top with another layer of dental cement. The implant was then
569 mounted to a steel post to stabilize the spine. The gel foam was removed to expose the DRG, and
570 one steel wire from the adapter was carefully inserted between the dura and spinal cord as a
571 reference. A thin co-axial cable (1 mm diameter) from the headstage was then connected to the
572 adapter of the implant.

573 Electrodes were pulled from borosilicate glass capillaries to a tip resistance of 1 MΩ when filled
574 with 0.9% saline and cut to a length of 6-8 mm. Electrodes were held by a custom-built servo
575 motor controlled clamp, fitted onto a motorized manipulator (Scientifica). The electrode was
576 positioned over the DRG, and the other steel wire was placed into the saline of the electrode. The
577 electrode was then advanced into the L4 DRG and units were searched with the following
578 protocol: Pacinians were detected by applying a 40 mN 300 Hz vibration to the heel of the
579 hindlimb. The paw would occasionally be brushed or moved in order to detect proprioceptors or
580 other LTMR types. Once a unit was found, the electrode was positioned to maximize the
581 amplitude of evoked spikes to an amplitude of at least 1 mV. The electrode was then held in
582 place for 10 minutes to allow stabilization. If units were sufficiently stable, the exposed DRG
583 was then flooded with UV-curable resin. A fiber-coupled 405 nm LED (400 µm, 0.39NA fiber,
584 14 mW/mm^2 at the fiber tip) was used to cure the resin within three seconds of application,
585 fixing the electrode in place. Layers of resin were added to the electrode until reaching the
586 clamp, at which point the electrode was released and the clamp was retracted. The electrode, the
587 back of the electrode, and all wires were sealed in place using additional resin. Light was applied
588 for at least 2-3 additional minutes. The skin surrounding the implant was sutured together, and
589 skin contacting the implant was sealed to the implant using Vetbond. For Pacinian recordings,
590 vibration tuning properties were measured prior to recovery or after all behavior was performed
591 (see below). The tether was then disconnected from the headstage, and the animal was removed
592 from anesthesia and placed in its home cage to recover. The home cage was transferred to a
593 behavior room and the tether was re-attached to a headstage to begin recovery. Implantations
594 under anesthesia were performed within 3-4 hours. Animals were given 1-2 hours to recover
595 prior to beginning behavioral experiments.

Pain and discomfort were assessed post-operatively through careful monitoring of the animal's behavior. Animals typically awoke from anesthesia within 5-10 minutes and all animals recovered robust locomotor activity within an hour of recovery. Animals did not attempt to scratch the implant and did not obviously acknowledge its presence. Animals carried out many normal behaviors such as eating food, grooming, exploring novel environments, and maintaining vigorous movements. Mice did not avoid stepping on the ipsilateral hindlimb, nor did they attempt to lick, scratch, or manipulate the ipsilateral hindlimb.

Following behavior, animals were anesthetized again using isoflurane and transferred back to the implantation rig. As the amplitude of the recorded unit can gradually change over the course of several hours, it was confirmed that the unit observed during behavior fit the same tuning properties as the unit observed before the animal awoke. Further characterization of recorded units was also performed. For Pacinians, vibration tuning curves were either completed more fully, or a subset of vibration frequencies were re-measured to assess changes in sensitivity. At the end of the experiments, electrical stimulation was used to identify the exact position of the recorded unit's end organ. For LTMRs innervating hairs, the hair within the receptive field was plucked to ensure the units innervated hair. For Pacinian neurons, the skin was removed from the heel, ankle and lower leg and vibration was delivered to ensure the receptor was not cutaneous. The leg was then dissected to expose the fibula and tibia, and the fibula was electrically stimulated to confirm the location of the Pacinian. For proprioceptors, the leg was dissected to find the innervated muscle or tendon. Electrical stimulation was used to identify the location of the ending, and either lidocaine or lesion of the innervated muscle or tendon was used to confirm the approximate location of the end organ.

Recordings were amplified using a Multiclamp 700B commander (Molecular Devices) under the 100x AC differential amplification mode with an additional 20x gain. All signals were collected using 0.1 kHz high-pass filter and 3 kHz Bessel filter. In anesthetized mice, data were collected at 20 kHz using a Digidata 1550B. For awake recordings, the tether attached to the animal (30-50 cm in length) was connected to a passive commutator above the animal. The commutator was then connected to a CV-2B headstage held in place above the commutator. Electrophysiology data and accelerometer data were collected at 50 kHz using a National Instruments board (NI USB-6343).

626 **High-speed imaging**

627 Animals were imaged using two CCD cameras (FLIR, BFS-U3-16S2C-CS; BFS-U3-04S2C-CS)
628 capturing frames at 200 Hz. Cameras were mounted on articulating arms and could be moved for
629 different behaviors. An overhead LED (617 nm, 300 mW) was used to illuminate the imaged
630 area. In order to account for potential frame drops, videos were synchronized to
631 electrophysiology data by a small LED array timer visible in video frames. The LED array also
632 contained a threshold crossing live-triggered by the unit's firing as a secondary synchronization.
633 In some cases, the threshold was set to only detect a small subset of spikes to avoid saturation of
634 the LED. The LED array was typically below the behavioral arena or facing away from the
635 mouse and was not visible to the animal. In order to minimize desynchronization of unit activity
636 and video frames, data were collected in 15-second epochs.

637 **Mechanical stimuli (anesthetized)**

638 For Pacinians, vibration tuning curves were collected using a custom-built mechanical stimulator
639 as previously described[38]. Vibrations were generated by a DC motor with a blunt probe (3 mm
640 diameter). The probe was placed on the location of greatest sensitivity for the Pacinian, always in
641 the area of the heel. Responses to indentation were collected from the same location on the
642 hindlimb as vibration responses. The motor was driven by a custom-built current supply
643 controlled by a data acquisition board (Digidata 1550B, Molecular Devices) with static forces
644 calibrated using a fine scale. Delivered stimuli were recorded through a Hall-effect current
645 sensor in series with the motor. For proprioceptors, a pair of blunt forceps were used to rotate the
646 limb around different joints, typically the ankle or knee, to preliminarily identify the innervated
647 muscle or tendon. For hair innervating LTMRs, a brush or brief air puffs (5 PSI via 20 gauge
648 needle) was used to identify the receptive field. For glabrous skin LTMRs, von Frey filaments
649 were used to identify the receptive field, and the indentation threshold was determined using the
650 mechanical stimulator and verified using von Frey filaments. For proprioceptors and cutaneous
651 LTMRs, assessment of the receptive field or area of innervation was captured using a CCD
652 camera (FLIR, BFS-U3-13Y3C-C, 100 FPS) for later analysis.

653 **Behavioral tasks**

654 Following implantation, animals were kept in their home cage. The top of the cage was removed
655 and the animal remained tethered to the commutator throughout all experiments. Different

behavioral arenas and setups were moved to the mouse, replacing its home cage. The headstage and commutator were attached to a large frame by an arm with an adjustable position and height. The arm was attached via cable and pulley to a counterweight. The headstage and commutator could also be detached from the behavioral frame and carried briefly by the experimenter for tasks that required more flexible movement, such as during climbing.

Locomotion: animals were placed on a flat open acrylic surface and allowed to roam freely. Animals naturally explored the surface. For locomotion in bedding, animals were placed in an acrylic corridor with home cage bedding. Animals explored the corridor and were encouraged to run back and forth.

Digging: Animals were placed into a long acrylic corridor filled with black sand. Some animals naturally would burrow in sand at the end of the corridor to build a makeshift nest. No training was needed, and many animals naturally began to dig in sand. Other animals were not interested in digging, and no effort was made to make them burrow. Following the sand arena, animals were placed briefly in a shallow, warm water bath to remove excess sand from their extremities. They were then carefully dried with a paper towel and returned to their home cage.

Substrate vibrations: The edges of sandpaper (Aluminum oxide grit 36) or cardboard were secured to two rails with double-sided tape. Between the rails the sandpaper or cardboard lightly rested on top of sound insulation foam. An accelerometer was taped to the underside of the surface. Barriers were erected at two edges of the surface without making contact. The other two edges were left exposed for camera access. Animals were placed on the surface and allowed to roam freely. A wrench was brushed across the sandpaper 40-50 times at a consistent speed and light pressure (approximately 0.13 m/s; 0.5-1 N force). In some cases, a separate set of motions was performed with variable speed and pressure. For cardboard, the experimenter's gloved finger was used instead of a wrench. For foam, an acrylic chamber with open top was used. A block of foam with accelerometer attached was placed into the acrylic arena, with an approximately 1 mm gap between the foam and the walls. The mouse was placed on top of the foam and the experiment's gloved finger was moved across the surface of the foam to generate vibrations, as for other surfaces.

Climbing: An aluminum rail (300 x 25 mm) was secured to a post. Nuts (1/4" taps) were glued to the rail as potential holds for the mouse, spaced apart by approximately 5 cm. The post was first

686 angled at 20 degrees and the top of the post reached a 6 x 6” steel platform. Animals were not
687 trained to climb, and performed the task naturally, preferring the stability of the steel platform to
688 the sloped rail. Animals were placed on the lower end of the rail and allowed to climb. A block
689 of sound insulation foam was placed beneath the rail in case the animal fell, but falls were
690 extremely rare. Once the animal successfully reached the steel platform, they were allowed to
691 rest briefly. Then the animal was placed on the lowest point of the rail again for another trial of
692 climbing. If animals climbed the rail with ease, the angle of the rail was adjusted to a steeper
693 slope, to a maximum of 45 degrees. Animals were placed on the climbing rail 10-20 times.

694 Long distance vibrations: To test long distance vibrations, a fallen tree branch (2.6 m length, 2-6
695 cm diameter, oak) was obtained from a nearby park. The branch spanned the maximum length of
696 the behavior room. One end was rested on a scaffold near an LED array and an articulating arm
697 for a camera. The other end of the branch was rested on a block of sound insulation foam over a
698 plate of acrylic. An acrylic barrier was placed 6-8 cm from the end in order to prevent the animal
699 from moving down the length of the branch. An accelerometer was attached to the tree branch
700 with tape next to the acrylic barrier. One camera was pointed to each end of the tree branch to
701 track movements of the animal, and the other camera was pointed at the other end where
702 mechanical stimuli were delivered. The animal was placed on the end with the barrier. The
703 branch rested 1-2 cm above an acrylic plate in case animals fell from the branch. The blunt end
704 of a paint brush was used to tap or make mechanical contact with the far end of the branch on the
705 other side of the room.

706 Lifting: Animals on an acrylic platform were suspended in the air by lifting them either by the
707 recording tether or the base of their tail. Animals were kept suspended for 2-6 seconds and lifted
708 just far enough to have the limbs avoid contact with the platform.

709 **Analysis**

710 Processing: Videos were processed to detect frame drops based on LED timers. Missing frames
711 were replaced with the frame prior, with typically 1-2% of frames lost. Spikes were detected by a
712 template search, but spikes could easily be discriminated by amplitude threshold crossing alone.

713 Video analysis: PSTHs were generated using either video or accelerometer data (see below for
714 accelerometer alignment). Videos were analyzed using custom written Python scripts. Videos
715 were labeled manually for event times of interest. For locomotion, the time of footfall was

defined as when the foot made contact with the ground following a swing phase. For surface vibration, the beginning of vibration was defined as the start of detectable probe movement. Video of traces and audio of thresholded spikes were generated in Matlab and combined with synchronized video for supplemental material using Premiere Pro (Adobe).

Limb tracking: In some cases, motion of limbs or objects was tracked. Tracking was performed semi-automatically using the video labeler tool in Matlab. For locomotion, tracking was performed on the tip of the hindlimb (digits). For digging, the centroid of the forelimb was tracked. For slip, the centroid of the hindlimb was tracked.

Accelerometer data: In a subset of experiments, externally generated vibrations were detected using an analog accelerometer. Vibration amplitude was measured as the root mean square of raw accelerometer data. For alignment to data, accelerometer z-data was full-wave rectified and smoothed using a moving average, and vibrations generated from probe motion or taps on different substrates were detected by threshold crossing and the timings of these events were used to generate rasters. In a separate experiment without mice, power spectra shown in **Fig. 3** were generated. 30-40 probe motions were collected as performed during behavior experiments and raw accelerometer data during probe motion was concatenated. A similar length of baseline data without any motion was collected. Power spectra of probe motions were collected, and the power spectrum of the baseline data without probe motion was subtracted.

To determine the amplitude of phone vibration (see main text), the accelerometer was attached to a cellular phone (iPhone 13, Apple) and a similar experiment was performed with the phone vibrating. In order to estimate the displacement amplitude of vibrations, we examined accelerometer data from the smallest stimulus that activated a Pacinian as mice sat on the tree branch. The largest component of these stimuli could be approximated by a 400-500 Hz sinusoidal waveform. We then calculated the displacement with a 500 Hz sine wave of the acceleration given by:

$$D = \frac{gA}{2\pi^2 F^2}$$

Where g is 9.8 m/s^2, A is the peak acceleration amplitude, and F = 500 Hz.

For plots in **Fig. 3k**, a sigmoid function was fit to the data with baseline constrained to 0. For plots in **Fig. 4g**, a linear fit was performed constrained to go through the origin. In **Fig. 4h-k**, a single exponential was fit with y-offset constrain to 0.

Data availability

Source data for this study will be included upon acceptance of the manuscript. Additional datasets may be obtained from the corresponding authors upon reasonable request.

Code availability

Custom scripts used in this study will be available upon acceptance of the manuscript, or upon request from the corresponding authors.

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AUTHOR CONTRIBUTIONS

JT performed all experiments and analysis. JT and DDG wrote the paper.

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