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Spotlight

Shaking Paws Is Not the Same as Shaking Hands

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A recent *Nature* paper shows that activity in rodent forelimb somatosensory cortex is related to the animal's behavioral report of vibration intensity and identifies candidate mechanoreceptors responsible for the cortical response. Results highlight striking anatomical and neural differences from primates.

The primary function of sensory systems is to transform raw sensory signals into actionable perceptions. This transformation includes the physical filtering associated with the sensor itself, as well as the neural processing that combines primary sensory signals into the more complex representations that guide behavior. Understanding the cascade from sensory transduction in the periphery to central representations and to perception and action is a fundamental goal of sensory neuroscience.

A recent study by Prsa et al. (2019), published in *Nature*, exploits a broad suite of experimental tools to trace out exactly such a transformation: the authors identify how neurons in layer 2/3 of mouse forelimb primary somatosensory cortex (L2/3 fS1) represent vibrotactile stimulation of the mouse forelimb; they relate this cortical representation to the animal's behavior and, finally, identify a candidate set of mechanoreceptors responsible for the cortical activity. Calcium imaging and electrophysiological recordings demonstrate that L2/3 fS1 neurons code for a vibrotactile "intensity" feature, which combines vibration frequency and amplitude. Careful behavioral experiments show that the L2/3 neuronal responses are consistent with the pattern of errors during a mouse's performance on a vibrotactile discrimination task. Lastly, histological and optogenetic experiments point to a candidate set of peripheral receptors that could drive the observed cortical responses. Taken together, the results of this series of experiments indicate that the coding properties of L2/3 neurons in mouse fS1 resemble those found in auditory cortical regions (Tao et al., 2017) and are surprisingly different from the coding properties of neurons in the primate hand cutaneous pathway (Harvey et al., 2013).

Prsa et al. (2019) first used calcium imaging to show that the responses of individual L2/3 fS1 neurons are selective for specific frequencies of sinusoidal vibrotactile stimuli delivered to the mouse forepaw. The population of fS1 neurons was found to cover the spectral range of stimuli tested, suggesting a somatosensory analogy to the well-known tonotopic coding in auditory cortex. However, when vibration amplitude was varied along with frequency, the neuron's preferred frequency shifted. The neurons showed the same responses for high-frequency, small-amplitude vibrations as they did for low-frequency, high-amplitude vibrations, implying instead a neural correlate of "perceptual intensity."

Prsa et al. (2019) then performed behavioral experiments that demonstrate a correspondence between the fS1 neural responses and the animals' behavior. Mice were trained on a go/no-go task to indicate whether vibration frequency was "high" (>450 Hz, go), or "low" (<450 Hz, no-go). After achieving baseline performance, animals were presented with catch trials in which stimulus amplitude also varied. When low-frequency stimuli were paired with high amplitudes, or vice versa, animals showed an amplitude-dependent shift in perceived frequency. Quantitatively, the trade-off between amplitude and frequency in the behavioral experiment could be predicted by the trade-off observed in the S1 neural representation, suggesting a neural correlate of perceptual intensity discrimination that incorporates both frequency and amplitude.

A similar perceptual trade-off between frequency and amplitude is also found in the visual and auditory systems (Campbell and Robson, 1968; International Standardization Organization, 2003). It is interesting that the trade-off described in Prsa et al. (2019) appears monotonic, while in human vision, audition, and somatosensation, some regions are optimal or enhanced (Figure 1) (Mountcastle et al., 1972). Notably, only frequencies between 300 and 600 Hz were tested in the rodent; it will be important for future work to explore the shape of the perceptual intensity curve across a wider range of frequencies.

A separate set of juxtasomal recordings complement the calcium imaging and behavioral measurements. These recordings showed that L2/3 fS1 neurons did not phase lock to the vibratory stimulus; rather, phase-locked spiking, which exists in the periphery (Talbot et al., 1968), is transformed into a rate in L2/3 that covaries with intensity. Representing vibrotactile features with a rate code stands in sharp distinction to the temporally precise and phase-locked code for vibration observed in primate S1 cortex (Harvey et al., 2013). The observed phase locking in primate cortex, and lack thereof in rodent L2/3 neurons, suggests that there may be a meaningful difference in the way that cortex represents tactile stimuli between species.

Given that the cortical representation of vibratory stimuli differs from primate to rodent, Prsa et al. (2019) next aimed to identify peripheral drivers of the L2/3 activity. They focused specifically on whether Pacinian corpuscles (PCs), which are known to optimally respond to vibration frequencies in the range tested in

this study (Mountcastle et al., 1972), could be responsible for the observed L2/3 responses. Three complementary experiments were performed to assess the role of PCs in driving the cortical response to vibrations. First, Prsa et al. (2019) sectioned the entire forelimb and stained for PCs. The majority of PCs were found near the middle of the forelimb, adjacent to the bone. Very few PCs were found in the mouse paw dermis, in distinct contrast to the high density of PCs found in the dermal layers of the primate hand (Kumamoto et al., 1993). Second, Prsa et al. (2019) demonstrated that the responses of L2/3 neurons were abolished after afferents were sectioned at the level of the biceps but remained intact (albeit significantly altered) after pharmacological blockade of nerve transmission from the paw. These results suggest that L2/3 neurons integrate over both paw and forelimb, perhaps compromising spatial resolution for sensitivity. Spatial integration across such a large region of skin could help explain the absence of phase locking, as temporal information about vibrations will be lost through tissue damping. Lastly, Prsa et al. (2019) expressed channelrhodopsin in PC and Meissner afferents to optogenetically stimulate these mechanoreceptors while recording calcium signals in L2/3 neurons. By placing the stimulating LED either close to the highest density of PCs in the forelimb (as determined by the histological sectioning) or at various locations on the paw, Prsa et al. (2019) were able to evoke responses in the same L2/3 neurons that show vibration-induced responses, indicating a mechanoreceptive drive. They reason that because Meissner receptors optimally respond at less than 50 Hz, they are not the primary drivers of the L2/3 signal.

The work of Prsa et al. (2019) suggests a number of follow-up experiments to refine our understanding of the cortical representation of vibratory stimuli. Would perturbation of the L2/3 activity (perhaps via optogenetic manipulation) alter the behavioral report during the psychophysical experiments? Such a finding would help to more directly show that L2/3 is a neural substrate of vibratory "perceptual intensity." In addition, further experiments are needed to more clearly identify the role of PCs in generating the L2/3 fS1 vibratory response; other mechanoreceptor types may also shape the neural activity. Although Meissner afferents are optimally tuned to lower frequencies, they also have significant responses to stimulation above 100 Hz (Talbot et al., 1968). Also, the vibratory stimuli themselves are likely to interact with the tissue in a way that generates signal components at a variety of frequencies. Given that the L2/3 neurons appear to integrate vibration information across the forelimb and that L2/3 neurons discard temporal phase-locking information, it seems reasonable that L2/3 neurons would integrate signals from multiple receptor types. To answer these types of questions, it would be particularly informative to measure the calcium signals in L2/3 during optogenetic stimulation of slowly adapting mechanoreceptor populations and observe whether these vibrotactile-responsive neurons indeed remain silent.

The proximity of the PC endings to the bone, along with the fS1 rate code for stimulus intensity, lead Prsa et al. (2019) to speculate that the mouse forelimb may be specifically adapted to sense substrate vibrations. This functional role makes sense given that rodent forepaws are primarily load bearing and that sensing substrate vibrations is particularly important for burrowing animals. Although rodents can use their forepaws quite dexterously to handle and manipulate food (Ballermann et al., 2000), they often rely on their vibrissae for detailed tactile exploration (Carvell and Simons, 1990). In contrast, primates use their hands not only to manipulate objects, but also for extensive tactile exploration and to extract details about shape and texture. These major distinctions in the functional role of forelimb vibration sensing between primates and rodents may explain the differing anatomical layout of mechanoreceptors as well as the neural representation in S1.

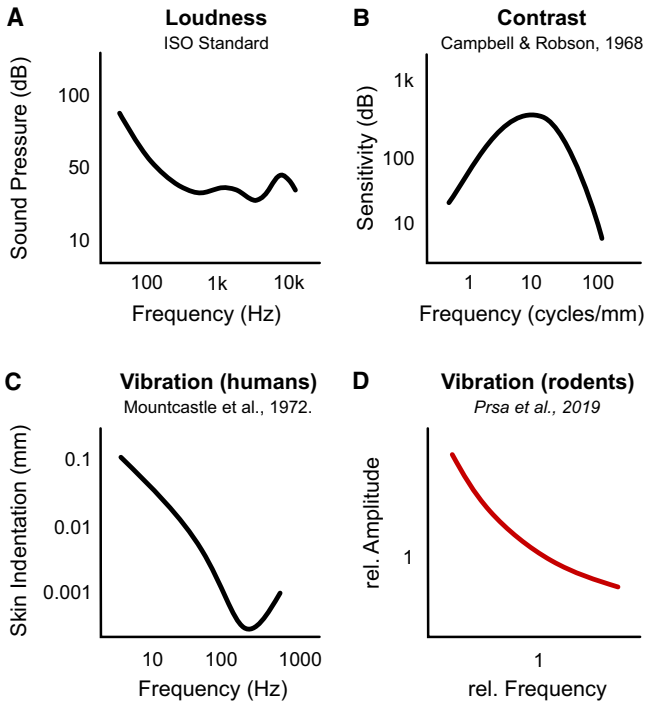

Figure 1. Qualitative Illustration of Equal Sensation Contours for Audition, Vision, and Touch

(A) ISO standard of human perception of loudness as a function of frequency (International Standardization Organization, 2003).

(B) Human sensitivity to contrast with respect to spatial frequency (Campbell and Robson, 1968).

(C) Human perception of displacement magnitude of vibrotactile stimuli with respect to vibration frequency (Mountcastle et al., 1972).

(D) Perceived amplitude of vibrotactile stimuli in rodents as reported in Prsa et al. (2019). Note that amplitude and frequency are relative to a learned reference value.

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