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Stimulus selectivity and brain state underlie sparse activity in mouse vibrissal cortex

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The reliable and efficient encoding of sensory information is a fundamental function of the brain, yet it remains unclear how the sensory-evoked activity of individual neurons contributes to population-level representations of sensory stimuli. In 1972, Horace Barlow proposed that the brain should operate sparsely, i.e. that a stimulus should drive a small subset of neurons drawn from a larger population, with sensitivity to a given stimulus shaped by the circuit mechanisms that determine the activation of individual neurons (Barlow, 1972). In keeping with this view, sparse population activity has been observed across the mammalian sensory cortices, including the rodent vibrissal primary somatosensory cortex (vS1) in which upper layer excitatory neurons respond sparsely to single-whisker stimulation. A recent study shows that juxtacellular stimulation of individual excitatory neurons in rat vS1 is sufficient to bias sensory-guided decision-making, highlighting the importance ascribed to the activity of individual neurons within population-level representations (Tanke *et al.* 2018). Notably, this effect was found specifically for neurons that were selective for the delivered stimulus, though the question remains as to the circuit mechanisms which determine this selectivity.

In comparison to dense responses, sparse responses to specific stimuli confer a number of computational advantages, including the efficient transfer of information and an enhanced population memory capacity owing to minimal

overlap of stimulus representation. As such, sparse coding is widely applied as a framework with which to investigate the role of individual neurons in sensory processing. However, the interpretation of experimental data is difficult as there are a number of scenarios that can give rise to sparse neuronal activation in response to sensory stimuli (Barth & Poulet, 2012). Trial-to-trial variability in stimulus-evoked activity, caused by changes in synaptic function or neuronal excitability, can lead to the appearance of sparseness. However, a similar effect can be observed if the size of the active population remains small and consistent across trials. Thirdly, apparent sparseness may be a product of brain state or anaesthesia. Finally, if the subset of responsive neurons is determined by the stimulus specificity, the size of the active population may be underestimated if the appropriate stimulus is not delivered. In a recent article in *The Journal*, Ranjbar-Slamloo & Arabzadeh (2019) sought to explore these scenarios *in vivo* by combining manual stimulus presentation and whisker tracking methods whilst recording from vS1 of awake mice.

In order to characterise the neuronal activity evoked by whisker stimuli, the authors first delivered ‘well-controlled’ stimuli using a piezoelectric actuator whilst performing loose cell-attached recordings of neurons in layer 2/3 (L2/3) of vS1. Recorded neurons were clustered into putative regular spiking (RS) and fast spiking (FS) populations based upon their action potential waveform, and their stimulus-evoked responsiveness was assessed using a population sparseness index, with a value of 1 indicating the activation of a single neuron in an otherwise silent population, and a value of 0 indicating equal activation of all neurons in the population. L2/3 RS sparseness was 0.73 in response to the strongest stimulus, as compared to <0.40 in FS neurons. Interestingly, a previous study from the same authors found L2/3 RS sparseness to be 0.31 in response to the same stimulus in anaesthetised mice (Ranjbar-Slamloo & Arabzadeh, 2017). Notably, this effect is only revealed by strong stimuli, with RS sparseness in response to a weaker stimulus reported as 0.75 and 0.73 for awake and anaesthetised mice, respectively.

To investigate whether observed sparseness in awake animals reflected an insufficient variety of stimuli, the authors next delivered a range of manual stimuli in combination with a spike-triggered average analysis method to identify any features of stimuli which drive activity in individual neurons. In response to manual stimulation the responsive pool of RS neurons in L2/3 increased from 23% to 84%. Taken together, the results presented by Ranjbar-Slamloo & Arabzadeh (2019) suggest that in awake mice the majority of L2/3 RS neurons in vS1 will fire if presented with the appropriate stimulus, and that stimulus selectivity underlies sparseness.

The findings of Ranjbar-Slamloo & Arabzadeh (2019) raise a number of questions with respect to the suitability of stimuli selected to investigate sensory systems. Typically, carefully controlled, simple stimuli are chosen in order to isolate individual features of the sensory environment in a consistent and unbiased manner. However, such a stimulus regime rests on the assumption that the experimenter is aware of what constitutes a salient feature to a given neuronal population within the sensory area under investigation. Famously, Hubel and Wiesel discovered by accident that neurons in primary visual cortex are most strongly driven by oriented edges: they inadvertently moved a projector slide edge across the visual field of their experimental animal after failing to elicit strong responses using spot stimuli previously shown to drive retinal ganglion cells (Hubel & Wiesel, 1959). The responses to manual stimulation observed by Ranjbar-Slamloo & Arabzadeh (2019) indicate that some neurons in awake barrel cortex may be more sensitive to naturalistic events such as taps, pushes and slips, as opposed to simply encoding the deflection of a given whisker. Electrophysiologists are constrained by both the limited selection of stimuli that can be presented in a recording session and difficulties associated with interpreting responses to stimuli that contain a complex combination of naturalistic features. This problem is not limited to vS1 – it is possible that stimuli commonly used to investigate other sensory systems also lack sensitivity to the stimulus feature selectivity of individual neurons. This possibility is highlighted by recent

computational work in which virtually unlimited numbers of stimuli can be presented to characterise the response profile of virtual neurons. Using ‘artphysiology’ in deep convolutional neural networks trained on naturalistic images, it was shown that individual units in intermediate processing layers show similar responses to abstract receptive field mapping stimuli as higher visual areas in biological brains, but can in fact be maximally driven by more complex conjunctions of features in natural images, such as dog faces (Pospisil *et al.* 2018).

The observation that sparseness of RS neurons in response to a single high velocity stimulus increases in awake as compared to anaesthetised mice suggests that brain state also influences sparseness in vS1. Given that the sensory features encoded by an individual neuron are shaped by the inputs it receives (Harris & Mrsic-Flogel, 2013), it seems unlikely that changes in brain state alter the absolute selectivity of neurons and may instead influence their sensitivity. The recording setup of Ranjbar-Slamloo & Arabzadeh (2019) has the advantage of being unbiased with respect to the baseline activity of recorded neurons; however, it does not report subthreshold activity. A prominent feature of active whisking is characterised by the decorrelated subthreshold membrane potential (V_m) of neighbouring vS1 neurons in comparison to quiet wakefulness (Crochet *et al.* 2011). A decorrelated V_m increases population signal-to-noise, but if a stimulus sufficiently drives activity in a certain number of neurons within a highly correlated population, the probability of

neighbouring neurons being recruited to the stimulus-evoked response would be higher than that in a weakly correlated population, effectively increasing the sensitivity of individual neurons. Urethane anaesthesia is known to induce slow wave-like events, characterised by highly correlated V_m . This may account for the observation that RS response sparseness is lower in anaesthetised mice, but only for strong stimuli. Future work could exploit recent advances in voltage imaging which make it possible to monitor both subthreshold and stimulus-evoked activity *in vivo*, presenting opportunities for the investigation of the relationship between population V_m and sparseness.

One drawback of the sparseness index used by Ranjbar-Slamloo & Arabzadeh (2019) is that different population response distributions can produce a similar sparseness value (Rolls & Tovee, 1995; Vinje & Gallant, 2000). The authors account for this by plotting sparseness against the fraction of neurons which respond to a given stimulus; however, there was not always a negative correlation between the fraction of responsive neurons and sparseness. The response distribution of a population may prove important, for example, when considering the response properties of FS neurons which exhibit similar sparseness values during spontaneous activity and in response to whisker stimulation. The authors report that the percentage of FS neurons responsive to standard stimulation is 76%, with a mean spiking response of 1.46. Simulating these conditions generates a population response distribution with a

sparseness value of 0.27 (Fig. 1B). However, a near-identical sparsity index could reflect a distribution in which the activity of the FS population is approximated by randomly sampling across a range of firing rates, something which could be true for FS neurons firing under spontaneous conditions (Fig. 1A). Additionally, because the authors averaged responses across trials in order to focus on population sparseness over time, they are unable to address the extent to which the active population is consistent across trials. This makes it particularly difficult to speak to the different scenarios, outlined above, which can lead to the appearance of sparseness.

Finally, in order to fully understand the implications for sparse *vs.* dense coding in vS1, it is important to investigate to what extent the response to the different categories of manual stimuli is also selective. If the population of neurons, for instance, showed dense responses to slips, pushes and taps, a dense code would look more likely, and we would simply conclude that vS1 is not sensitive to simple piezo deflections. It would be particularly interesting to see if the trial-to-trial variability is lower for certain stimulus categories indicating whether such types of stimulation are better suited to the response tunings of neurons in the barrel cortex. Due to the adaptive nature of manual stimulation used by the authors, it has not been possible in this paper to revisit the sparseness measure for individual manual stimulus categories. Nevertheless, the types of manual stimulation that elicited responses in this study could be used to inform a more controlled and

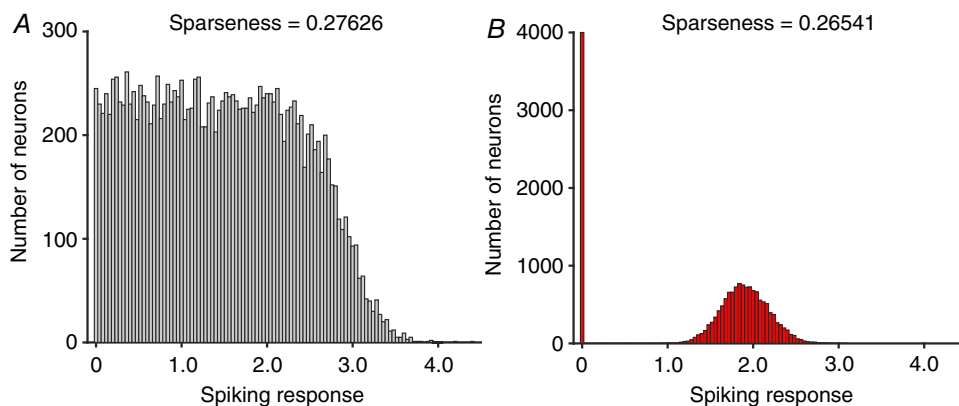


Figure 1. Different response distributions produce similar sparseness values

Two spiking response distributions from 1000 simulations of a population of 17 neurons yielding sparseness index values of ~ 0.27 . In both cases, target spiking rate is 1.46, corresponding to reported values for the fast spiking population in response to standard stimulation. The simulated response for each neuron was sampled as a Poisson process over 25 trials. A, the target spiking rate of neurons is chosen randomly from a range of values ($0-2 \times 1.46$). B, only 76% of neurons are active and have an identical target spiking rate per trial.

comprehensive stimulation protocol that could provide further support for stimulus selectivity as a driver of sparse coding of sensory features in barrel cortex.

Elucidating the mechanisms which dictate the sensory-evoked activity of individual neurons is key to understanding population representations of sensory stimuli. This study by Ranjbar-Slamloo & Arabzadeh (2019) represents a welcome contribution, raising a number of important questions with respect to the suitability of experimental stimuli, and providing insight into the nature of sparse activity in vS1.

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Additional information

Competing interests

None declared.

Author contributions

All authors contributed to the conception or design of the work and drafting the work or revising it critically for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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