Spatial Navigation Engages a Distributed Neural Representation

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Abstract

Navigation is a complex goal-directed behavior that relies heavily on sensory processing. A key center is the hippocampal formation, where well-known 'place cells' and 'grid-cells' encode the animal's position. Correlations with spatial position have also been found in other brain regions, including retrosplenial, visual, and even olfactory cortex. However, spatial processes are often not distinguishable from sensory, motor, and reward processes. To distinguish the contribution of different processes to the spiking activity of individual neurons distributed across the brain, we use an experimentally controllable virtual reality corridor, Neuropixels recordings, and reduced-rank ridge regression. We find that indeed, spatial, but also sensory, motor, and reward processes, are distributed widely across the brain.

Keywords: Neuropixels; brain-wide; spatial navigation; ridge regression

Introduction

Spatial navigation is a complex behavior that depends on multiple processes, such as spatial (i.e. cognitive map), sensory, reward, and motor coding. Despite this complexity, research has primarily focused on key regions such as the hippocampal formation, where well-known 'place cells' and 'grid-cells' encode the animal's position (Moser et al., 2008; O'Keefe & Dostrovsky, 1971).

Even in the hippocampus, neurons' spatial encoding relates to sensory landmarks (Gothard et al., 1996; O'Keefe & Burgess, 1996), hence disentangling the different processes is essential for correctly interpreting navigation-related information.

Using a virtual reality (VR) corridor with two visually identical halves, responses to landmarks in the visual cortex were discovered to be spatially modulated (Diamanti et al., 2021; Saleem et al., 2018). Spatial coding was additionally found in retrosplenial, posterior parietal, and olfactory cortex (Chen et al., 1994; Krumin et al., 2018; Mao et al., 2017; Poo et al., 2022).

Building on this foundational work, we ask to what extent spatial navigation engages a distributed representation of different cognitive processes. We use Neuropixels probes to record from populations of neurons in different brain regions in an adapted version of the VR corridor, allowing us to distinguish spatial from sensory, reward, and motor coding. Our unbiased approach shows that indeed, navigation-related processes such as sensation, motion, reward, and spatial position, are widely distributed.

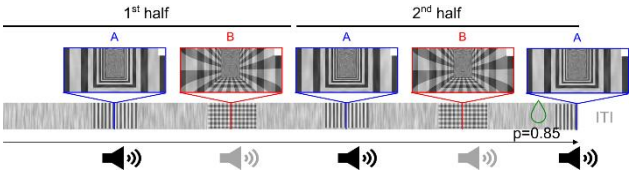

Figure 1: virtual linear corridor with two sensory identical halves (A and B repeat), a probabilistic reward, and a variable ITI with a grey screen after reaching 100cm.

Methods

We used Neuropixels probes to record in mice navigating a virtual linear corridor, recording 15,694 well-isolated neurons (66 insertions in 24 mice) from regions including visual, somatosensory, retrosplenial, and motor cortex, the hippocampal formation, the dorsal thalamus, striatum, and midbrain. On each trial mice traversed a corridor consisting of two sensory-identical halves (**Figure 1**). The gain of the running wheel varied across trials to decouple physical and virtual position. Contrast of visual and loudness of auditory landmarks also varied to distinguish sensory and spatial signals.

We predicted each neuron's activity using reduced-rank ridge regression (4R) (Izenman, 1975; Steinmetz et al., 2019), summing predictors such as a "place field" (generic function of position, within or across halves of the corridor) with temporal kernels for sensory stimuli, reward, and running speed.

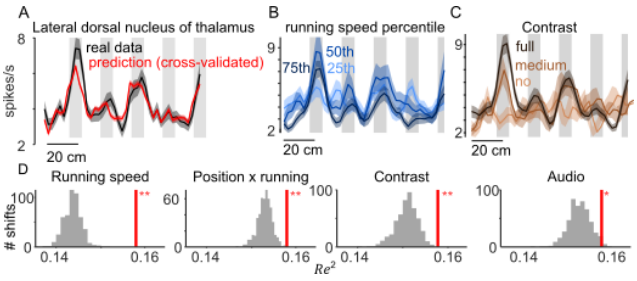

Figure 2: Reduced-rank ridge regression for example neuron. **A.** Average ± s.e. (spikes/s) activity across spatial position. Real data in black, prediction from the full-model (cross-validated) in red. **B**. Real data divided for different average running speed percentiles (across trials). **C.** Same as in (B) for different visual contrasts. **D.** R^2_{shift} distributions (in grey) for running speed, the interaction of position and running speed (see also B), contrast (see also C), and audio. The red line indicates R^2_e of the full model. *, p<0.05; **, p<0.01.

We computed R^2_e (fraction of explainable variance explained) on the full-model based on the cross-validated prediction versus real data (**Figure 2A**). To test for differences across areas, while controlling for mouse and session identity, we applied mixed-effects

models. Post-hoc pair-wise comparisons were Holm-Bonferroni corrected.

Next, we circularly shifted one of the predictors (e.g. all temporal kernels for predictor 'running speed') at a time by a random amount of time points (keeping trials intact) for 500 times, building a distribution of R^2_{shift} values **(Figure 2D**). We computed a p-value for each predictor's contribution as the probability for observing R^2_e in this distribution (note that the maximum p-value depends on the number of shifts).

To test whether the number of significant neurons per predictor was larger than expected by chance, we performed Holm-Bonferroni corrected binomial tests (**Figure 3B-E**). To test whether strength of sensory tuning during passive presentation, such as receptive field and frequency tuning to visual and auditory stimuli, could explain responses in the VR corridor, we applied logistic regression.

Results

Our full model was able to explain the responses of 62.54 ± 12.0% (mean ± s.t.d. across areas) neurons with more than 1% of their total explainable variance, with a lower bound of 36.75% in the dorsal auditory cortex, and an upper bound of 83.72% in the ventral posterior complex of the thalamus. In general, neurons from different areas had significantly different R^2_e values ($F_{31,17266}$=7.67, $p<10^{-32}$, mixed-effects model, **Figure 3A**). Specifically visual, auditory, primary motor, hippocampal, striatal, and thalamic regions had higher R^2_e values than retrosplenial, secondary motor, and anterior cingulate cortex.

Non-spatial predictors increased explainable variance explained significantly. For example, running speed significantly increased R^2_e in 50.5 ± 14.6% of neurons across areas, and this percentage was higher than chance in all tested areas (all p<0.001) (**Figure 3B**). Reward significantly increased R^2_e in 16.2 ± 8.4% of neurons, which was higher than chance in some visual, sensory, motor, hippocampal, striatal, and thalamic regions (**Figure 3C**). Sensory position significantly increased R^2_e in 10.1 ± 4.8% of neurons, and this percentage was higher than chance in most visual and hippocampal regions, dorsal retrosplenial, primary motor, and some thalamic regions (**Figure 3D**).

Nevertheless, spatial predictors (i.e. position x half of the corridor) also significantly increased R^2_e in 12.8 ± 6.7% of neurons, and this percentage was higher than chance in anterior, primary, and posteromedial visual cortex, lower-limb related primary somatosensory, retrosplenial, and motor cortex, some thalamic regions, and hippocampal regions **Figure 3E**). In many regions, neurons that increased R^2_e for either sensory or subjective position, were more likely to increase R^2_e for both.

Finally, we tested whether neurons with tuning to visual and auditory stimuli outside the VR, were more likely to encode certain predictors in the VR corridor. Indeed, the strength of auditory and visual frequency tuning significantly correlated with an increase in R^2_e for spatial predictors (i.e. position x half).

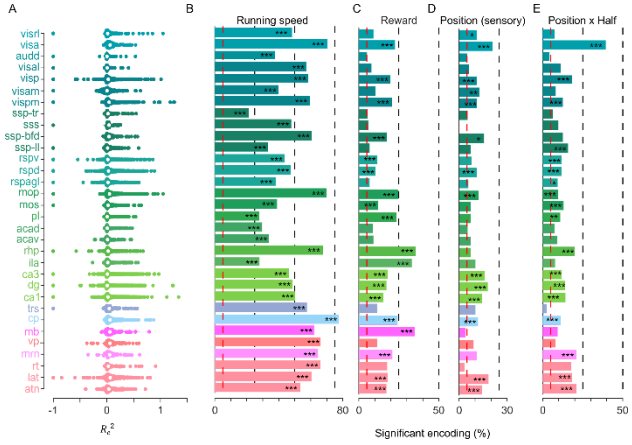

Figure 3: 4R results. **A.** total explainable variance explained for every neuron, sorted by area (Allen Brain atlas nomenclature and color scheme). Note that R^2_e<0 indicates the mean firing rate is a better predictor than the model. **B.** percentage of neurons per area with significant increase in R^2_e for running speed. ***,p<0.001. **C-E.** Same as (B) for reward, sensory position, and position x half. *, p<0.05

Discussion

Our results show that spatial navigation indeed engages distributed representations of both spatial and non-spatial processes. In line with the literature, about 15% of neurons in hippocampal regions significantly encode spatial position. Additionally, hippocampal neurons encode non-spatial predictors, such as running speed, reward, and sensory position.

With our brain-wide Neuropixels recording approach, we find that many regions outside the hippocampus, including striatal and thalamic regions, also encode spatial position. Interestingly, many neurons show mixed selectivity to both sensory and spatial predictors in the VR corridor. In line with this finding, spatial tuning in the VR corridor correlates with the strength of tuning to sensory stimuli outside of the VR corridor. These findings suggest that, as was previously suggested for the hippocampus, spatial tuning is anchored to sensory landmarks across the brain. Moving forward we will integrate single-neuron and population analyses, and leverage chronic Neuropixels recordings to track evolving distributed navigation-related signals over time (Bimbard et al., 2025; van Beest et al., 2025).

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