Age-Related Changes in Neural Noise in a Decision-Making Task

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Abstract

Classical theories suggest that age-related cognitive decline may be caused by increased neural noise. To explicitly test this hypothesis in behaving animals, we quantified single-neuron noise (using Fano Factors) in the cortex, hippocampus, and thalamus of young and old mice. Preliminary results suggest that thalamic neurons show higher trial-to-trial variability in old animals. This work will help us to understand alterations of neural function that may contribute to age-related cognitive decline.

Keywords: aging; electrophysiology; mouse; neural noise

Introduction

Aging is characterized by impairments in decision-making, memory and learning. Classical theories state that this cognitive decline arises from higher levels of 'noise', defined as trial-to-trial variability in neural responses to the same stimulus, and thus the effective signal-to-noise ratio in the central nervous system decreases with age (Cremer & Zeef, 1987; Crossman & Szafran, 1956; Salthouse & Lichty, 1985; Welford, 1981). Studies on anesthetized monkeys have found that noise in single cortical neurons (Yang et al., 2009) and local circuits (Wang et al., 2019) increases with age. However, the behavioral consequences of this variability are still unknown, and neural noise changes in aging have not been quantified in neural structures beyond cortex.

Recent technical advances allow us to investigate neural noise in large-scale recordings from behaving animals (Urai et al., 2022). Here, we analyzed recordings from multiple brain regions (cortex, hippocampus, and thalamus) of mice performing a standardized perceptual decision-making task (The International Brain Laboratory et al., 2021). We then quantified trial-to-trial firing rate variability of single neurons, using the Fano Factor, a measure widely used to characterize neural variability (e.g., Churchland et al., 2010; Yang et al., 2009). We tested the hypothesis that older mice exhibit higher levels of neural noise, which may ultimately contribute to decreased decision-making capabilities.

Methods

We used a public dataset of extracellular Neuropixel recordings (Jun et al., 2017) in young mice (N = 63, 45 male, mean age = 6, range 4 - 9 months) (International Brain Laboratory et al., 2022) and additional recordings in old mice (N = 20, 13 male, mean age = 16, range 10 - 19 months). Recordings were acquired using standardized pipelines for a visual decision-making task in mice (The International Brain Laboratory et al., 2021) (Figure 1a). We filtered recording sessions and 'good' neurons, which passed quality control criteria as defined in (International Brain Laboratory et al., 2022a; 2022b). After quality control, we included 48 recording sessions from young mice and 14 sessions from old mice. Note that preprocessing is preliminary, and that we aim to include more sessions in our final analyses.

The Fano Factor (FF) is defined as the spike count variance over trials divided by the spike count mean:

$$Fano\ Factor\ = \frac{variance(spike\ count)}{mean(spike\ count)}$$

The Fano Factor calculation was limited to neurons with a firing rate >1 spikes/second, to ensure sufficient data for estimating the variance. The Fano Factor time course was calculated using a sliding window method (width = 0.1s, step = 0.02 s) for each neuron, and then averaged within each brain area. The code is at github.com/Fenying-Zang/mouse_age_FF.

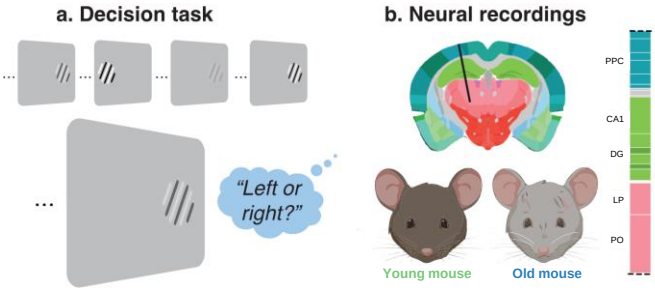

Figure 1. (a) Schematic of the visual decision-making task. **(b)** Extracellular recording using Neuropixels probes. The targeted trajectory goes through the posterior parietal cortex (PPC), hippocampal field CA1 (CA1), dentate gyrus (DG), lateral posterior nucleus of the thalamus (LP), and posterior nucleus of the thalamus (PO).

Results

Neural yield

We compared the neural yield (number of neurons per recording) between young and old animals for each target brain area (Figure 2). Old mice have fewer neurons overall recorded in the PPC, CA1 and DG, and fewer 'good' neurons in the PPC and CA1. Future work will investigate if this is caused by superficial tissue damage (as the dura of old mice was harder to penetrate), or reflects age-related neuron loss.

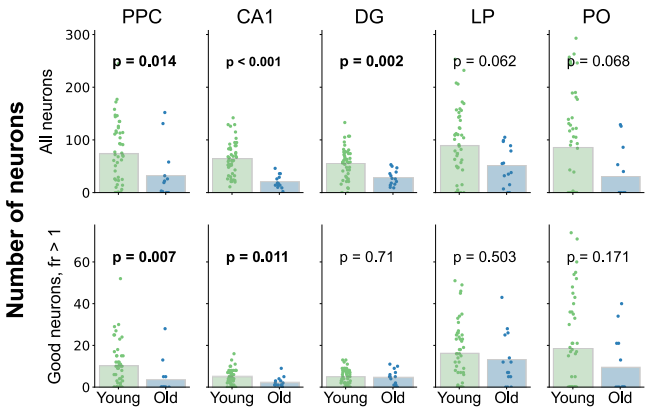

Figure 2. Neural yield for young and old mice in five target brain areas. *p*-values from a nonparametric Mann-Whitney U Test.

Neural response and neural noise

To test if aging increases neural noise, we focused our preliminary analysis on areas LP and PO, where the young and old groups both have sufficient numbers of neurons (n > 100). We found that old mice have more neural noise (larger Fano Factors) as compared to young mice in these thalamic areas (Figure 3). In the cortex or hippocampus, where we recorded smaller sample sizes, we did not observe a significant group difference.

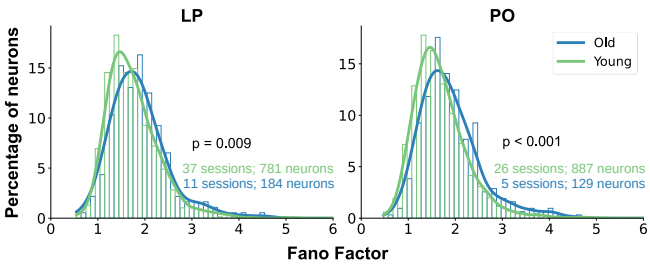

Figure 3. Distribution of Fano Factors (calculated based on spikes occurring between 100 - 200 ms after stimulus onset) for neurons in LP and PO areas of the young and old groups. Note that we set x-axis limits, thus a few neurons with a Fano Factor > 6 are not shown here. *p*-values from a nonparametric Mann-Whitney U Test.

Neural variability decreases ('quenches') upon stimulus onset in various cortical regions and species, including a wide range of cortical regions of monkeys (Churchland et al., 2010; Poland et al., 2019), the PPC of rats (Licata et al., 2017), and the olfactory cortex of both mice (Iurilli & Datta, 2017) and rats (Miura et al., 2012). However, a previous study on rhesus macaques found that neural variability in the thalamic nuclei was unaffected by stimulation (Poland et al., 2019). To investigate the temporal dynamics of neural variability, we aligned the time course of firing rate and Fano Factor to stimulus onset. As expected, stimulus onset caused clear increases in the firing rate in both young and old mice (Figure 4, left). The decline in the Fano Factor was assessed by comparing the Fano Factor at 200 ms after stimulus onset to that at 100 ms before stimulus onset, following the methodology used by (Churchland et al., 2010). In young animals, Fano Factors decreased after stimulus onset in LP and PO (Wilcoxon signed-rank test, both $p < 0.001$), replicating previous findings on the same dataset (International Brain Laboratory et al., 2022a). Preliminary analysis of the old mice also showed a declining trend after stimulus onset in LP and PO, although this decline was not statistically significant (Figure 4, right). Future work will further investigate the temporal dynamics of neural variability across multiple brain areas, its dependence on task conditions (stimuli/responses), and its change with age.

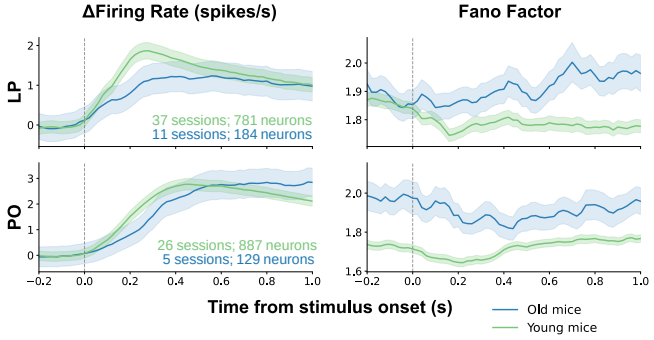

Figure 4. Change in firing rate from pre-stimulus baseline and Fano Factor averaged over all neurons in LP and PO area, aligned to stimulus onset. Shaded areas show standard error of the mean across neurons.

Conclusion

We examined the effect of aging on neural noise, quantified using large-scale extracellular recordings in mice. Preliminary results suggest that old mice show higher trial-to-trial neural variability in thalamic areas.

Our next steps will be extending our analysis to other brain areas (PPC, CA1, and DG) by including more datasets of old mice. Future work will investigate different cell types, and extend the current analysis to the local circuit level by exploring noise correlations between neurons. We also plan to link age-related changes in neural noise to decision-making behavior. The findings will facilitate our understanding of changes in neural functioning that may contribute to cognitive decline associated with aging.

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