Within burst spike variability is significantly higher in $\alpha - CAMKII^{T305D}$ mice

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February 8, 2002

Abstract

We present studies of within-burst inter-spike interval (ISI) variability in α-calmodulin kinase II mutant ($\alpha - CaMKII^{T305D}$) mice. In-vivo recordings show that within-burst ISIs are highly variable compared to wild type. The average spike rates between the two groups were not significantly different. Further, $\alpha - CaMKII^{T305D}$ mice have been shown to exhibit LTP deficiencies in slice preparations and other

unpublished results show that these mice show severe spatial learning deficiencies. This study, which is the first of it's kind to the best of our knowledge, leads to the possibility of a relationship between within-burst ISI variability and behavioral deficits in-vivo.

1 Summary

Pyramidal cells in the hippocampus (place cells) are thought to encode spatial information because in general they fire when the animal is in specific regions of the environment (place fields) [4],[3]. The present study investigates the firing characteristics of place cells in region CA1 of mice with a threonine to aspartate mutation at position 305 of the α-calmodulin kinase II ($\alpha - CaMKII^{T305D}$). This group is henceforth referred to as mutants. This mutation interferes with calmodulin binding and therefore with kinase activation resulting in impaired long term potentiation LTP in the CA1 region of the hippocampus. At the same time profound deficits in hippocampal-dependent learning tasks (Morris water maze, contextual fear conditioning) accompany the mutation (detailed paper in preparation)[1].

Place cells from the CA1 region of the hippocampus were recorded extracellularly in the awake, behaving animals. The mutant group consisted of six animals with thirty two unique cells isolated and recorded from over eighty one sessions in all. Thirty four cells were recorded from the wild-type group consisting of six animals over ninety four sessions. Each session lasted for about twenty minutes. The average firing rates for the cells were not significantly different; a t-test for firing rates by session across did not reject the hypothesis for equality of firing rates.

Bursts were defined as spike events for which the inter-spike intervals between two successive spikes were less than 10ms and when the spike heights successively decreased. This definition was derived according to the usual bursting patterns found in place cells[2].

We found that in mutants, the fraction of bursts to total spikes was significantly less than that in wild type (6.39% in mutants vs 12.41% in wild type). Furthermore, the ISI histograms consistently showed a distinct shift of the peak towards right for the mutant group. This prompted us to analyze the within-burst firing frequency for these cells further. We found that after isolating the bursts and examining the ISI for spikes that constituted a burst, the bursting characteristics were radically different, as can be seen from figure 1. Figure 1 shows density estimator plots for within-burst ISIs. The density estimator used a gaussian kernel with the Silverman's "rule of thumb" for bandwidth selection [5]. For each of the density estimates

shown, we tested for equality of the distributions using the Kolmogorov-Smirnov test [6] and found a p value of around 10^{-16} for each of the test, meaning that with almost certainty the two samples arose from different distributions.

In order to also entertain the possibility that within-burst firing rate characteristics may not be different for the two groups, we computed the mean within-burst ISI values. For each such burst the density of the mean within-burst ISI is plotted in figure 2. It is evident from figure 2 that this metric also differs significantly across the groups. Again, Kolmogorov-Smirnov test for equality of densities gave a p value of vanishingly low (of the order of 10^{-16}) values between two groups.

2 Conclusion

We have shown here that the mutants which show severe deficits in spatial learning tasks also show high variability in within-burst inter-spike intervals. This leads to some scintillating questions about the dynamics of cells in-vivo and how they could be linked to LTP deficiency observed in slice recordings as well as behavioral deficits in spatial tasks. More sophisticated statistical analysis of the data at hand is being performed in this direction to guide future modeling studies. To the best of our knowledge, this is the first comparison of within-burst ISI distributions in a mutant model that shows severe learning disabilities.

References

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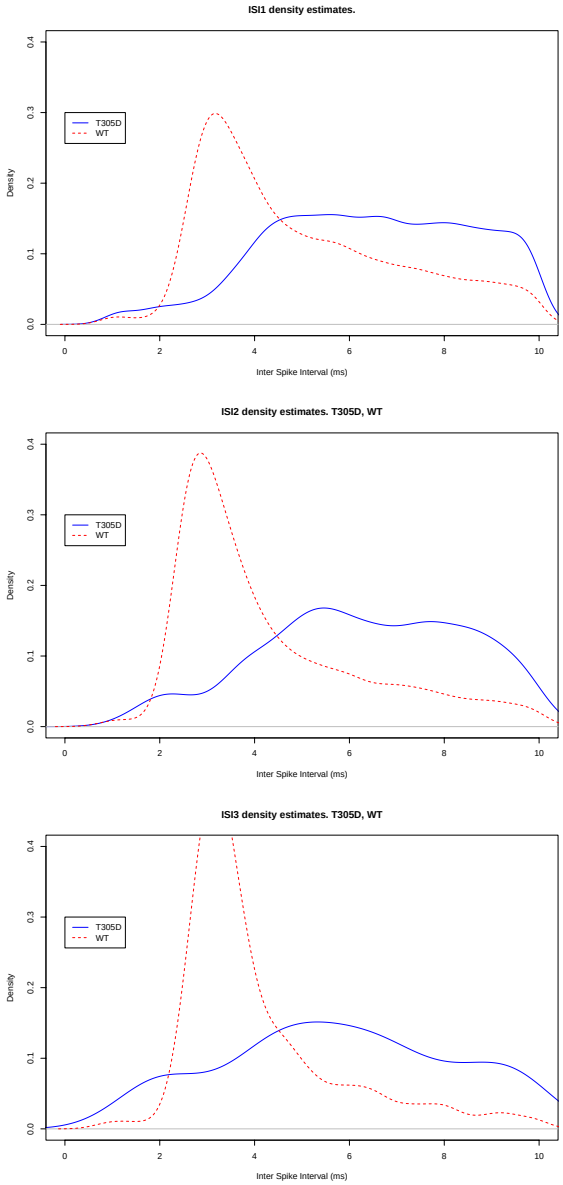

Figure 1: Distribution of within-burst ISI. ISI1, ISI2, ISI3 are the inter-spike-interval between first and second spike, second and third spike, and third and fourth spike in a burst respectively. Kolmogorov-Smirnov test for equality of densities gave a p value vanishingly close to 0 for each of the density estimates above

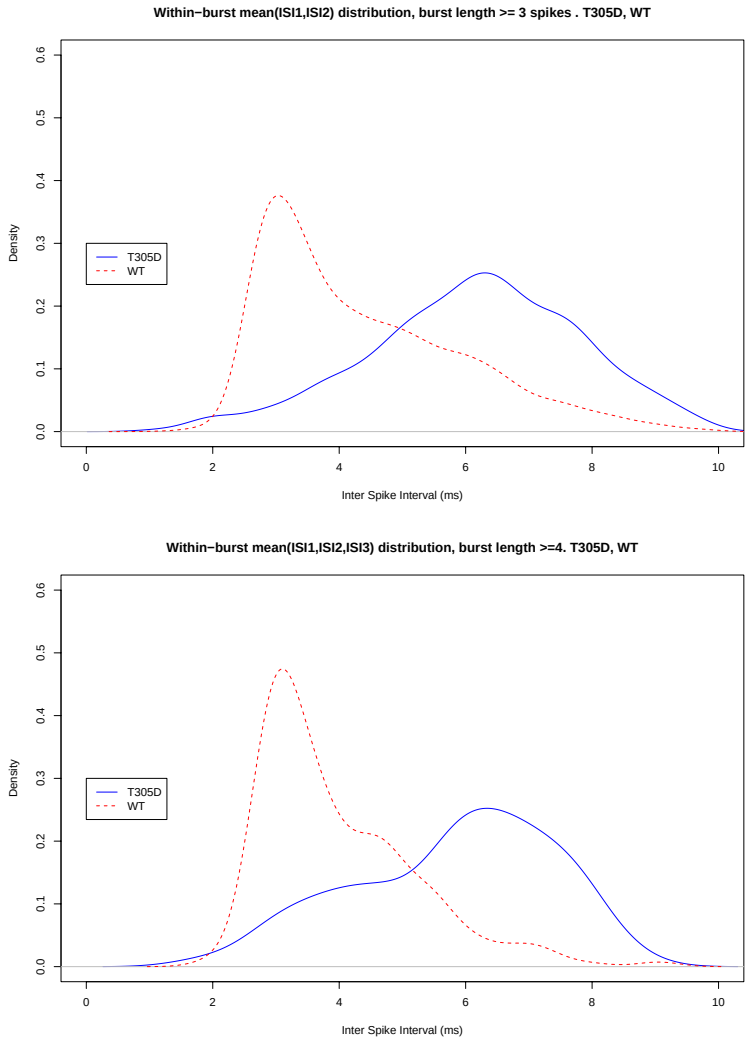

Figure 2: Distribution of within-burst mean ISI. Kolmogorov-Smirnov test for equaliy of densities gave a p value of vanishingly low values for each of the density estimate above