

Neural Correlates in the Amygdala of Extreme Responders to Pavlovian Threat Conditioning



Introduction

In Pavlovian auditory Threat Conditioning (PTC), an initially neutral conditioned acoustic stimulus (CS), after being associated with an aversive unconditioned stimulus (US), typically an electric shock, acquires the ability to induce conditioned responses (CR) such as freezing.

The Amygdala is essential for this form of associative learning and memory. The CS and the US information converge in the Lateral Nucleus of the Amygdala (LA) cells. On its part, the Central Nucleus of the Amygdala (CeA) regulates conditioned threat responses.

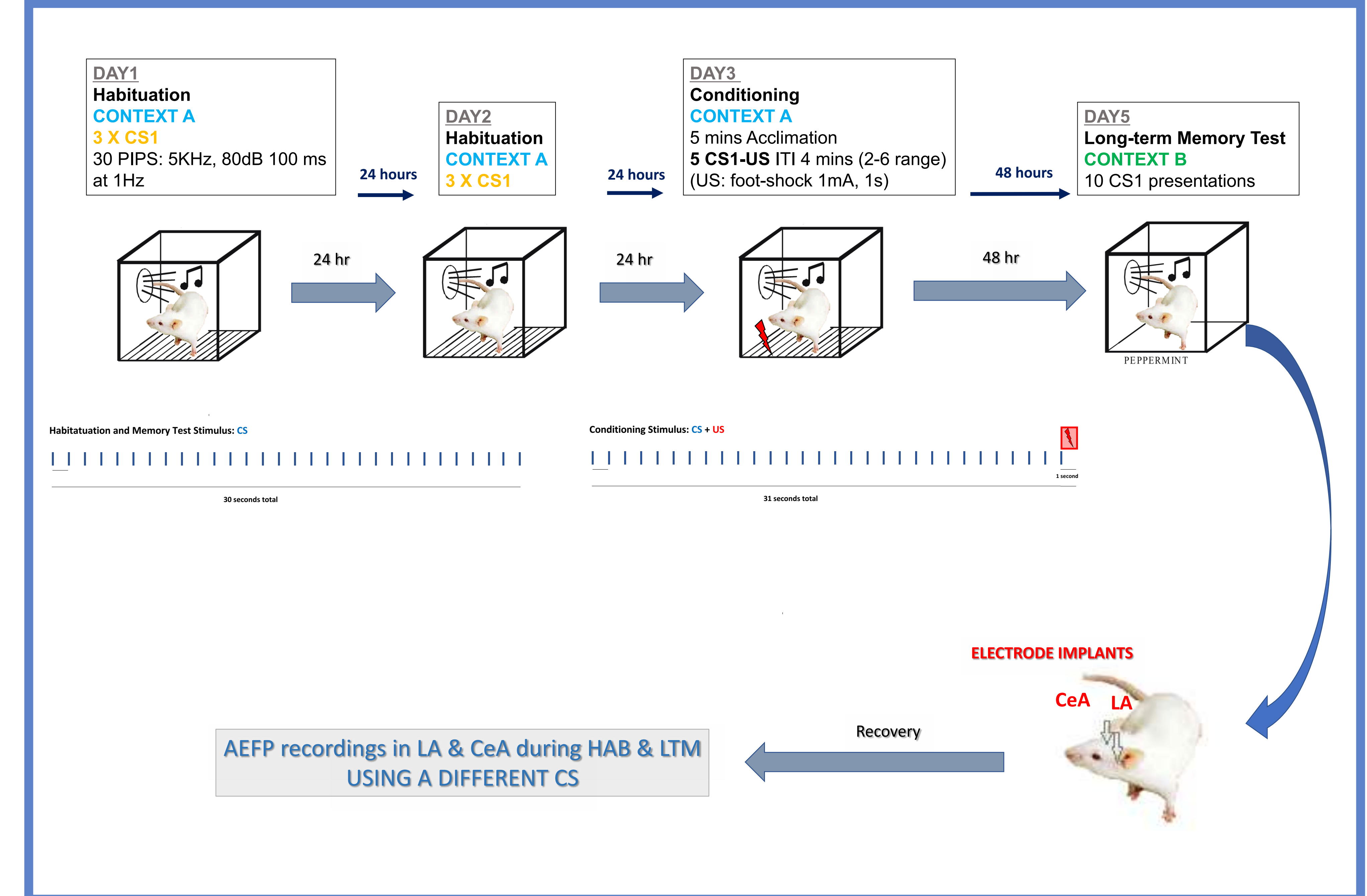
Most of what is known about PTC and its underlying brain circuitry is based on experiments in which the data is analyzed by averaging measures of different individuals. However, there is great variability on individual conditioned responses.

The use of central tendency measures assumes population homogeneity, and therefore is potentially overlooking the neurobiological basis that might explain exaggerated behaviors.

Objectives

- To establish subpopulations of rats based on their individual different reactivity to the Conditioned Stimulus
- To identify potential correlations between phenotype and the neural activity in LA and Ce
- To identify molecular or/and electrophysiological markers of different reactivity

Methods



Results

Figure 1.- As expected the individual values of freezing follows a normal Gaussian distribution (D'Agostino & Pearson Omnibus K2=3.458)

Figure 2.- Three distinct behavioral phenotypes are found after performing an Unsupervised hierarchical cluster analysis based on Euclidean distances between the average amount of freezing during LTM test of each individual. A) Dendrogram constructed from the Euclidean distance matrix. Height Ratio: 71.9% B) Scatter Plot with depicting the 3 clusters in the space.

Figure 3.- When memory is tested 48 hours after conditioning, the 3 groups show significantly different level of freezing to each CS presentation (A). The extinction rate and the final level of extinction is significantly different depending on the groups (B). A: Two-way ANOVA $F(18,590)=2.423$ $p<0.0009$; B: Two-way ANOVA $F(2,118)=11.69$ $p<0.0001$

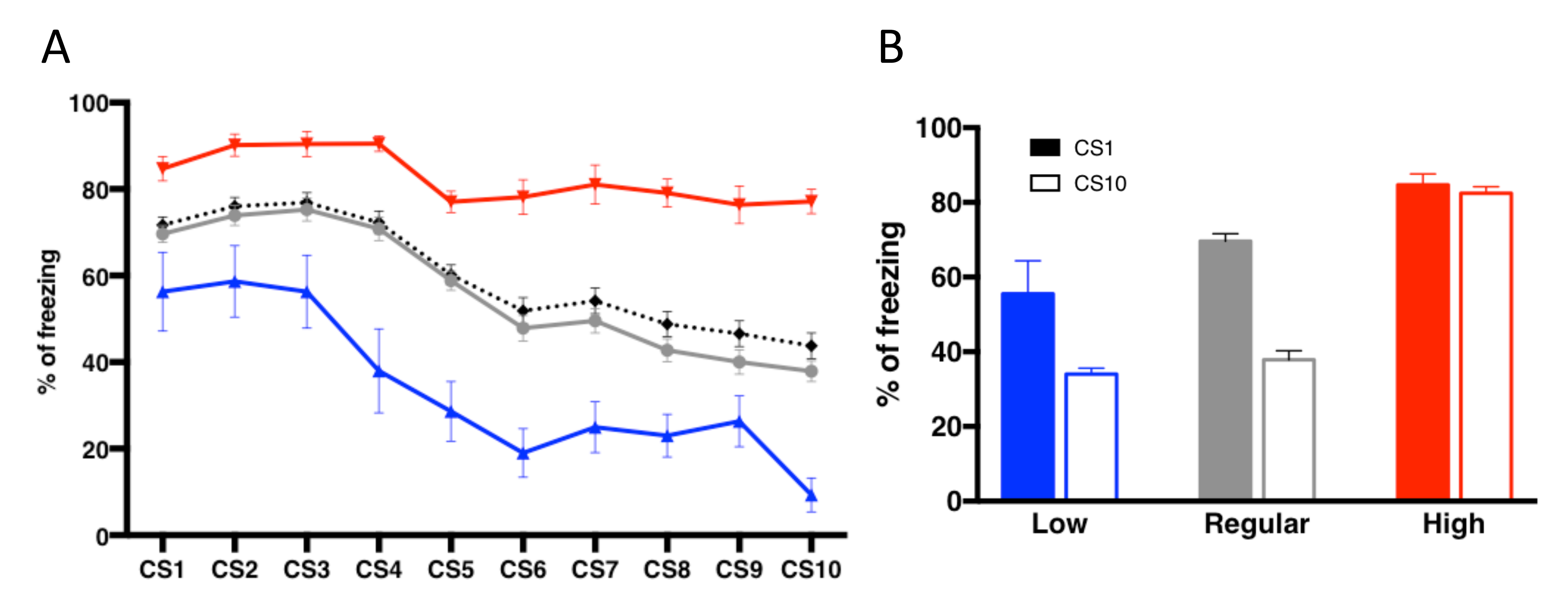
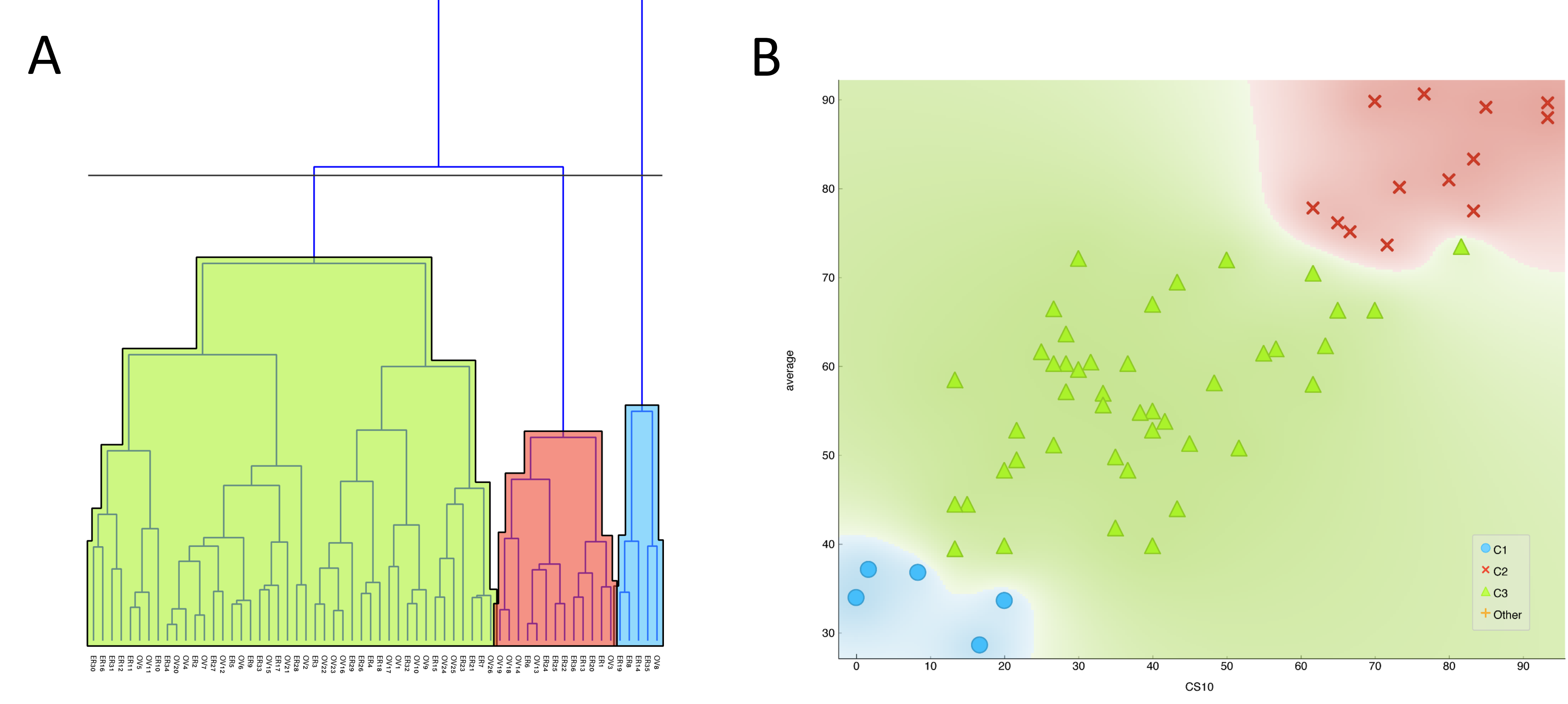
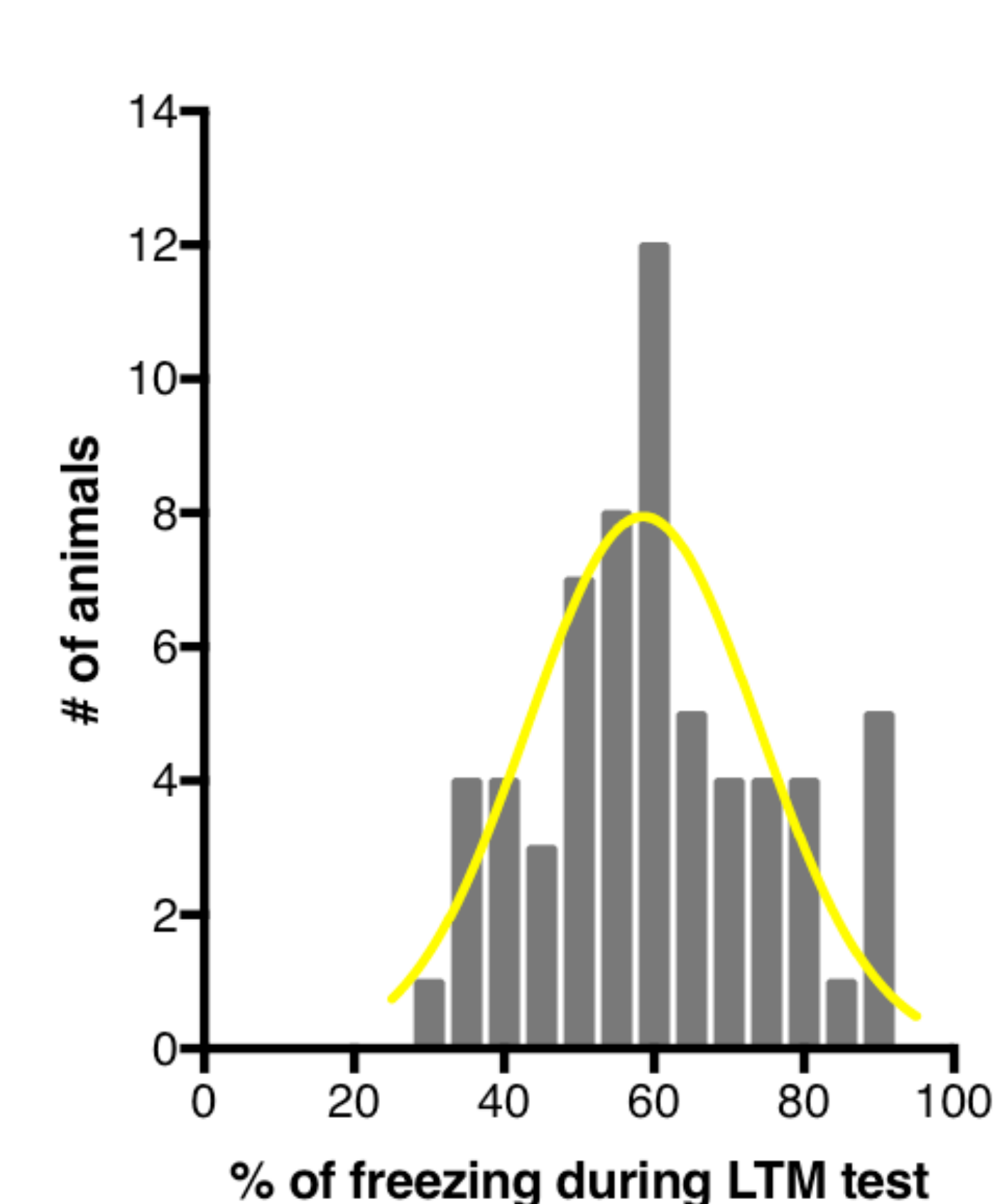
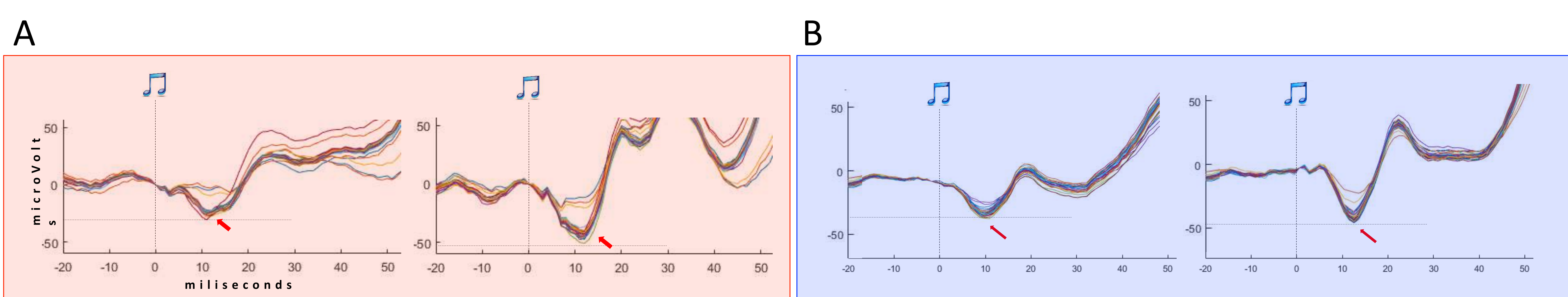


Figure 4.- Tone-evoked field potential in the Lateral Nucleus of the Amygdala shows higher potentiation in the animals naturally exhibiting high freezing responses to the conditioned stimulus compared with the low freezers. Example traces of one animal belonging to the high freezers group (A) and to the low freezers (B) during baseline (left graph of each panel) and during Long-Term Memory test (right graph of each panel)

Conclusions

- Unsupervised data clustering results in 3 clearly different group of animals based on their individual freezing response. Animals showing regular freezing are approximately 70%, 20% exhibit exaggerated freezing while 10% show very low freezing.
- Low-freezers extinguished faster than do regular-freezers. The repeated presentation of 10 CSs is not enough to observe any extinction in the high-freezers.
- There is a differential neural activity in the Lateral Nucleus of the amygdala matching the level of freezing of the high and the low freezers.
- Finding group-related differential neurophysiological characteristics might be key to understand and potentially treat psychiatric conditions characterized by over-responsivity to auditory stimuli.



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