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Neural, behavioral and genetic modulators of fear conditioning: examples form human and animal research

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The goal of the present dissertation is an investigation of the mechanisms regulating the acquisition of cued as well as contextual conditioned fear, with a focus on two brain structures which play a critical role in processing aversive learning, such as the amygdala and the hippocampus. According to the translational framework on which this thesis is based we provide three studies, two of which are performed on human participants and one is performed on laboratory animals.

Using structural magnetic resonance imaging, in the first study we demonstrated that the volumes of the amygdala and the hippocampus play dissociable roles in the modulation of cued fear conditioning. In particular, we showed that the amygdala volume is positively associated with the magnitude of autonomic learning, as indexed by the differential skin conductance responses, but it had no significant effect on the declarative contingency learning, as assessed by the differential CS-US contingency ratings. Further, we showed that the hippocampal volume positively and significantly impacts on the declarative contingency learning, without having significant effect on the autonomic component. These results are the first to show that structural properties of amygdala and hippocampus modulate human fear conditioning and underline the importance of individual differences in the morphology of these two brain regions in regulating a basic aversive learning task, such as fear conditioning. These data are relevant because bridge the gap between previous human lesion and functional neuroimaging studies, which have consistently reported a double dissociation between these two structures relative to the two learning components during fear conditioning.

In the second study we showed that a genetic risk variant for alcoholism significantly affects amygdala activation during the acquisition of conditioned fear, using functional magnetic resonance imaging. Additionally, carriers of the risk allele showed significantly reduced activation in the insula, another region fundamental in fear conditioning. These data indicate that reduced activity in these two structures during aversive learning might represent an endophenotype of alcohol dependence.

Moreover our results further promote fear conditioning as a suitable paradigm to investigate not only anxiety disorders but also disorders related to abnormal impulsivity or risk-taking behaviors, such as alcoholism.

Finally in the third study we investigated a potential role of physical exercise as an intervention tool for PTSD symptoms after trauma exposure, within the framework of an animal model that accounts for both associative and non-associative components of the PTSD pathophysiology. We found no influence of physical exercise on contextual fear conditioning or on non-associative learning measures, such as freezing behavior to an acoustical tone in a novel environment. Similarly, no between groups differences could be detected in the acoustical startle reflex. However, we reported significantly increased anxiety levels in exercised mice, compared to sedentary controls. These data are in line with previous studies showing no effect of running protocols on contextual fear conditioning, and indicate that voluntary free running has the potency to altering emotional behavior in mice.