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Contextual Modulation of Associative Learning and the Role of Resting State Brain Activity in Posttraumatic Stress Disorder

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In the present dissertation we addressed neuronal changes in PTSD using an activation-based and a resting state-based approach with a special focus on brain areas involved in abnormal activation in PTSD such as amygdala, hippocampus, ventromedial prefrontal cortex (vmPFC), dorsal anterior cingulate cortex (dACC) and insula. Our attention was directed to the mechanisms mediating increased return of fear and the association of PTSD symptoms with aberrant brain activity as well as aberrant resting state connectivity. In both studies we compared PTSD patients with trauma-exposed but unaffected controls (non-PTSD) and trauma-naïve healthy controls (HC).

In the first study, subjects underwent an ABC fear conditioning and extinction procedure, where two CSs were presented in front of virtual reality scenes. One of them (CS+) was paired with a slightly painful electrical stimulation (US) during acquisition, whereas the other one was never paired with the US (CS-). During extinction, there were no CS-US pairings. After acquisition (context A) and extinction (context B), the participants were brought to a novel context C and again confronted with the CSs. Self-reports, skin conductance responses (SCR) and functional magnetic resonance imaging (fMRI) were measured simultaneously. We found elevated return of fear in the PTSD patients indicated by larger differential SCR compared to non-PTSD and HC and larger differential amygdala and hippocampus activity compared to HC. Increased amygdala activation was positively correlated with numbing and vmPFC activity was positively correlated with behavioral avoidance even though there were no functional group differences in this region of interest. Additionally, PTSD patients failed to appropriately reduce subjective arousal to the CS- over the course of the experiment and to the CS+ during extinction. Taken together, the results of study 1 support the hypothesis that PTSD is characterized by aberrant activity within regions of the neurocircuitry model, which leads to deficient extinction maintenance. Furthermore, our data confirm a general inability of PTSD patients to correctly identify safety signals and modulate fear responses based on this information. Such dysfunctional mechanisms seem to contribute to PTSD symptoms and represent a probable cause for relapse, whereas resilient subjects appear to benefit from protective mechanisms.

In the second study, subjects underwent a resting state scan and functional connectivity was analyzed using an amygdala seed and independent component analysis (ICA) as well as correlations with symptom severity. The seed-based approach revealed increased left amygdala – the left insula coupling in PTSD versus nonPTSD, which positively correlated with re-experiencing intensity. Compared to HC, both trauma-experienced groups showed higher positive correlations of the left amygdala and the right putamen as well as the right insula. The ICA did not reveal any group differences, i.e. in DMN connectivity. In summary, study 2 indicates that altered amygdala-insula coupling and decreased amygdala-putamen coupling, but not DMN connectivity, contribute to the pathophysiology of PTSD. Hyperconnectivity between the left amygdala and the left insula differentiated patients from resilient subjects and was linked to re-experiencing intensity. This result suggests that a stronger functional link between somatic sensations and emotional appraisal might lead to increased anticipation of negative events in PTSD, which potentially explains characteristic symptoms such as hyperarousal and negative alterations in mood and cognition.