

36. Mechanisms via Which Traumatic Stress Leads to Persistent Fear in Male and Female Rats

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Background: PTSD has a higher prevalence rate in women when compared to men. However, mechanisms via which this sex difference manifests are not well understood. The goal of this study was to examine this sex difference within the single prolonged stress (SPS) rodent paradigm of traumatic stress.

Methods: In experiment 1 we examined the role of estrogen receptor activation prior to SPS in facilitating SPS effects on fear and extinction memory in female rats. In experiment 2 we examined the effects of SPS on acquisition and extinction of freezing and avoidance in male and female rats. In experiment 3 we used functional and structural MRI to identify circuits that were sensitive to traumatic stress in male and female rats.

Results: In experiment 1 ($n = 145$) we observed that nuclear estrogen receptors facilitate extinction retention deficits in SPS/female rats, but levels of freezing were variable during extinction testing. In experiment 2 ($n = 48$), the ability to avoid prevented extinction retention deficits in SPS/male rats. Non-stressed female rats used avoidance to lower levels of freezing during an extinction test and SPS disrupted this relationship. In experiment 3 ($n = 32$) SPS disrupted PFC functional connectivity and enhanced the ACC and IL volume in male rats. In female rats SPS enhanced hippocampal-CeA functional connectivity and enhanced CeA volume.

Conclusions: Together, these findings suggest that activation of nuclear estrogen receptors facilitate SPS effects in female rats and traumatic stress may lead to persistent fear in male and female organisms via different behavioral and neural processes.

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Keywords: PTSD, Extinction Learning and Recall, Anterior Cingulate Cortex (ACC), Amygdala, Hippocampus

37. Electroencephalographic Microstates During Sleep and Wake in Schizophrenia

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Background: Schizophrenia is associated with aberrant connectivity between neural assemblies. This dysconnectivity produces multiple abnormalities in electroencephalographic data collected from people with schizophrenia. Microstate analysis is a technique for modeling electroencephalographic

data with a small set of recurring voltage topographies. Several papers have described microstate abnormalities in schizophrenia. However, these studies have only examined resting state data. Sleep spindles are known to be decreased in schizophrenia, which suggests that there may also be sleep-related microstate abnormalities.

Methods: We recorded high-density electroencephalographic data during wake and sleep from 114 patients with schizophrenia and 79 age matched controls. We used a modified k-means analysis to segment the data into a common set of six microstates which were then fit back to the data. We calculated coverage, duration, explained variance, occurrence, and spatial correlation, as well as microstate transition probabilities.

Results: Multiple comparison corrected ANOVAs revealed a complicated set of case/control, frequency, and sleep/wake dependent differences. The transition from quiet rest to sleep is marked by a shift from microstates A, B, and C to microstates D, E, and F. Average microstate duration increased with sleep depth and this effect was greater in cases than controls. Wake microstate sequences were more complex in controls. During NREM sleep, two microstates were associated with sleep spindles and two were associated with slow oscillations.

Conclusions: Wake and sleep have different microstate parameters in patients with schizophrenia compared to control participants. These differences point to cortical dysfunction that may not be detectable with other approaches.

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Keywords: Schizophrenia, EEG Microstate Analysis, Sleep

38. Transcranial Focused Ultrasound of the Amygdala Down-Modulates Fear Neural Circuit Activation and Facilitates Fear Extinction

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Background: Transcranial focused ultrasound (tFUS) is a novel noninvasive brain stimulation method that can target brain tissue millimeters in the diameter anywhere in the brain. This superior spatial and depth specificity enables the neuromodulation of deeper subcortical brain regions previously inaccessible by other noninvasive methods. The amygdala is a deeper brain region that plays a central role in fear processing. We investigated whether tFUS of the amygdala could change neural and subjective measures of fear.

Methods: Thirty healthy individuals underwent Blood Oxygen Level Dependent (BOLD) functional Magnetic Resonance Imaging (fMRI) in a 3T Siemens Prisma MRI scanner during a fear-inducing task before and after active or sham tFUS of the left amygdala. Participants received mild electrical shocks during the task and were asked to rate their anxiety. An SPM12 flexible factorial was used to determine the effects of active tFUS during the high shock risk trials compared to the low shock risk trials, relative to sham tFUS.

Results: Participants who received active tFUS showed decreased left amygdala ($F(1,24)=5.44$, $p=0.03$), hippocampal ($F(1,28)=4.27$, $p=0.05$), insular ($F(1,28)=3.05$, $p=0.04$), and dorsal anterior cingulate ($F(1,28)=5.85$, $p=0.02$) BOLD activation during the fear-inducing trials, compared to the sham tFUS group. The decrease in left amygdala BOLD activation was correlated with a decrease in anxiety ratings ($r(23)=0.414$, $p=0.05$).

Conclusions: These results suggest that tFUS can be used to change BOLD activation in subcortical regions such as the amygdala, as well as its associated emotional correlates. Future studies can investigate the use of tFUS in individuals with clinical levels of fear and anxiety.

Funding Source: Tiny Blue Dot Foundation

Keywords: Low Intensity Focused Ultrasound, Amygdala, Fear Extinction, Anxiety

39. Subcortical Brain Volumes in Social Anxiety Disorder: An Enigma-Anxiety International Mega-Analysis of 37 Samples

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Background: Multiple studies have investigated subcortical brain volumes in patients with social anxiety disorder (SAD). Their results are often inconsistent, probably due to variations in methodological approaches, such as study-specific sample selections based on age and clinical characteristics.

Methods: Within the framework of the ENIGMA-Anxiety Working Group, we performed a mega-analysis to investigate subcortical volumes in adults and adolescents with SAD relative to healthy controls (HC). Individual participant data from 37 international samples ($n=1115$ SAD, 2775 HC) were obtained using ENIGMA-standardized protocols for image

segmentation and quality control. Linear mixed-effects analyses were adjusted for comparisons across seven bilateral subcortical regions using family-wise error (FWE) correction. Mixed-effects d effect sizes were calculated.

Results: Patients with SAD showed smaller bilateral putamen volume than controls (left: $d=-0.077$, $p_{FWE}=0.037$; right: $d=-0.104$, $p_{FWE}=0.001$), and a significant interaction between SAD and age was found for the left putamen ($r=-0.034$, $p_{FWE}=0.045$). Smaller bilateral putamen volumes (left: $d=-0.141$, $p_{FWE}<0.001$; right: $d=-0.158$, $p_{FWE}<0.001$) and larger bilateral pallidum volumes (left: $d=0.129$, $p_{FWE}=0.006$; right: $d=0.099$, $p_{FWE}=0.046$) were present in adult patients with SAD, but no volumetric differences were apparent in adolescents with SAD. Comorbid anxiety disorders and age of SAD onset were additional determinants of SAD-related volumetric differences in subcortical regions.

Conclusions: Subtle alterations in subcortical brain volumes in SAD were identified. Heterogeneity in age and clinical characteristics might partly explain inconsistent previous results. Future longitudinal studies are needed to further explore the association between alterations in subcortical volumes and SAD illness progression from adolescence into adulthood.

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