

# Understanding PTSD as a Memory Disorder: *Cognitive and Neural Biomarkers of Overgeneralization and Impaired Reward Learning in Women Survivors of Sexual Violence*

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We propose to study women survivors of sexual violence who exhibit symptoms of post-traumatic stress (PTS), including emotional numbness, increased arousal and anxiety, flashbacks, hyper-vigilance to threat, and disruption of sleep, including recurrent nightmares. If these symptoms persist for over a month, they can lead to a diagnosis of *Post-Traumatic Stress Disorder* (PTSD). The long-term goal of our research is to understand why some women, in the aftermath of sexual violence, show resilience to mental health problems, while others are at higher risk for PTSD. Critical gaps exist in our current neurocognitive and psychiatric understanding of PTSD, hindering progress towards developing new therapies that might eventually replace the range of often ineffective therapies currently available. With the predominance of military-funded research on PTSD being done mostly in male soldiers following combat trauma, there is a notable paucity of research on PTSD in women who have experienced sexual violence. It is important to expand our understanding of PTSD in women survivors of sexual violence because: (a) risk factors for PTS in survivors of sexual violence may be different than for those who experienced combat trauma, and (b) some PTSD symptoms are more common in women than in men, and others more common in men. While our study will mitigate this gender gap, the resulting findings may also be broadly applicable to a wider range of PTSD etiologies and patients.

Traditionally, PTSD has been viewed as an anxiety or stress disorder, and thus has most often been modeled—in both rodents and humans—using fear-conditioning paradigms that engage the amygdala and prefrontal cortex. However, the P.I., Gluck, and his colleagues at Rutgers University have argued that PTSD is usefully characterized as a cognitive disorder with specific and dissociable learning and memory deficits which should be evident even in non-fear learning paradigms, such as the categorization or discrimination of abstract stimuli (Levy-Gigi et al., 2012). This perspective, combined with the unique targeted population of women survivors of sexual violence, leads to the following aims for this study:

## Specific Aims

**Specific Aim #1. Identify neurocognitive systems for learning and generalization that differ between those with high levels of PTS compared to those who have been more resilient to PTS.**

**Hypothesized Overgeneralization Deficit:** In PTSD, a traumatic event may cause the memory of that event to become identified with a very broad class of other stimuli, leading to overgeneralization of traumatic memories. For example, after being bitten by a particular dog, one might develop a fear response that generalizes to all dogs. Gluck and Myers's previous neurocomputational models of hippocampal-region function (Gluck & Myers, 1993, 2001; Myers, et al., 1996) imply that an overactive **entorhinal cortex** will result in diminished stimulus specificity for a new memory, which could lead to overgeneralization of memories, as seen in PTSD (Anastasides et al., 2015; Kostek et al., 2014). **Resulting predictions:** Women with the most severe PTS symptoms will show resting-state hyperconnectivity within the **medial temporal lobe**, especially to the entorhinal cortex, that will be associated with a greater tendency to **overgeneralize learning** to novel similar stimuli.

**Hypothesized Reward-Feedback Learning Deficit:** Learning about the positive (rewarding) consequences of safe stimuli (e.g., other friendly dogs) is known to be dependent on **basal ganglia** circuits. This suggests that the resistance to extinction of inappropriate overgeneralized threat inferences seen in PTSD may be the result of an impaired ability to learn that approaching these other stimuli can be safe and potentially rewarding (Myers et al., 2013). **Resulting predictions:** Women with the most severe PTS symptoms will show

hyperactivation in the ventral striatum, particularly the nucleus accumbens, and, altered brain connectivity within the **basal ganglia**, including a shift in resting-state connectivity from the left to the right, associated with impaired **reward-feedback learning** (Mattfeld et al., 2011).

**Specific Aim #2. Characterize how sleep patterns observed over multiple nights of home monitoring in those with high levels of PTS, modulate neurocognitive differences in learning and generalization.**

Sleep dysfunction is among the most widely reported symptoms of PTSD. Alterations in Rapid-Eye-Movement (REM) sleep are commonly found (Germain, 2013), though Slow-Wave-Sleep (SWS) deficiencies are also reported (Kobayashi et al., 2007). Given the important role of sleep for learning, both prior to training as well as for post-training memory consolidation, a full characterization of learning and generalization in PTSD should account for variations in sleep quality. **Resulting Predictions:** (a) Lower levels of SWS—a state known to be key for memory consolidation and hippocampal-cortical dialogue—will be associated with excessive activity in the medial temporal lobe during learning and, consequently, to overgeneralization during test, while, (b) reduced duration and coherence of REM sleep—known to be key for emotional processing and procedural learning—will be associated with impaired reward-learning and higher rates of PTS symptoms, an effect exacerbated if REM sleep occurs in the presence of atypical autonomic arousal.

**Research Methods:** We will recruit 60 women, ages 18-55, from around Newark, NJ, who are survivors of past sexual violence. Our local partners for community-engaged outreach and recruitment with whom we have been working collaboratively for the last two years include local community centers that treat, shelter, and support women victims of sexual violence and abuse. All participants are assessed for PTS symptomology using the civilian PTSD Check List (PCL-5). In addition to medical and psychiatric history, they receive a standardized neuropsychological battery. They also do two computer-based category learning tasks—developed and extensively studied previously by Gluck, Myers, and colleagues—to assess medial temporal lobe contributions to **generalization transfer of learning** (Myers et al. 2002; 2008) and basal ganglia contributions to **reward-based feedback learning** (Bodi et al., 2009; Shohamy et al., 2005). The feedback learning task is administered in a 3T MRI magnet at Rutgers, followed by 30 minutes of resting state scan. Participants then complete three nights of sleep monitoring, wearing a mobile head-mounted EEG-based sleep monitor to quantitatively measure their sleep in the familiar environment of their own homes. While sleeping, they also wear monitors to record heart-rate variability and galvanic skin response, measures of autonomic arousal.

**Future Directions.** A clearer understanding of PTSD as a neurocognitive disorder will open up several new avenues for future research, including: (1) Do individual differences in specific PTS symptoms, such as re-experiencing trauma, correspond to cognitive variations in learning and generalization (Anastasides et al., 2015)? (2) Can individual differences in sleep quality predict future development of PTS symptoms? (3) Can individual differences in cognition or sleep predict which people will, or will not, show the greatest benefit from current behavioral treatments for PTSD, including trauma-focused Cognitive Behavioral Therapy (CBT) and sleep-specific therapies such as CBT-Insomnia (Talbot et al., 2014)? (4) Can individually-tailored neurocognitive interventions be used to prevent the development of PTSD?

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