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Improving Medication-Enhanced Psychotherapy Options For PTSD: The Potential of Oxytocin as a Treatment for Hypervigilance in Women With A History of Childhood Sexual Abuse and Related PTSD

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ABSTRACT

Childhood sexual abuse (CSA) is a notable public health concern, affecting a significant proportion of girls in high-income countries. A considerable number of CSA survivors develop Post-Traumatic Stress Disorder (PTSD) by adolescence, which is often considered to be a lifelong disorder with severe emotional and social consequences. Women with CSA-related PTSD display hypervigilance, which is characterized by significantly increased fear network activity and poor top-down control over the amygdala. This meta-analysis examines the potential of intranasal oxytocin (OT) as a treatment for hypervigilance symptoms in women with CSA-related PTSD. The evidence reviewed suggests that intranasal oxytocin can help normalize the aberrant connectivity between the amygdala and the dorsal anterior cingulate cortex, which is associated with increased fear network activity and hypervigilance in these individuals. By targeting these physiological changes, intranasal oxytocin has the potential to improve the effectiveness of psychotherapy for PTSD in women with a history of childhood sexual abuse. However, it is important to note that more research is needed to fully understand the potential of intranasal oxytocin as a treatment for CSA-related PTSD and to determine the optimal dose and administration method.

KEYWORDS

Childhood Sexual Abuse • Hypervigilance • Intranasal Oxytocin • PTSD • Amygdala • Medication-Enhanced Psychotherapy

Introduction

Childhood sexual abuse (CSA) is defined as any sexual act perpetrated against a minor through the use of threat, force, intimidation, or manipulation[5]. Studies by Gilbert et al. (2008) and Collin-Vezina et al. indicate that between 15% and 31% of girls in high income countries, such as Australia, New Zealand, Canada, and the United States, are exposed to CSA during their childhood[5,8]. However, due to the hidden nature of CSA and a multitude of other factors, these figures may not accurately reflect the true extent of the issue. Studies relying on self-reports have reported CSA rates of 12.7%, which are significantly higher than the 0.4% reported in official inquiries[5].

Surviving CSA poses a significant risk of developing negative mental health outcomes, behavioral issues, and suicidal ideation[8]. Approximately one-third of maltreated children are reported to develop depression by their late twenties, and sexual abuse has been consistently linked to a doubled risk of attempted suicide[8]. A comparative analysis of mental disorders in Australia found that compared with physical abuse, which accounted for 5% of mental disorders, sexual abuse accounted for 13% of mental disorders when taking into account the context in which the sexual abuse occurred[8].

Childhood sexual abuse is associated with a high risk of developing posttraumatic stress disorder (PTSD). Studies indicate that the risk of PTSD is higher in victims of childhood sexual abuse compared to victims of others forms of childhood maltreatment, with onset often starting at a young age. Research conducted by Collin-Vezina et al. found that up to half of sexually abused school-aged girls showed clinical levels of PTSD symptoms[5]. Individuals with PTSD often experience a range of distressing symptoms, such as recurrent intrusive thoughts, flashbacks, distressing dreams, exaggerated startle response, hypervigilance, and difficulty sleeping[17]. These symptoms can significantly impact daily life and have long-lasting effects, with remission times often measured in many years. In a study of 8,941 participants diagnosed with PTSD, Chapman et al. found that the median time to remission was 14 years, with 36.6% of participants continuing to exhibit symptoms 30 years after onset[4]. Women in the study were found to have a 12.9% lifetime risk of PTSD[4].

Trauma-focused psychotherapies have been considered the best practice for treating patients with PTSD[10,21]. Examples of such therapies include cognitive reprocessing therapy, prolonged exposure therapy, and eye movement desensitization and reprocessing therapy (EMDR)[19]. Although these first-line psychotherapies are effective for many patients, there is limited evidence to support the underlying theoretical rationale[19]. Additionally, research indicates that current treatment methods for PTSD are only effective in half of the patient population[7]. Further research is needed to better understand the efficacy of these therapies and to improve treatment outcomes for patients with PTSD.

Salience Processing and Fear Habituation in CSA-Related PTSD

Studies have revealed that various physiological complications in patients with Post-Traumatic Stress Disorder (PTSD) can greatly impact treatment outcomes and therapy adherence. Brown et al. (2014) investigated the relationship between PTSD and functional connectivity in the basolateral amygdala (BLA) and cortical regions such as the ventromedial

prefrontal cortex (PFC), anterior cingulate cortex (ACC), insula, and inferior frontal gyrus (IFG). The study included 42 participants, 20 of which were diagnosed with PTSD and 22 as trauma-exposed controls. The results showed that the PTSD group had stronger resting-state functional connectivity than the control group between the left BLA and a region spanning from the pregenual ACC to dorsomedial PFC and stronger connectivity between the right BLA and the dorsal ACC (dACC)[3].

Rabinak et al. (2011) also investigated the connectivity between the amygdala and the ACC, mPFC, insula, and hippocampus in a smaller study of 34 male veterans, 17 of which were diagnosed with PTSD. The results showed increased resting-state connectivity between the right amygdala and the insula in the PTSD group compared to the combat-exposed controls. However, it is important to consider the smaller sample size and potential differences in connectivity patterns due to varying trauma types.

The results of both studies suggest that patients with PTSD exhibit altered connectivity patterns between the amygdala and key regions in the salience network, such as the anterior cingulate cortex and the ventromedial prefrontal cortex. These findings support the growing body of evidence that physiological factors play a crucial role in the treatment and direction of future treatment plans for PTSD.

In their study, Bremner et al. (2002) investigated the neural correlates of emotionally valenced declarative memory in women with childhood sexual abuse (CSA)-related post-traumatic stress disorder (PTSD) and compared them to women without abuse or PTSD. Ten women with CSA-related PTSD and 11 women without abuse or PTSD underwent positron emission tomographic (PET) measurement of cerebral blood flow during resting state and during the retrieval of neutral and emotionally valenced word pairs. The results showed that women with CSA-related PTSD had increased activation in several brain regions, including the motor cortex, visual association cortex, cerebellum, left inferior parietal lobule, and right middle temporal gyrus during the retrieval of emotionally encoded words. In contrast, these women showed decreased blood flow in the orbitofrontal cortex, anterior cingulate cortex, and medial prefrontal cortex, as well as in the left fusiform, inferior and middle temporal gyrus, and left hippocampus[1]. This difference in experimental design, which measured brain activation and blood flow during a triggering condition and a neutral condition, highlights that not only do abnormal connectivity patterns exist while at rest, but they are also altered during a trigger.

In a comprehensive review of research on cognitive and emotional alterations in PTSD, Forster et al. (2017) found that the ventral anterior cingulate cortex (ACC) and ventromedial prefrontal cortex play a role in inhibiting amygdala activity through top-down control. However, this control is diminished in individuals with PTSD, resulting in heightened fear conditioning and poor fear extinction. The authors explain that decreased activity in the ventral ACC during a triggering event leads to hyperactivity in the amygdala, whereas increased activity in the dorsal ACC leads to inhibited amygdala activity and hyporeactivity. However, Forster et al. also note that it is possible for an individual with PTSD to exhibit both hyper- and hypo-activity in the amygdala, depending on the context of the situation[7].

A study conducted by Rinne-Albers et al. (2016) offers a tentative explanation for the existence of aberrant patterns in PTSD. Their study aimed to test the hypothesis that adolescents with a history of childhood sexual abuse have decreased white matter integrity, and recruited 22 adolescents with PTSD related to childhood sexual abuse and 30 healthy adolescents as controls. The researchers used fractional anisotropy (FA), a type of diffusion tensor imaging (DTI), to assess the structural integrity of white matter in adolescents who experienced psychotrauma. They noted that FA reflects the degree of water diffusion directionality, which in white matter can be influenced by structural factors such as axonal density, organization, and myelination.

Rinne-Albers et al. found that the PTSD group had lower FA values in the genu, midbody, and splenium of the corpus callosum (CC) in comparison to the control group ($p < 0.05$), as well as lower FA values in the body of the left hemisphere CC adjacent to the splenium ($p < .075$). The researchers claimed that these smaller FA values in the CC of the PTSD group could be attributed to increased radial diffusivity (RD) and mean diffusivity (MD), which are markers of demyelination (reduced development of the myelin sheet) and dysmyelination (aberrant development of the myelin sheet), respectively.

The corpus callosum plays a critical role in facilitating "cross-talk" between the brain's hemispheres, and damage to the corpus callosum can impair disparate brain functions. Rinne-Albers et al. suggested that the demyelination in the corpus callosum observed in the PTSD group may account for the atypical connectivity between the amygdala and the salience network that has been reported in PTSD[16].

A study by Pechtel et al. (2013) aimed to explore the relationship between behaviors observed in PTSD and physiological aspects related to these behaviors. To do so, they recruited 56 women, including 15 with CSA-related major depressive disorder (CSA + MDD), 16 with only MDD, and 18 healthy controls. The participants underwent electroencephalography (EEG) during a Probabilistic Stimulus Selection Task, designed to probe reinforcement learning.

In the learning phase of the task, the participants were presented with one of three pairs of stimuli, A-B, C-D, or E-F, and instructed to select the image with the highest chance of being correct as quickly and accurately as possible. Pechtel et al. found that the control group showed smaller (less negative) event-related potentials (ERP) amplitudes compared to the CSA + MDD and MDD groups on correct A-B trials ($p = .001$). The study also found that the CSA + MDD group had significantly lower activation in the subgenual anterior cingulate cortex (ACC) during correct responses compared to the MDD group ($p = .01$). Additionally, the CSA + MDD group showed higher activation during incorrect responses than the control group[13].

These findings suggest that individuals with CSA-related PTSD rely more heavily on negative reinforcement than positive reinforcement during adaptive decision making and struggle with positive reinforcement and making decisions based on previously rewarded information. Pechtel et al.'s study provides evidence for the relationship between PTSD behaviors and physiological aspects related to these behaviors and highlights the importance of considering the influence of CSA on PTSD.

The study conducted by Bremner et al. (2005) aimed to examine the correlation between fear acquisition and fear extinction in women with Childhood Sexual Abuse (CSA)-related Post-Traumatic Stress Disorder (PTSD). A total of 19 participants were involved in the study, with 8 diagnosed with CSA-related PTSD and 11 without childhood abuse or PTSD serving as the control group.

To measure cerebral blood flow, Bremner et al. utilized Positron Emission Tomography (PET) scans and recorded heart rate and skin conductance during fear acquisition and extinction. The experiment consisted of exposing the participants to a blue square on a screen, followed by an electric shock to the forearm during the fear acquisition phase. During the extinction phase, the blue square was presented without a shock. On the second day, shocks were randomly delivered when the blue square was not present.

Bremner et al. found that during the fear acquisition phase, participants with CSA-related PTSD showed increased activation in the amygdala, left superior temporal gyrus, right inferior frontal gyrus, cerebellum, and posterior cingulate, compared to the control group. In contrast, during the fear extinction phase, participants with CSA-related PTSD exhibited decreased function in the orbitofrontal cortex, medial prefrontal cortex, and visual association cortex[2].

These results suggest that women with CSA-related PTSD have abnormally increased fear acquisition, as evidenced by the significant activity in the amygdala and adjacent regions. Additionally, the decreased function in the medial prefrontal cortex, which plays a role in inhibiting amygdala activity, suggests impaired fear extinction in participants with CSA-related PTSD.

The findings of Bremner et al. (2005) align with those of Forster et al. (2017), who posited that individuals with PTSD exhibit poor fear inhibition and reduced extinction of conditioned fear responses, a manifestation of disruption in the ACC-amygdala circuit. Forster et al. observed that hyperactivity of the amygdala, often linked to hypervigilance in PTSD, may heighten reactivity to emotional stimuli and enhance priming of emotions and emotional representations in the limbic system.

Forster et al. noted that a reciprocal relationship between ventral ACC hypofunction and amygdala hyperactivity could be responsible for the inability to suppress or extinguish traumatic-related fear responses in PTSD. The amygdala, according to Forster et al., not only plays a role in fear conditioning but also in emotional salience and encoding emotional relevance or value, affecting attention, motivation, autonomic and behavioral responses.[7]

Given that female victims of childhood sexual abuse exhibit elevated activation in the subgenual anterior cingulate cortex when subjected to negative reinforcement, diminished function in the medial prefrontal cortex and anterior cingulate cortex during fear extinction, and increased resting-state connectivity between the basolateral amygdala and the anterior cingulate cortex, there is potential for developing pharmacological therapies to address these physiological deficiencies.

Hypervigilance and Chronic Hyperarousal

According to Richards et al. (2014), hypervigilance and attentional bias towards threat play a crucial role in the manifestation of PTSD symptoms, which greatly affect the daily life of patients.

Similarly, anxiety also involves hypervigilance. Richards et al. found that individuals with high levels of anxiety display a selective attentional bias towards threat, directing their attention towards threatening stimuli instead of neutral ones. This bias involves either a vigilant watch for threat or the maintenance of attention on threat.[15]

Hypervigilance, according to Richards et al., serves to keep the cognitive system alert and ready to detect high priority signals that may pose a threat to survival. The alerting network enables individuals to respond to high priority stimuli by maintaining activation in the cognitive system, either over an extended period of time (hypervigilance) or in response to warning signals. When hypervigilant for threat, individuals rapidly scan their environment for potential threats with a narrow focus of attention and frequent eye movements, or maintain a broad focus of attention until a threatening stimulus is encountered[15].

The findings of Kimble et al. (2013) are in line with these claims. In their study of 71 undergraduate students, they aimed to examine the impact of manipulating hypervigilance on a forward feedback loop as measured by self-reported anxiety, visual attention, and autonomic arousal. The results showed that the hypervigilance condition resulted in significantly more eye fixations and sectors hit during visual scanning compared to the pleasant and control conditions ($p < .05$). Additionally, the hypervigilant condition was associated with significantly larger pupil sizes compared to the control condition ($p < .01$). Kimble et al. concluded that hypervigilance is not only present in the presence of threat, but also associated with increased efforts to search for threat.[9]

Women with PTSD exhibit significantly higher levels of hypervigilance compared to men with PTSD, as reported by Tekin et al. (2015)[17]. This state of heightened alertness can negatively impact a victim's daily life, causing difficulties such as sleep disturbances due to excessive startle responses and difficulty focusing in school or work due to the constant need to be aware of their surroundings. Research has linked hypervigilance to abnormal amygdala connectivity[18]. Terburg et al. (2012) conducted a study on five women with Urbach-Wiethe disease (UWD), a rare genetic disorder marked by calcifications in the bilateral amygdala, and 16 healthy controls. Participants were instructed to choose adjectives to describe clips of faces that morphed from neutral to emotional states while undergoing fMRI scanning. Results showed that the UWD group had significantly higher fear-bias scores compared to the control group when viewing fearful faces ($p = 0.020$ for fear-neutral, $p = 0.008$ for fear-happy)[18]. This suggests a physiological connection between hypervigilance in women with PTSD related to childhood sexual abuse.

However, hypervigilance is not only linked to the bilateral amygdala. In a study by Kleshchova et al. (2019), which involved 24 trauma-exposed women and 20 control women with no trauma exposure, the researchers tested amygdala connectivity at rest and during the viewing of novel and familiar affective scenes using fMRI scanning. They found that trauma-exposed women had greater resting connectivity between the left amygdala and the vACC compared to the control group (z-score = 3.98). Additionally, they found that during both novel and familiar scenes, the trauma-exposed women showed greater amygdala-vACC connectivity (novel, $p = 0.020$; familiar, $p <$

0.001). However, while the control group showed greater amygdala-vACC connectivity during the novel scenes compared to the familiar scenes (p = 0.010), the trauma-exposed women showed no difference in amygdala-vACC connectivity between the two conditions (p = .536)[11].

This research suggests that the higher baseline connectivity between the amygdala and the subgenual anterior cingulate cortex, which is commonly observed in women with childhood sexual abuse-related PTSD, and the lack of change in connectivity between novel and familiar scenes, may indicate a state of chronic hyperarousal and constant hypervigilance. The constant heightened connectivity between the subgenual anterior cingulate cortex and the amygdala is believed to be the cause of this state of hypervigilance. Therefore, pharmacological treatments aimed at reducing this heightened connectivity may help alleviate the symptom of hypervigilance in PTSD related to childhood sexual abuse.

The significance of hypervigilance in PTSD extends beyond the personal lives of patients; it has also been linked to the effectiveness of therapy and treatment resistance. In a study of 43 PTSD patients and 25 combat controls, who underwent trauma-focused therapy for 6-8 months and underwent an fMRI scan before and after treatment to determine if persistent PTSD patients exhibit increased activation of the amygdala, dACC, insula, vmPFC, and hippocampus in response to negative stimuli, van Rooij et al. (2016) found that the pretreatment Clinician-Administered PTSD Scale (CAPS) score was higher in persistent PTSD patients due to the presence of more hyperarousal symptoms. They noted that the re-experiencing and avoidance/numbing symptoms did not significantly differ between remitted and persistent patients before treatment. The persistent PTSD patients showed a significantly higher bilateral dACC (p = 0.015) and insula (p = 0.025) response compared to both combat controls (dACC, p = 0.011; insula, p = 0.045) and remitted patients (dACC, p = 0.012; insula, p = 0.009), with no significant main effects of time or interaction observed[20].

Van Rooij et al. (2016) found that pretreatment activation of the bilateral dACC, insula, and amygdala in response to negative stimuli was a significant predictor for persistent symptoms, even after controlling for potential confounding factors such as pretreatment PTSD severity, comorbidity, pharmacotherapy status, number of treatment sessions, age, education level, and early traumatic experiences. They also found that the final regression models for the dACC, insula, and amygdala significantly predicted post-treatment CAPS score (dACC, p = 0.020; insula, p = 0.046; amygdala, p = 0.009)[20]. This study not only suggests that hypervigilance plays a role in the effectiveness of psychotherapy for treating PTSD, but also that the abnormal connectivity between the amygdala and the subgenual anterior cingulate cortex, which has consistently been observed in individuals with CSA-related PTSD, is a significant predictor for symptom severity after several months of trauma-focused therapy.

Given that hypervigilance leads to higher levels of fear and distress, increased reliving of traumatic memories, and difficulty disengaging from negative stimuli in individuals with CSA-related PTSD, as well as its connection to therapy success, hypervigilance is one of the most debilitating and important symptoms of PTSD and deserves priority in treatment.

Oxytocin as an Enhancement for Medication-Enhanced Psychotherapy

In recent years, oxytocin (OT), a neuropeptide, has gained attention in the Netherlands as a possible treatment for PTSD due to its anxiolytic and prosocial effects. However, there is a scarcity of studies on the potential of OT to reduce hypervigilance in PTSD and the few studies on its effect on PTSD are not always conclusive.

Flanagan et al. (2019) tested the hypothesis that individuals with PTSD from childhood trauma would show greater amygdala reactivity to fearful faces than those who experienced childhood trauma but did not develop PTSD, and that OT would decrease amygdala reactivity in the PTSD group. They recruited 38 individuals, 19 in the PTSD group and 19 in the control group. Participants self-administered 24IU OT intranasally 45 minutes before two fMRI sessions, during which they viewed a series of 56 same-gender faces depicting different emotions and were asked to identify the gender[6].

The results showed no significant differences between the PTSD and control groups in terms of fMRI signal magnitude in either the left or right amygdala regions of interest. There were also no significant main effects of drug condition or interactions between drug condition and group. However, the study found a significant negative correlation between the change in amygdala response due to the drug condition and CTQ scores in both the left and right amygdala in the PTSD group, but not in the control group[6]. This study suggests that OT may have a limited effect on reducing hypervigilance in individuals with PTSD from childhood trauma.

The study by Flanagan et al. did not find conclusive evidence of oxytocin having a significant effect on amygdala response. To shed light on this issue, the study by Koch et al. (2016) is considered. Koch et al. aimed to investigate the hypothesis that PTSD patients would have decreased connectivity between the basolateral amygdala (BLA), centromedial amygdala (CeM), and ventromedial prefrontal cortex (vmPFC), and increased connectivity between the BLA and CeM and the insula and dorsal anterior cingulate cortex (dACC). The study recruited a total of 56 participants (20 male and 20 female controls and 21 males and 16 females with PTSD) and had them undergo three appointments, including a baseline session and two fMRI sessions.

The results showed a significant group by sex by drug interaction effect regarding the functional connectivity of the right CeM with the left vmPFC in male PTSD patients ($p = 0.032$). Under placebo, male PTSD patients showed significantly less right CeM to left vmPFC connectivity compared to male trauma-exposed controls ($p < 0.001$), while no differences were found in female participants ($p = 0.890$). Oxytocin administration resulted in enhanced connectivity between the right CeM and left vmPFC in male PTSD patients ($p = 0.004$), but not in female PTSD patients or trauma-exposed controls (all $p > 0.05$)[12].

Koch et al. also found a significant group by sex by drug interaction effect regarding the connectivity of the right BLA with the bilateral dACC. Oxytocin administration decreased connectivity between the right BLA and right dACC in female PTSD patients ($p = 0.001$) and tended to decrease right BLA to left dACC connectivity in female PTSD patients ($p = 0.023$) and male trauma-exposed controls ($p = 0.023$). Under placebo, there was significantly greater right BLA to right dACC connectivity in female PTSD patients compared to female trauma-exposed

patients ($p = 0.001$), which was absent after oxytocin administration ($p = 0.902$)[12].

Koch et al. reported that compared to placebo, oxytocin administration in PTSD patients was associated with lower ratings of subjective anxiety ($p = 0.044$) and nominally lower ratings of nervousness ($p = 0.055$), but not with happiness or sadness (all $p > 0.05$). The authors noted that the ratings of anxiety, nervousness, happiness, and sadness prior to drug administration did not differ between scanning sessions (all $p > 0.05$) and that the reductions in anxiety and nervousness were not significantly correlated with the alterations in amygdala functional connectivity with the vmPFC or dACC (all $p > 0.05$). Koch et al. found that the Clinical Assessment of PTSD (CAPS) total and subscale scores were not significantly correlated to the functional connectivity measures under placebo (all $p > 0.05$)[12].

After reviewing Koch et al.'s study, it's possible that Flanagan et al. didn't use a high enough dose of oxytocin or that they didn't measure the right outcomes. It's also worth noting that while intranasal oxytocin has been successful in both genders, it may be more effective as a treatment for women when it comes to hypervigilance. According to Kimerling et al. (2018)[10], women are twice as likely to suffer from PTSD and often have more severe symptoms than men. This is supported by a study by Tekin et al. (2015) that found that Yazidi migrants who suffered from PTSD and depression, women reported significantly higher rates of flashbacks, intense psychological distress, and hypervigilance than men[17].

Given that oxytocin has been found to reduce anxiety and nervousness, decrease excessive amygdala activity, and decrease connections between the dorsal anterior cingulate cortex and the amygdala in women with PTSD related to childhood sexual abuse (CSA), it may be an effective treatment for hypervigilance in conjunction with psychotherapy.

Conclusion

In conclusion, the consequences of childhood sexual abuse are severe and long-lasting, with a high prevalence rate[8] and a significant risk of developing PTSD[5], a chronic mental illness with persistent symptoms for a third of patients[4]. Despite current psychotherapy treatments having limited efficacy for PTSD patients[7], there is a pressing need for further research into enhancing psychotherapy and developing effective treatment plans for childhood sexual abuse victims with related PTSD.

Numerous studies have demonstrated physiological abnormalities in female victims of childhood sexual abuse, including increased activation in the subgenual anterior cingulate cortex during negative reinforcement[13], reduced function in the medial prefrontal cortex and anterior cingulate cortex during fear extinction[2], and elevated resting state connectivity between the basolateral amygdala and the anterior cingulate cortex[3]. The connection between the amygdala and the anterior cingulate cortex has been implicated in hypervigilance in CSA-related PTSD, leading to increased levels of fear, distress, reexperiencing of trauma memories, and difficulty disengaging from negative stimuli[2] as well as other harmful behaviors[20]. Hypervigilance symptoms have also been linked to therapy success in PTSD[20], highlighting the need for effective treatments that target these physiological issues.

In light of these findings, oxytocin shows promise as a potential aid for medication-enhanced psychotherapy for

hypervigilance in women with CSA-related PTSD. Oxytocin has been found to decrease nervousness, anxiety, and aberrant amygdala hyperactivity, as well as reduce excessive connectivity between the dorsal anterior cingulate cortex and the amygdala[12], which has been linked directly to hypervigilance. However, more clinical trials are needed to establish the effectiveness of oxytocin in relation to PTSD hypervigilance, particularly in other major high-income countries. These findings demonstrate the need for continued research into innovative treatments for PTSD hypervigilance.

References

1. Bremner, J.D., Vythilingam, M., Vermetten, E., Southwick, S.M., McGlashan, T., Staib, L., Soufer, R., & Charney, D.S. (2002). Neural correlates of declarative memory for emotionally valenced words in women with posttraumatic stress disorder related to early childhood sexual abuse. *Journal of Biological Psychiatry, 53*(10), 1-9. https://doi:10.1016/S0006-3223(02)01891-7

2. Bremner, J. D., Vermetten, E., Schmahl, C., Vaccarino, V., Vythilingam, M., Afzal, N., Grillon, C., & Charney, D. S. (2005). Positron emission tomographic imaging of neural correlates of a fear acquisition and extinction paradigm in women with childhood sexual-abuse-related post-traumatic stress disorder. *Journal of P\sychological Medicine*, *35*(6), 1–11. https://doi/10.1017/s0033291704003290

3. Brown, V.M., LaBar, K.S., Haswell, C.C., Gold, A.L., McCarthy, G., & Morey, R.A. (2014). Altered resting-state functional connectivity of basolateral and centromedial amygdala complexes in posttraumatic stress disorder. *Journal of Neuropsychopharmacology*,*39*, 1-8. https://doi/10.1038/npp.2013.197

4. Chapman, C., Mills, K., Slade, T., McFarlane, A.C., Bryant, R.A., Creamer, M., Silove, D., & Teesson, M. (2011). Remission from post-traumatic stress disorder in the general population. *Journal of Psychological Medicine, 42*(8), 1-7. https://doi:10.1017/S0033291711002856

5. Collin-Vezina, D., Daigneault, I., & Herbert, M. (2013). Lessons learned from child sexual abuse research: prevalence, outcomes, and preventative strategies. *Journal of Child and Adolescent Psychiatry and Mental Health, 7*(22), 1-6. https://doi.org/10.1186/1753-2000-7-22

6. Flanagan, J.C., Sippel, L.M., Santa Maria, M.M.M., Hartwell, K.J., Brady, K.T., Joseph, J.E..(2019). Impact of Oxytocin on the neural correlates of fearful face processing in PTSD related to childhood trauma. *European Journal of Psychotraumatology*,10(1), 1-12. https://dx.doi.org/10.1080/20008198.2019.1606626

7. Forster, G.L., Simons, R.M., & Baugh, L.A. (2017). "Revisiting the Role of the Amygdala in Posttraumatic Stress Disorder". In *The Amygdala- Where Emotions Shape Perception, Learning and Memories.* https://doi/10.5772/67585

8. Gilbert, R., Widom, C., Brown, K.m Fergusson, D., Webb, E., & Janson, S. (2008). Burden and consequences of child maltreatment in high-income countries. *The Lancet, 373*, 1-10. https://doi:10.1016/S0140-6736(08)61706-7

9. Kimble, M., Boxwala, M., Bean, W., Maletsky, K., Halper, J., Spollen, K., & Fleming, K. (2014). The impact of hypervigilance: evidence for a forward feedback loop. *Journal of Anxiety Disorders, 28*(2), 1-5. https://doi.org/10.1016/j.janxdis.2013.12.006

10. Kimberling, R., Allen, M., & Duncan, L. (2018). Chromosomes to social contexts: sex and gender differences in ptsd. *Journal of Current Psychiatry Reports, 20*(114), 1-7. https://doi.org/10.1007/s11920-018-0981-0

11. Kleshchova, O., Rieder, J., Grinband, J., & Weierich, M. (2019). Resting amygdala connectivity and basal sympathetic tone as markers of chronic hypervigilance. *Journal of Psychoneuroendocrinology, 102*, 1-9. https://doi.org/10.1016/j.psyneuen.2018.11.036

12. Koch, S.B., van Zuiden, M., Nawijn, L., Frijling, J.L., Veltman, D.J., & Olff, M.(2016). Intranasal oxytocin normalizes amygdala functional connectivity in posttraumatic stress disorder. *Journal of Neuropsychopharmacology*,*41*(8),1-9. https://doi/10.1038/npp.2016.1

13. Pechtel, P., & Pizzagalli, D.A. (2013). Disrupted reinforcement learning and maladaptive behavior in women with a history of childhood sexual abuse: a high-density event-related potential study. *JAMA Psychiatry*,70(5),1–8.http://dx.doi.org/10.1001/jamapsychiatry.728

14. Rabinak, C., Angstadt, M., Welsh, R., Kennedy, A., Lyubkin, M., Martis, B., & Phan, L. (2011). Altered amygdala resting-state functional connectivity in post-traumatic stress disorder. *Frontiers in Psychiatry, 2*(62), 1-6. https://doi:10.3389/fpsyt.2011.00062

15. Richards, H., Benson, V., Donnelly, N., & Hadwin, J. (2014). Exploring the function of selective attention and hypervigilance for threat in anxiety. *Journal of Clinical*

Psychology Review, 34(1), 1-13. https://doi.org/10.1016/j.cpr.2013.10.006

16. Rinne-Albers, M.A.W., van der Werff, S.J.A., van Hoof, M., van Lang, N.D., Lamers-Winkelman, F., Rombouts, S.A., Vermeiren, R.R.J.M, & van der Wee, N.J.A. (2016). Abnormalities of white matter integrity in the corpus callosum of adolescents with PTSD after childhood sexual abuse: a DTI study. *Journal of European Child and Adolescent Psychiatry,* 25, 1-8. https://dx.doi.org/10.1007/s00787-015-0805-2

17. Tekin, A., Karadag, H., & Sar, V. (2016). Prevalence and gender differences in symptomatology of posttraumatic stress disorder and depression among iraqi yazdidis displaced into turkey. *European Journal of Psychotraumatology, 7,* 1-7. https://doi:10.3402/ejpt.v7.28556

18. Terburg, D., Morgan, B., Montoya, E., Hooge, I., Thornton, H., Hariri, A., Panksepp, J., Stein, D., & van Honk, J. (2012). Hypervigilance for fear after basolateral amygdala damage in humans. *Journal of Translational Psychiatry, 2,* 1-8. https://doi:10.1038/tp.2012.46

19. Thompson-Hollands, J., Marx, B., & Keane, T. (2020). Enhancing outcomes for ptsd treatment: commentary on "treatment augmentation for posttraumatic stress disorder: a systematic review". *Journal of Clinical Psychology: Science and Practice, 27*(1), 1-3. https://doi-org.proxy.library.vcu.edu/10.1111/cpsp.12326

20. van Rooik, S., Kennis, M., Vink, M., & Geuze, E. (2016). Predicting treatment outcome in ptsd: a longitudinal functional mri study on trauma-unrelated emotional processing. *Journal of Neuropsychopharmacology, 41*(4), 1-8. https://dx-doi-org.proxy.library.vcu.edu/10.1038%2Fnpp.2015.257

21. Wagenmans, A., Van Minnen, A., Sleijpen, M., & De Jongh, A. (2018). The impact of childhood sexual abuse on the outcome of intensive trauma-focused treatment for PTSD. *European Journal of Psychotraumatology. 9*(1). 1-10. https://doi.org/10.1080/20008198.2018.1430962