# Physiological and Biological Testing and Assessment of Post-Traumatic Stress Disorder

## Pruebas fisiológicas y biológicas y evaluación del Trastorno de Estrés Postraumático

## Testes fisiológicos e biológicos e avaliação do Transtorno de Estresse Pós-Traumático

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## Abstract

This review essay investigates the biological and physiological consequences of PTSD to deepen its academic understanding, alongside an analysis of psychobiological testing and assessment procedures. Psychological responses to traumatic events can be acute stress reactions or stress disorders. One among them is post-traumatic stress disorder (PTSD). When people experience a traumatic event, such as death, terror, or physical injury, they tend to demonstrate fear, helplessness, or hopelessness. Patients displaying other symptoms like re-experiencing the trauma, avoidance, or hyper-arousal also indicate

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PTSD. Experiencing extended PTSD may cause significant health problems, whether biological, such as the dysfunction of stress-responsive neurobiological systems, or physiological, such as hypertension and heart disease. Previous studies of trauma survivors reported a strong link between physical and mental health. The cumulative literature in psychology shows that traumatic exposure can cause disturbing effects in the short and long term. This review will contribute to developing an understanding of the biological markers of PTSD. This paper specifically deals with biological and physiological testing and assessment of PTSD. It includes widely utilized biological assessments and summarizes a general multi-model assessment to identify PTSD symptoms.
*Keywords:* PTSD; psychobiological testing; biological assessment; multimodal assessment; physiology of PTSD; biological bases of PTSD.

## Resumen

Las respuestas psicológicas a acontecimientos traumáticos pueden dar lugar a estrés agudo, trastornos de estrés o trastornos de estrés postraumático (TEPT). Cuando las personas experimentan un evento traumático, como la muerte de un ser querido, terror o daño físico, tienden a mostrar miedo, impotencia o desesperanza. Mostrar otros síntomas como volver a vivir aquellas experiencias, evasión o hiperexcitación indica TEPT. Sufrir el TEPT a largo plazo puede causar problemas de salud importantes, ya sean biológicos, como la disfunción de los sistemas neurobiológicos sensibles al estrés; o fisiológicos, como la hipertensión y enfermedades cardíacas. Sin embargo, la literatura psicológica deja poco o ningún espacio para tales consecuencias sobre la salud. Para proporcionar información sobre este tema, la presente revisión tiene como objetivo investigar las consecuencias biológicas y fisiológicas del TEPT, y las pruebas y evaluaciones psicobiológicas relacionadas. Esta revisión de la literatura puede contribuir al desarrollo de marcadores biológicos de TEPT.
*Palabras clave:* TEPT; prueba psicobiológica; evaluación; evaluación multimodal; fisiología TEPT; bases biológicas TEPT.

## Resumo

As respostas psicológicas a eventos traumáticos podem levar a estresse agudo, transtornos de estresse ou transtorno de estresse pós-traumático (TEPT). Quando as pessoas vivenciam um evento traumático, como a morte de um ente querido, terror ou danos físicos, elas tendem a demonstrar medo, desamparo ou desesperança. Mostrar outros sintomas, como reviver essas experiências, evitação ou hiperexcitação, indica TEPT. Sofrer de TEPT de longa duração pode causar problemas de saúde significativos, sejam eles biológicos, como disfunção de sistemas neurobiológicos sensíveis ao estresse; ou fisiológicos, como hipertensão e doenças cardíacas. No entanto, a literatura psicológica deixa pouco ou nenhum espaço para a discussão de tais consequências para a saúde. Para fornecer informações sobre esse tópico, a presente revisão tem como objetivo investigar as consequências biológicas e fisiológicas do TEPT, assim como testes e avaliações psicobiológicas relacionados. Esta revisão de literatura pode contribuir para o desenvolvimento de biomarcadores para TEPT.
*Palavras-chave:* TEPT; testes psicobiológicos; avaliação; avaliação multimodal; fisiologia TEPT; base biológica TEPT.

## Biological Aspects of Post-Traumatic Stress Disorder (PTSD)

Even though studies on trauma started over a hundred years ago with Freud, Bluer, and Janet, PTSD entered the DSM (diagnostic and statistical manual) nomenclature only forty years ago in 1980 in DSM III (Van der Kolk, 2014). Psychological and physiological health consequences of traumatic experiences are well researched and reported now. Studies of veterans, civilian populations, and children revealed a strong link between psychic trauma and physiological health results (Luft et al., 2012).

Traumatic experiences in adult or early life may cause a set of psychological symptoms. Traumatized people have difficulties in being able to forget

their unbearable and unforgettable horrifying past. They use drugs, alcohol, self-mutilation, or blockout (Van der Kolk, 2014). Even patients not qualified for the full-blown PTSD diagnosis, with a partial presence of PTSD symptoms, still show depression, increased aggression toward the self and others, depersonalization, dissociation, and poor family and occupational functioning (Van der Kolk, 2000). Tsai et al. (2012) study with Iraq and Afghanistan veterans reported 52 % of PTSD along with significant problems with romantic partners, family problems, less social support, lower life satisfaction, and poor social adjustment. They emphasized the importance of improving social functioning as a mediating factor for treatment.

Psychological literature lacks insights into how personal experiences of traumatic events and PTSD lead to various health problems. In contrast, this issue has become an increasing concern of biological researchers in the last decade (Morris et al., 2012; Zoladz & Diamond, 2013). Such literature merits scrutiny to provide some insights into the issue. To this aim, the main purpose of this review is to investigate the physiological and biological health consequences of traumatic experiences and elaborate related psychobiological testing and assessment.

Traumatic experiences cause psychological problems and cause victims of severe childhood trauma to be at far greater risk of alcoholism, depression, drug abuse, suicide attempts, smoking, having more sexual partners, sexually transmitted diseases, physical inactivity, obesity, heart disease, cancer, lung disease, skeletal fractures, hepatitis, stroke, liver diseases, and diabetes (Van der Kolk, 2000). They can also produce physical symptoms. A study by Pietrzak et al. (2012) with older adults reported disorders like tachycardia, hypertension, chronic aging disorders, gastritis, angina pectoris, poor physical functioning, and arthritis. In their study, full PTSD was coupled with lifetime mood, drug use, anxiety, borderline and narcissistic personality disorder, and poor psychological functioning. Schnurr et al. (2000) study with WW II and Korean War combat veterans reported arterial, gastrointestinal and dermatological conditions, smoking, alcohol abuse, and weight problems even after a long time since military service. Similarly, Qureshi et al. (2009) reported medical conditions of cardiovascular disease, arthritis, asthma, chronic pain, diabetes mellitus, and gastrointestinal problems in adult PTSD patients.

It is possible physical symptoms can be observed even before the psychological symptoms. Physical symptoms can be fibromyalgia, chronic fatigue and autoimmune diseases. Therefore, it is important to treat the whole organism, including the body, mind and brain (Van der Kolk, 2014). On the other hand, physical assaults, traffic accidents, and traumatic brain injuries can also cause traumatic reactions. It seems that body and mind work vice-versa. Praag et al. (2022) found a prevalence of 13.5 % PTSD and poor performance on the subtest of cognitive task switching and delayed verbal recalling in a traumatic brain-injured civilian sample. It appears that physical illnesses, injuries, and surgical operations may affect the development of PTSD or similar residual effects. For instance, Bryant (2022) reported a link between traumatic brain injury and PTSD, such that mild traumatic brain injury can be a risk for PTSD and those two conditions can coexist. A Chinese study reported COVID-19 as a significant risk factor for mental illnesses, especially PTSD (Liang et al., 2020). In a recent Italian study, Tarsitani et al. (2021) reported 10.4 % diagnosis of PTSD and 8.6 subthreshold PTSD, 3 months after hospitalization because of the COVID-19 pandemic. Female sex, obesity, and previous mental health conditions were listed as risk factors for developing PTSD. In a similar study, three months after the COVID-19 pandemic began, Alshehri et al. (2020) reported 24.8 % of PTSD rates in Saudi Arabia.

PTSD often leads to poor diet, smoking, and an inactive lifestyle that can cause serious medical conditions (Rauch et al., 2006). Therefore, being exposed to traumatic life events can lead to psychological and physiological health problems, which may not necessarily be detected at the same time. Some of the health symptoms may take years to appear or to be undetected (Palgi et al., 2015). For example, physiological symptoms may be observed later, such as hypertension, heart disease, and post-accident-related stress. As a result of prolonged stress, other physiological and biological health-related risks may also increase. The study by Luft et al. (2012) focused on a huge number of World Trade Center rescue and recovery workers and police officers in the aftermath of 9/11 and found a strong correlation between PTSD and respiratory symptoms, which together become persistent health issues even after a decade or more. In Dollinger's (1985) case studies on fifth and sixth-grade children exposed to a lightning-strike disaster, physiological responses included back and limb pain, fatigue, and appetite loss. A greater heart rate response (HRR) to a loud voice is also one of the most frequently noted psychophysiological responses (Orr et al., 2002).

Furthermore, there was a nuclear power plant accident in 1979 in the USA, called Three Mile Island Incident. Children imitated their parents or significant others as a model for how to respond or appraise the incident. Similar to their parents, children were also significantly affected and suffered from PTSD symptoms or chronic stress (Messo, 2013). In a study on the psychobiological effects of the island incident, Baum and Fleming (1993) showed that long-lasting elevations in blood pressure and functional changes in the immune system were corollaries of chronic stress. As many as five or six years after the incident, such results were accompanied by higher levels of urinary norepinephrine, epinephrine, cortisol, and increased sympathetic arousal. These effects occurred in the first year and continued for up to six. Stress-related symptoms began to recede seven or eight years after the incident. By the tenth year, most of the symptoms had faded away and victims had fewer psychological and physiological effects. Similar findings were reported for those exposed to toxic landfills for up to three years (Baum & Fleming, 1993).

It appears that psychological traumas are one of the most important public health problems in today's world. Childhood sexual abuse, assault, rape, domestic violence, wars, ethnic clashes, and natural disasters are widespread (Van der Kolk, 2000). PTSD is a common diagnosis in psychiatric hospitals. PTSD with depression is the most common diagnosis (Macy, 2002). More recent studies show that children are at risk for a variety of reasons. For example, Jankowski et al. (2022) reported parental substance misuse as an issue for children who have been referred to child protection services. Parental substance abuse puts children, especially older ones, at multiple risks for traumatic experiences and endangers their psychological adjustment and well-being. According to Obuobi-Donkor et al. (2022) in today's world, military personnel and firefighters are at greater risk for PTSD. In their comprehensive review, they reported the prevalence of PTSD as being 57% of firefighters and 37.8% of military personnel. They listed demographic factors, job factors, social support, injuries, physical and psychological factors, and some of the individual traits as the predictor factors of PTSD. It appears that firefighters and military personnel who are in charge of protecting people and priorities are at great risk, therefore, policymakers should pay close attention to public health concern of safety personnel and their needs.

Furthermore, Brubaker and Milner (2015) argued about scarce research on female soldiers and veterans exposed to sexual and combat-related difficulties. They believed that the experience of war is different for women compared to men and this has changed significantly from the

experience of previous to today's wars. Therefore, there is a need for new perspectives for identification and intervention, particularly for female military personnel. Public health policies for female soldiers need to be looked at closely because it seems that females' experiences are more difficult than men and their perception is also different, so the consequences are likely to be different as well. Public policies contribute to the conceptualization and definition of mental health problems.

Unfortunately, traditionally PTSD was seen as a war-related phenomenon and used combat-related trauma exposures and language, but civilian versions of traumatic adversities are somehow ignored. These formulations of PTSD do not reflect its epidemiology. Most people who develop the disorder have not experienced combat-related exposure and many non-combat traumas carry a higher risk of PTSD. This approach might constrain public discourse and policy about the disorder and may create sociocultural barriers for the victims to pursue mental health services (Purtle, 2016).

Such health consequences refer to the role of cognitive appraisal and coping with trauma and PTSD (Larkin et al., 2014). A sudden threat and its negative assessment may in turn generate negative emotional, behavioral, and biological responses. When individuals get caught unprepared, they fail to regulate their biological responses to a traumatic event (Olff et al., 2005). Supporting this study, Delahanty et al. (2005) reported a strong association between the initial physiological response to trauma and PTSD. Pitman et al. (2006) confirmed that individuals who experience great fear during traumatic events are more likely to show intense emotional reactions and thus eventually experience PTSD. Conducting an extensive meta-analysis, Pole (2007) also concluded that PTSD is associated with elevated psychophysiology. However, a scrutiny of these findings raises concerns for related psychophysiological and psychobiological testing and assessment. Therefore, the purpose of this review is also to meet this concern by examining the physiological and biological health consequences of PTSD.

## Psychobiological Testing and Assessment of PTSD

There are new technologies available that can help us fully understand the mechanism of psychiatric disorders, especially PTSD. For example, imaging and biomarkers, along with technological and medical advance developments can significantly help researchers to understand and identify it (Bourla et al., 2018). There are also several diagnostic tools for psychobiological assessments of health risks associated with PTSD; for example, the Yohimbine Infusion, Lactate Infusion, corticotrophin- and thyrotropin-releasing hormone tests, and urine tests of epinephrine and norepinephrine.

Yohimbine is an α-2-receptor antagonist that can induce flashbacks, panic, and the startle reflex, particularly in patients with panic disorder. The intravenous infusion is useful to demonstrate the induction of panic and intrusive symptoms (Southwick et al., 1993) or to show an enhanced acoustic startle reflex in a subgroup of PTSD patients (Morgan et al., 1995). Utilizing this tool, Ornitz and Pynoos (1989) investigated the exaggerated startle reflex in children exposed to sniper fire in a schoolyard. Exaggerated startle appeared to be specific to PTSD and consistent with chronic brainstem dysfunction (McNally, 1991). However, these responses could also be associated with comorbidity or other factors rather than being necessary indicators of PTSD. Therefore, there is no suggestion or indication that Yohimbine infusion could be a universal diagnostic tool for PTSD.

Another diagnostic tool similar to Yohimbine is the Lactate Infusion, which could be used to precipitate panic attacks (Rainey et al., 1990). However, the expected response only occurs in patients concurrently suffering from PTSD and panic

disorder. Hence, Lactate Infusion is also less likely to be a general diagnostic tool. It would only be useful for those who fulfill the complete list of PTSD symptoms. As for corticotrophin- and thyrotropin-releasing hormone tests, they could be applied to assess the psychobiological consequences of PTSD. However, the corticotrophin- (Smith et al., 1989) and thyrotropin-releasing hormone tests fall short in diagnosing PTSD (Reist et al., 1995).

Finally, urine tests of epinephrine and norepinephrine could allow for an assessment of the pathophysiology of PTSD. Norepinephrine is one of the major central nervous system (CNS) effectors of the human stress response (Geracioti et al., 2001). As Geracioti et al. (2001) noted there were no direct measures of CNS norepinephrine in PTSD. Instead, indirect measures allowed for testing both plasma and urinary norepinephrine concentrations in PTSD patients in resting condition. Nevertheless, previous clinical data show that patients with PTSD exaggerated CNS responses to noradrenergic activation. Yet, the situation in the CNS during the baseline was largely unclear. Only some of the studies reported baseline urinary excretion of norepinephrine (Kosten et al., 1987; Spivak et al., 1999). For further clarification, Geracioti et al. (2001) focused on PTSD patients who suffered severe combat-related trauma. They reported that baseline CNS noradrenergic tone was higher in patients with chronic PTSD than in the healthy comparison group. Furthermore, this pathophysiologic finding was directly related to the severity of the disorder's clinical manifestations. This finding suggests that cerebral spinal fluid (CSF) norepinephrine concentrations are positively correlated with a number of PTSD symptoms.

The brain secretes stress chemicals, which continue even after the threat has passed. That is why trauma survivors are always in a state of alarm. It appears that there is a biochemical imbalance in trauma patients. Adrenaline helps to fight difficult situations. Adrenaline can also raise heart rates and blood pressure when the survivors were talking about their experiences. The stress hormones of traumatized people can easily rise disproportionality out of real danger or threat, which takes longer to come back to normal levels (Van der Kolk, 2014).

Wingenfeld et al. (2015) recruited 613 adult outpatients from two Veterans Affairs medical centers. Among the participants, 199 had current PTSD, 100 had lifetime PTSD, and 314 never had PTSD. The researchers measured 24-h urinary norepinephrine, epinephrine, dopamine, and cortisol using tandem mass spectrometry. They assessed lifetime and current PTSD with the Clinician-Administered PTSD Scale (CAPS, a widely structured interview for diagnosing PTSD). Patients with current PTSD had significantly higher norepinephrine levels than those without PTSD, whereas those who never had PTSD showed the highest cortisol values. As for those with lifetime PTSD and without PTSD, the former exhibited lower cortisol values than the latter. These findings indicated increased norepinephrine secretion and decreased cortisol in PTSD. Such changes could lead to adverse health outcomes in patients with PTSD.

As a result, the etiology of PTSD has become a promising concern of biochemical, neuro-endocrinological, and physiological research. A growing body of physiological research has been conducted on psychobiological testing and assessment of PTSD. However, psychobiological research and assessment of PTSD face significant challenges in two major issues, a lack of a definitive test and a clear definition of PTSD (O'Brien, 1998). PTSD is composed of clinically heterogeneous groups of symptoms and is defined on a phenomenological basis, but inadequately reflecting the underlying pathophysiology. This has been an increasingly recognized limitation, the knowledge gap in the etiological underpinnings of psychiatric disorders (Zannas et al., 2015). As O'Brien (1998) argued, a definitive test and assessment of PTSD will not be possible unless psychobiological research precisely defines what PTSD is and identifies who

does or does not has it. Nevertheless, well-designed studies are using different tests or measurements, such as the Dexamethasone Suppression Test and Magnetic Resonance Imaging. Using different tests and measurements allow for a multimodal assessment of PTSD.

## Dexamethasone Suppression Test (DST) for Cortisol and Noradrenalin Levels

Given the comorbidity of depression and PTSD, including their overlapping symptoms, DST has been used in several studies. For example, Yehuda et al. (2004) used it to compare the cortisol responses of patients with PTSD to those with major depressive disorder. The test was conducted the morning after administering a 0.5 mg dose of Dexamethasone (DEX) at 11 pm. The results indicated lower levels of plasma and saliva cortisol in patients with PTSD, that is, PTSD is associated with the greater suppression of cortisol. In contrast, major depressive disorder emerged as an important predictor of cortisol suppression, regardless of trauma background. As a result, patients with either PTSD or depression showed strong cortisol hyper-suppression. This suggests that cortisol response to DEX can be a sensitive measure of PTSD. This sensitivity seems to be the reason for the conflicting results of earlier studies on patients with both PTSD and depression (Halbreich et al., 1988; Kudler et al., 1987). However, a later review of the evidence for neuropathology of stress-related changes in PTSD (Lucassen et al., 2014) showed that patients with a major depressive disorder could be non-suppressors. Accordingly, DST may help differentiate between patient groups but is not necessarily useful for individual patients (i.e., DST is of little use for distinguishing PTSD from suppression).

PTSD patients may also show lower or at least not elevated urinary cortisol levels and thus alterations of the glucocorticoid receptor (GR) sensitivity (Yehuda, 2009). This may reflect a pre-existing vulnerability trait that increases the probability of developing PTSD after a traumatic event experience. Cortisol levels in PTSD reflect pre-trauma characteristics; this may function as a precipitator or facilitator of the disorder after trauma exposure. Thus, biological vulnerability explains why some people experience arousal and distress and develop constant arousal, while others are able to move on with normal life (Yehuda, 2009). Similarly, Van der Kolk (2014) stated that constantly elevated stress hormones might cause memory and attention problems, irritability, and sleep problems.

By administering DEX to veterans with PTSD and comparing them to veterans and non-veterans without PTSD, Yehuda et al. (1995) examined cortisol and lymphocyte GR numbers. Combat veterans with a PTSD diagnosis showed a larger number of baseline GRs than their counterparts. But only veterans with PTSD showed a decline in the lymphocyte GR number after the DEX administration. In earlier studies (Mason et al., 1986; Yehuda et al., 1990), veterans with PTSD demonstrated a sustained elevation in urinary catecholamine but had lowered cortisol levels. However, this finding was not replicated in later studies (Pitman & Orr, 1993). The earlier studies also reported that urinary noradrenaline levels are relatively high in PTSD groups. Mason et al. (1986) remarked that while neither of these measures can be used confidently to distinguish PTSD subjects from those with other major psychiatric disorders, the ratio of the two can do so, with 78 % sensitivity and 89 % specificity. This promising consideration, however, needs a larger-scale study. The suggested way of distinguishing between patients with PTSD and those with major psychiatric disorders requires a careful collection of 24-hour specimens with a methodology that might make general use as a simple clinical diagnostic tool difficult, even if the work were to be widely replicated.

Thus, cortisol levels in the aftermath of trauma also have the potential to predict remission and

relapse. Yehuda et al. (2009) measured morning plasma cortisol excretion, urinary free cortisol and metabolites cortisone, 5-tetrahydrocortisol, 5-tetrahdydrocortisol, and tetra hydrocortisone for patients who received 14 sessions of cognitive behavioral therapy after the World Trade Center attacks. The findings show that urinary cortisol levels declined over time in the non-responder group, and they continued to have lower cortisol in follow-up measurements. Yehuda et al. (2009) speculated that cortisol levels continue to decline as PTSD becomes more chronic and treatment-resistant. Similar findings were also reported in previous studies with rape victims (Resnick et al., 1995), motor vehicle accident survivors (Delahanty et al., 2003), and ice storm victims (Anisman et al., 2001). Such alterations to levels of cortisol and urinary catecholamine occur not only among adult patients but also in children with PTSD. Delahanty et al. (2005) found a significant link between initial urinary cortisol levels and subsequent acute PTSD symptoms. They hereby argued that urinary cortisol and epinephrine levels might have a predictive potential for chronic PTSD. Hence, urinary hormone levels (cortisol and epinephrine) soon after significant traumatic experiences may have a diagnostic value.

Lowered plasma cortisol levels measured in saliva can also be indicative of stress in children as young as nine months old (Gunnar et al., 1992). Perroud et al. (2014) asserted that such an effect can be explained by the transmission of parental PTSD to offspring (i.e., the transmission of epigenetic processes, such as the methylation status of the GR gene). Perroud et al. (2014) compared 25 women exposed to the Tutsi genocide during pregnancy and their children with 25 women of the same ethnicity, pregnant during the same period but not exposed to the genocide and their children. They investigated PTSD and depression severity, plasma cortisol, GR, mineralocorticoid receptor (MR) levels, and methylation status of GR gene promoter regions. The result showed that the transmission of PTSD to the offspring was associated with the transmission of biological alterations of the Hypothalamic-Pituitary-Adrenal (HPA) axis.[1] Compared to the non-exposed mothers and their children, women exposed to the genocide had lower cortisol and GR levels and higher MR levels.

Similarly, Yehuda et al. (2005) reported lower cortisol levels in the infant offspring of mothers who developed PTSD after exposure to the World Trade Center attacks when they were pregnant. Like their mothers, the babies also had low salivary cortisol levels. Such lower cortisol levels due to parental PTSD also occurred in adult children of Holocaust survivors. In a 10-year follow-up study on Holocaust survivors with PTSD, Yehuda, Morris, Labinsky, Zemelman, and Schmeiedler (2007b) found that cortisol levels could affect the long-term persistence of PTSD; therefore, there was a general decrease in their cortisol levels. In a further study, Yehuda, Blair, Labinsky, and Bierer (2007a) compared the offspring of Holocaust survivors having PTSD with subjects whose parents had not been exposed to the Holocaust. Using radioimmunoassay, plasma cortisol and DEX were tested. This test revealed that cortisol suppression and parental PTSD were closely linked. This result indicated that parental PTSD was significantly associated with offspring's post-DEX cortisol levels. In other words, parental PTSD was predictive of the prevalence of PTSD in their offspring.

Moreover, the children of Holocaust survivors with PTSD also reported more emotional abuse and physical neglect. This suggests that exposure to adversity could lead to alterations in GRs, pointing to a molecular link between early environmental adverse events and their interactions with genetic expression. An early traumatic experience in association with the genetic and gender effect can cause the development of neuroendocrine

[1] The major neuroendocrine system that regulates the stress response.

dysregulation in PTSD (Olff et al., 2005), which in turn results in PTSD development. The HPA axis is one of the main systems for regulating the psychophysiological stress response. Therefore, its activity is identified by individual responses to stressful events. After stressful events, the hypothalamus secretes a corticotrophin-releasing hormone and other neuropeptides that release adrenocorticotropic hormones from the pituitary gland (Xie et al., 2010). Alterations of the HPA axis are hereby one of the main features of PTSD pathophysiology (Yehuda, 2009).

In other words, early traumatic experiences, such as childhood abuse, may influence the functional development of the HPA axis and thus alter the basal rhythms and reactivity of the HPA system in adulthood (Gunnar & Donzella, 2002). According to Heim and Nemeroff (2009), early life exposure to trauma may lead to long-term effects on the HPA reactivity (i.e., chronic stress fosters disease by increasing activation of the HPA axis). However, some studies on individuals with PTSD symptoms showed the opposite (i.e., decreased activation). For example, Miller et al. (2007) reported lower levels of HPA activity in individuals with PTSD symptoms. Mehta and Binder (2012) also presented consistent findings with this neurobiological evidence for alterations of the HPA axis in individuals with PTSD.

As a result, there is cumulative evidence that dysregulation in cortisol levels occurs in PTSD patients. However, the evidence remains vague, inconclusive, or inconsistent. It is unclear if the dysregulation in cortisol is a cause or a result of PTSD (Olff et al., 2005). Further research is needed for a thorough understanding of this issue, clarifying either the biological causes or consequences of PTSD. Research in the last 50 years has advanced, and we have seen PTSD get categorized as a physioneurosis and provide new insight for understanding its nature and treatment. The most important developments are the neurobiological underpinnings and treatment.

Recent cutting-edge developments in neuroimaging and related fields or neurosciences have opened new avenues to understand the complex relationships between psychological, psychiatric, biological, and neuroanatomical aspects of PSTD and provided opportunities for new therapeutic approaches to treat trauma survivors (Van der Kolk, 2000). In the same way, Nisar et al. (2020) argued that traditional methods of researching PTSD have not been sufficient for diagnosis, measurement, treatment and following its progression. Unfortunately, there is no biomarker diagnostic available for PTSD. A better understanding of neuroimaging genetic techniques is necessary for the development of specific approaches and biomarkers to diagnose and treat PTSD. Previous studies considered PTSD a systemic illness, which affects not only the brain but also the entire body. PTSD symptoms are likely to cover the spectrum of multiple biological domains, including genes, proteins, cells, tissues, and organic-level physiological changes. Therefore, the identification of these signals could be imperative in diagnostics, treatment decision-making, and knowing the risk factors for PTSD symptoms (Dean et al., 2020). Different technologies such as heart rate monitors, electroencephalography (EEG), audio recorders, and eye tracking are recently used to detect and analyze neurological and physiological symptoms of PTSD for diagnosis (Farrow & Jayarathna 2019).

## Magnetic Resonance Imaging (MRI)

Functional magnetic resonance imaging (fMRI) is utilized to measure the levels of blood oxygenation and flow in the brain to research the level of brain activity and detect abnormalities (Farrow & Jayarathna 2019). In the same fashion, PET (positron emission tomography) and fMRI can help to observe an individual's brain when they recall something from their past or get involved in certain

activities (Van der Kolk, 2014). This neuroimaging can determine which brain structures are affected and how different reminders of trauma mobilize them. Since 1999, studies utilizing neuroimaging of PTSD patients have also appeared.

To shed light on the issue of whether PTSD is the cause or the result of neurological dysfunctions, a series of psychobiological research utilized MRI-based measurements and suggested that lower hippocampal volume can be associated with PTSD. The research participants with higher susceptibility to PTSD showed smaller hippocampal volumes, abnormalities in the septum pellucidum (Bremner et al., 1995a; Talbot , 2004), and increased activations in the amygdala (Bremner, 2007). However, Yehuda et al. (2006) argued that a smaller hippocampal volume occurred in young soldiers but not in older combat veterans. Yehuda et al. maintained that as people get older, the size of the hippocampus decreases. This creates challenges in measuring the size of the hippocampus. Moreover, stress-induced changes in mitochondrial membrane potential are regulated by non-genomic and genomic actions of cortisol in hippocampal neurons (Zhang et al., 2006). The studies utilizing MRI-based measurements fall short of helping understand what causes hippocampal atrophy (Broekman et al., 2007), thereby falling short of shedding enough light on the main issue.

The issue becomes more challenging when considering the vulnerability factors in relation to trauma exposure. Pitman et al. (2006) argued that healthy nervous systems might protect individuals and provide resilience when they face an extremely traumatic event. In their study on identical Vietnam veteran twins, with—but not without—PTSD had HRRs to sudden loud tones. The twins did not differ in terms of increased neurological soft signs (NSSs), diminished hippocampal volume, or abnormal cavum septum pellucidum (CSP). This result proposes that family vulnerability factors may be the main determinant, that is, neurological dysfunction is not the result of PTSD.

In the brain of healthy individuals, subcortical gray matter and limbic structures (septal area, hippocampal, and amygdale) grow until the third decade of life (Jernigan & Sowell, 1997). However, in a series of earlier studies, adult women who have been victims of childhood sexual abuse showed a 5% reduction in the size of the hippocampal volume (Stein et al., 1997). A smaller size of the hippocampus (reduced by 12%) was detected in the brain of some other adult victims of childhood physical and sexual abuse (Bremner et al., 1997). A similar MRI scan confirmation study, involving 26 patients with combat-related PTSD and 22 control subjects, also detected an 8% reduction in the right hippocampal brain region of the patients (Bremner et al., 1995a). These earlier findings indicate that distressed survivors of traumatic events may develop hippocampal atrophy. However, this indication has not been confirmed by relatively recent evidence. Bonne et al. (2001) conducted MRI tests on 37 adult survivors of traumatic events within a week of the trauma and six months after the trauma. In the follow-up, 10 subjects had PTSD but they did not differ from those without in terms of hippocampal volume. Regarding this inconsistent result, Bonne et al. (2001) concluded with two reasons: First, the structural change in the hippocampus might occur as a result of exposure to prolonged trauma (more than six months of suffering). Second, the reduction might be due to substance or drug abuse. Thus, as DeBellis et al. (1999) argued, hippocampal atrophy, shown in the Bremner et al. (1997) and Stein et al. (1997), might be explained by the fact that the MRI scans were taken when the subjects were very young, during the period of normal development of subcortical structures. These two studies speculate that when a trauma, especially a prolonged trauma occurs during hippocampal maturation, it might hinder the natural growth of the hippocampus.

Such inconsistent results were also reported by other studies on combat-related PTSD (Uddo et al., 1993; Vasterling et al., 1998). These studies

showed that hippocampal functions were not impaired following a recent traumatic event, but frontal lobe tasks, such as attention and set shifting, were impaired. As such, memory deficits in children may occur as a result of traumatic events (McNally, 1991). For example, learning disabled children can be the result of severe exposure to incalculable stress, such as sexual abuse during childhood (Wolfe et al., 1989). According to Wolfe et al., involvement of the locus coeruleus and amygdala may implicate learning and memory disorders in adults. They further proposed that the performance of PTSD patients on a modified Strop test could be referred for a neuropsychological assessment of PTSD.

As a result, the above-mentioned studies provided either inconclusive or inconsistent evidence, which can be ascribed to the lack of precise tests or measurements. Researchers used a test or diagnostic tool according to their research aim. None of them prescribed exactly which test, measurement, or diagnostic tool should be used for a specific case or all cases. Almost all of them involved either veterans or adult victims of childhood sexual and physical abuse, and none of them involved patients exposed to natural disasters. This suggests further research on physiological/biological testing and assessment of PTSD should be conducted.

## Multimodal Assessment

As presented above, each test or diagnostic tool has its limitations. Therefore, over-reliance on a single diagnostic tool may lead to inaccurate assessments. An assessment of a case or some cases of PTSD may require more than one test or diagnostic tool. For a more accurate assessment, extensive literature suggests a multimodal assessment of the health consequences of PTSD (O'Brien, 1998). Such an assessment should include demographic variables, structured interviews, psychometric tests, rating scales, behavioral observations, reviews of related reports, and collateral confirmation of information. However, it should be noted that applying different tests while using the same data, as if they were independent of each other, does not mean a more accurate assessment. For example, several self-report questionnaires ask about PTSD symptoms or depression symptoms. Using more than one of these will not increase diagnostic accuracy, as it may be simple repetition. It seems that there are other factors to consider for a diagnosis of PTSD. A study by Pietrzak et al. (2012) of WTC rescue and police officers concluded that there is a need for a more inclusive and multi-dimensional conceptualization of PTSD, because regular screening tools may not pick up the syndrome even though the individuals continue to suffer from subsyndromal PTSD.

The etiology of PTSD is complex and multifactorial, emerging from complex interactions among traumatic events and multiple genetic factors (Zannas et al., 2015). It can be examined at least in three instances. First, PTSD may be the result of polygenetic inheritance. Broekman et al. (2007) argued the heritability of PTSD should be considered polygenic (i.e., different genes or interactions between them play an additional role in the onset of PTSD). However, this argument needs further exploration. Previous studies mainly focused on candidate genes and several neurobiological systems (e.g., the HPA axis, the serotonergic system, the dopaminergic system, the neurotropic system, and the GR, GABA, APO, BDNF, and NPY systems). Yet, studies have revealed inconsistent results. Consistent or replicable findings require further studies on the causal relationship between polygenetic inheritance and PTSD. Such experimental research should compare PTSD patient groups with healthy control groups, and trauma-exposed patient groups that did not develop PTSD (Broekman et al., 2007).

Second, being exposed to stress in the early developmental stages can result in neurobiological changes that eventually contribute to the individual's psychopathology (Heim & Nemeroff, 2002).

Early childhood abuse and neglect can significantly hinder hippocampus growth, which causes the misinterpretation of the sensory rate in case of any possible danger or threat to self (Van der Kolk, 2003). Individuals with adverse childhood experiences are more sensitive to stressful life events, rendering them more vulnerable to PTSD (Xie et al., 2010). Third is the transgenerational effect of PTSD or adversity on physiological (cortisol) response or development of PTSD in children (Yehuda et al., 2007a). These instances suggest that interactions between genetic inheritance and environmental adversity can affect the HPA axis function. The genetic factor may moderate the effect of early traumatic experience on the HPA axis, which in turn affects individuals' responses to stressful events later on (Xie et al., 2010). Hence, a multimodal assessment can better explain interactions between genetic inheritance and environmental adversity in association with PTSD and its biological health consequences (Broekman et al., 2007). These will help better understanding of specific genetic and environmental factors that increase the susceptibility to PTSD.

In some studies, the more accurate psychobiological assessment of PTSD patients requires a multidimensional examination, including biological health consequences, physical response, genetic inheritance, and parents exposed to traumatic life events. The epigenetics of PTSD, interactions between the genetic inheritance and personal experience of adversity, are recurring issues (Mehta & Binder, 2012). A multimodal assessment may enable researchers to predict who is at risk of PSTD, thereby facilitating the provision of effective and efficient intervention or treatment approaches for PTSD patients. To diagnose PTSD patients, clinicians mostly rely on symptom checklists, clinical history, self-reporting, and symptom severity and duration. There are also other ways to identify traumatic symptoms. For example, to predict PTSD or to identify its severity, intensity, and duration in patients, Zhang et al. (2009) suggested using biomarkers, which can be obtained from the patient's salivary blood, CSF, urine and tissue samples. Physiological responses, such as blood pressure, ECG, heart beating, neurotransmitters, 5-HT, dopamine, and GABA, can also be among the biomarkers. However, a widely accepted biological marker test for PTSD has yet to be provided.

Low serotonin levels in humans cause impulsivity and aggression. Patients with inward or outward aggression usually have early childhood trauma(s). SSRIs (selective serotonin reuptake inhibitors) are used to treat depression which can also help PTSD patients sleep well, control their emotions and less occupied with past events and impulses and decrease their aggressive behaviors). SSRIs can patients gain control over traumatic stimuli and understand their traumatic intrusions (Van der Kolk, 2014). New therapy approaches bring new perspectives on how traumatized individuals can be helped and treated. For example, providing a sense of security, providing anxiety management techniques, and providing new emotional processing can help victims significantly reduce their PTSD-related discomforts (Van der Kolk, 2000). Similarly, in a recent meta-analysis, Scoglio et al. (2020) argued about the strong association between PTSD and impairment in global social functioning. They believed that well-designed and evidence-based interventions can improve the social functioning of PTSD patients.

Azarang et al. (2018) discussed the issue of using information technologies to improve mental health services for trauma survivors by providing new treatment approaches or delivering trauma-related interventions. PTSD patients suffer from social isolation and demonstrate avoidance symptoms; therefore, the internet and cell phones can be used as means of treatment instead of traditional office-visit treatment. This would also save time and energy by avoiding commuting long distances. Consequently, telemedicine and telepsychiatry have been widely and effectively used during the height of the COVID-19 pandemic (Carmassi et al., 2020;

Brunt & Gale-Grant, 2022). Similarly, Yao et al. (2022) mentioned the application of virtual reality technology for using exposure treatment for PTSD patients. Other studies support similar treatments.

## Recent Technology in Research of Assessment and Treatment of PTSD

Advances in medical information processing technologies are evolving to provide useful tools for the early recognition of psychological disorders and the screening of at-risk groups (Bourla, 2018). The concept of electronic-PTSD (e-PTSD) can be examined in two main parts: the technologies available today that can be used in prediction and assessment, and the technologies that can be used in treatment.

One tool that can be used especially for screening studies is the digital phenotype, first described by Torous et al. (2017). Digital phenotype is an indicator of an individual digital level obtained by processing data from digital devices connected to the subject. The digital footprint can be used to passively determine the internet pages people visit or to reveal the environments in which people actively work/transact. In this exploration, not only the individual's habitual patterns of digital devices but also the data about the non-usage of devices are evaluated. For this purpose, the smartphone can be used frequently as research material as it is a device that is easily obtained and people carry it with them throughout the day. Smartphones offer many raw data such as the localization of people, their movement processes, their receiving and sending of messages, areas of interest and socializing groups, in an easily processable format.

The points most agreed upon in research regarding adapting new technological developments to the diagnosis of PTSD are reported as decreased heart rate variability, dissociation between the autonomic nervous system and total sleep time and increased skin conduction in severe cases (Bourla, 2018). Two computerized survey methods have emerged recently in the diagnosis processes of PTSD patients. One, the Computerized Adaptive Testing (CAT) (Gibbons et al., 2008), and two, the Embodied Conversational Agent (ECA) (Philip et al., 2017) methods.

The online passport obtained from digital data will also create the need for new legal regulations regarding the privacy, security, employment and data protection of patients' private lives. Many practical details, such as the search for health-related information on the internet and the status of legal institutions such as health insurance agencies, credit rating units of banks, or courts where individuals are summoned as witnesses of defendants. The fact PTSD has behavioral and mental dimensions may be an advantage for the use of patterns in employing the internet in diagnosis. Traces left on the internet enable the patient to distinguish PTSD from other diseases with similar symptoms, and this valuable distinctive information is spread over a long time and has immense value.

Current technological developments in the treatment of PTSD progress in three main ways: Videoconference, remote e-health applications, and virtual reality (Paul, Hassija & Clapp, 2012). It is difficult to predict how computer technology will affect the confrontation process conducted in a scenario full of elements that may trigger the traumatic event. Access to recognized treatment centers for trauma can be difficult, especially for disadvantaged groups such as children, adolescents, the impoverished, residents of rural areas, and racial minorities. Technical difficulties have been reported to be minimal and appeared to be restricted to problems logging into the videoconferencing software or slow-speed internet connections.

## Conclusion

The etiology of PTSD has become a main concern of physiological/biological research, whereas

psychological research has yet to be sufficiently conducted on how traumatic events and PTSD give rise to biological and physiological consequences. Given that psychological literature provides insufficient insights into this issue, this review has aimed to expound on biological and physiological aspects of PTSD and related psychobiological testing and assessment.

For a psychobiological assessment of PTSD, there are several diagnostic tools, such as Yohimbine Infusion, Lactate Infusion, hormone tests, and urine tests of epinephrine and norepinephrine. However, the literature suggests no conclusive test, tool, or measurement. Therefore, at best, an inaccurate assessment of PTSD takes place in several forms. First, physiological and biological responses can be associated with comorbidity or other factors rather than with PTSD. Second, the responses can only occur in a group of patients, such as those concurrently suffering from PTSD and panic disorder. Third, a single test has not yet been developed to diagnose PTSD. Fourth, the heterogeneous and phenomenological bases of PTSD inadequately reflect the underlying pathophysiology, which in turn set a limit on the urinary norepinephrine test. To tackle these issues, further research needs to have a definitive test and a clear definition of PTSD.

Nevertheless, well-designed studies are using the DEX suppression test. Given the comorbidity and overlapped symptoms of major depressive disorder (MDD) and PTSD, DEX has been used in many studies. DEX results have indicated a significant association between PTSD with the greater suppression of cortisol. However, cortisol response to DEX can be a sensitive measure, not allowing distinguishing between symptoms of PTSD and MDD in patients who have both disorders. Therefore, DEX is more likely to help differentiate between the patient groups; it is less likely to be useful for an assessment of patients with both PTSD and MDD.

Cumulative evidence in the psychobiological literature shows that early traumatic experience in association with genetic inheritance can cause the development of neuroendocrine dysregulation in cortisol levels in patients with PTSD (Olff et al., 2005). In other words, this association causes the dysfunction of the major neuroendocrine system which regulates psychophysiological responses to the stress response (i.e., the dysfunction of the HPA axis), which in turn results in the development of PTSD. However, the evidence remains unclear, inconclusive, or inconsistent. The main issue that should be clarified is whether the dysfunction of the HPA axis is a cause or a result of PTSD (Olff et al., 2005). Further research is needed to reveal either the biological causes or consequences of PTSD.

To clarify this issue, a series of psychobiological research utilized MRI-based measurement but fell short of shedding light on it. The problem is exacerbated by familial vulnerability to traumatic events. Neurological dysfunctions in patients with PTSD appear not to be a result of the disorder but of a familial risk or vulnerability factor (Pitman et al., 2006). In consequence, the etiology of PTSD is multifactorial, emerging from complex interactions among traumatic events and multiple genetic factors (Zannas et al., 2015). To conclude, PTSD can be examined from three angles First, PTSD may be the result of polygenetic inheritance, that is, different genes or interactions between genes trigger the onset of PTSD. Hence, the heritability of PTSD (as a causal relationship) should be considered in further research. Second, individual experience of a traumatic event in the early developmental stages can result in neurobiological changes, contributing to the psychopathology of individuals (Heim & Nemeroff, 2002) or rendering them more vulnerable to PTSD (Xie et al., 2010). Third, the transgenerational effect of PTSD (e.g., parents with a severe experience of a traumatic event) on physiological response or development of the disorder in children (Yehuda et al., 2007a). Interactions between these three aspects can be explained better through a multimodal assessment,

which may draw on biomarkers to predict PTSD or to identify its severity, intensity, and duration. However, a clinically validated biological marker test for PTSD is yet to be developed. For an accurate assessment, the extensive literature suggests that a multimodal assessment of the health consequences of PTSD should include demographic variables, structured interviews, psychometric tests, rating scales, behavioral observations, report reviews, and expert confirmation.

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