Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment considerations

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Introduction

Comorbidity between post-traumatic stress disorder (PTSD) and major depressive disorder is common, with approximately half of people with PTSD also having a diagnosis of major depressive disorder (MDD) across diverse epidemiological samples. There are two competing explanations for this comorbidity. The first is that the comorbidity reflects imprecision in symptom classification into the two disorders. Second, that the co-occurrence of PTSD and MDD is not an artifact, but represents a trauma-related phenotype, possibly a subtype of PTSD. Support for the latter explanation is inferred from literature that examines risk and biological correlates of PTSD and MDD, including molecular processes. Treatment implications of the comorbidity are considered.

Keywords: PTSD, MDD, comorbidity, glucocorticoid receptor, FKBP5

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Approximately half of people with post-traumatic stress disorder (PTSD) also suffer from Major Depressive Disorder (MDD). The current paper examines evidence for two explanations of this comorbidity. First, that the comorbidity reflects overlapping symptoms in the two disorders. Second, that the co-occurrence of PTSD and MDD is not an artifact, but represents a trauma-related phenotype, possibly a subtype of PTSD. Support for the latter explanation is inferred from literature that examines risk and biological correlates of PTSD and MDD, including molecular processes. Treatment implications of the comorbidity are considered.

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Evidence supporting PTSD/MDD comorbidity as an artifact of symptom overlap

The diagnostic criteria for a major depressive episode (MDE) have remained essentially constant across versions of the DSM from 1980 to 2013. There are 9 diagnostic criteria, and 5 must be present in order to meet diagnostic threshold. A DSM-III diagnosis required that 1 of the 9 criteria include depressed mood. In DSM-III-R and later versions, the criteria were revised such that the symptom of anhedonia could substitute for depressed mood. In contrast, the diagnostic criteria for PTSD have changed substantially over the same time period. Table I presents the symptom lists for the different versions of DSM. Note that the DSM-III-R, DSM-IV, and DSM-IV-TR versions are presented

| DSM-III | DSM-III-R/DSM-IV/DSM-IV-TR | DSM-5 |
|---------|----------------------------|-------|
| **Re-experiencing (Need 1)** | **Re-experiencing (Need 1)** | **Re-experiencing (Need 1)** |
| 1) recurrent and intrusive recollections | 1) recurrent and intrusive recollections | 1) recurrent and intrusive recollections |
| 2) recurrent dreams | 2) recurrent dreams | 2) recurrent dreams |
| 3) flashbacks | 3) flashbacks | 3) flashbacks |
| **Numbing (Need 1)** | **Avoidance or numbing (Need 3)** | **Avoidance (Need 1)** |
| 1) diminished interest | 1) efforts to avoid thoughts or feelings | 1) efforts to avoid thoughts or feelings |
| 2) detachment or estrangement from others | 2) efforts to avoid activities | 2) efforts to avoid activities |
| 3) constricted affect | 3) inability to recall an important aspect of the trauma | Negative alterations in cognitions and mood (Need 2) |
| **Hyperarousal (Need 2)** | **Hyperarousal (Need 2)** | **Hyperarousal (Need 2)** |
| 1) hyperalertness or exaggerated startle | 1) sleep disturbance | 1) sleep disturbance |
| 2) sleep disturbance | 2) irritability | 2) irritability |
| 3) guilt | 3) trouble concentrating | 3) trouble concentrating |
| 4) memory impairment or trouble concentrating | 4) hypervigilance | 4) hypervigilance |
| 5) avoidance of reminders | 5) exaggerated startle | 5) exaggerated startle |
| 6) intensification of symptoms | 6) reckless or self-destructive behavior | 6) reckless or self-destructive behavior |
| **3/12 symptoms required for diagnosis** | **6/17 symptoms required for diagnosis** | **6/20 symptoms required for diagnosis** |

Table I. PTSD symptom clusters from DSM-III to DSM-5.
together in one column, as the criteria did not change appreciably across these three versions. The PTSD symptoms that overlap with MDD are presented in red text and include anhedonia, sleep disturbance, and concentration difficulties; three symptoms that appear in the PTSD diagnosis across all versions of the DSM. The number of possible PTSD symptoms expanded from 12 in DSM-III to 20 in DSM-5. New symptoms that appear with iterations of the PTSD diagnosis are shown in blue text. The changes to the PTSD diagnosis in DSM-5 also brought forth a new symptom that overlaps between the two disorders, as guilt was added (back) to the PTSD diagnostic criteria. Note that this symptom was present in the original diagnostic description of PTSD in DSM-III.

PTSD first appeared in the DSM in 1980 and was comprised of 12 symptoms that were grouped into three clusters: Re-experiencing, Numbing, and a broad category of other symptoms. In the DSM-III-R/DSM-IV/DSM-IV-TR editions of the manual, the definition of PTSD was expanded to include 17 symptoms, grouped into three clusters. The principal revision was that several of the symptoms in the broad category were moved into the other two categories (eg, re-experiencing or avoidance) and this cluster was conceptualized as Hyperarousal. Additionally, several individual symptoms in the broad category were transformed into two symptoms, eg, one avoidance symptom became two avoidance symptoms. In the revision of DSM-IV to DSM-5 there were several changes. First, PTSD was removed from the anxiety disorders section and placed into a separate and new Trauma and Stressor-related Disorders section of the DSM. Second, the requirement that an individual experience “helplessness, fear, or horror” related to trauma exposure was eliminated. These two changes reflect the view that PTSD is no longer considered solely to be a fear-based anxiety disorder. Third, the total number of PTSD criteria was expanded from 17 to 20. Fourth, avoidance is now considered to be an essential element of PTSD, as at least one symptom of avoidance is required for diagnosis. Numbing symptoms were moved to a new and separate cluster in DSM-5 labeled Negative Alterations in Cognitions and Mood. Table II presents a comparison of DSM-IV-TR Cluster C criteria (Avoidance and Numbing) and how they have been reformulated for DSM-5 into Cluster C (Avoidance) and D (Negative Alterations in Cognitions and Mood).

The changes to the diagnostic criteria for PTSD over time, with the corresponding absence of change

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**Table II.** Comparison of Avoidance and Numbing symptoms of post-traumatic stress disorder in DSM-IV-TR versus DSM-5.

**DSM-IV-TR**

Criterion C: Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:

(C1) efforts to avoid thoughts, feelings, or conversations associated with the trauma (DSM-5 C1)

(C2) efforts to avoid activities, places, or people that arouse recollections of the trauma (DSM-5 C2)

(C3) inability to recall an important aspect of the trauma (DSM-5 C3)

(C4) markedly diminished interest or participation in significant activities (DSM-5 C4)

(C5) feeling of detachment or estrangement from others (DSM-5 C5)

(C6) restricted range of affect (eg, unable to have loving feelings) (DSM-5 C6)

(C7) sense of a foreshortened future (eg, does not expect to have a career, marriage, children, or a normal life span) (DSM-5 C7)

**DSM-5**

Criterion C: Persistent effortful avoidance of distressing trauma-related stimuli after the event (one required):

(C1) Trauma-related thoughts or feelings

(C2) Trauma-related external reminders (eg, people, places, conversations, activities, objects, or situations)

Criterion D: Negative alterations in cognitions and mood that began or worsened after the traumatic event (two required):

(D1) Inability to recall key features of the traumatic event (usually dissociative amnesia; not due to head injury, alcohol, or drugs)

(D2) Persistent (and often distorted) negative beliefs and expectations about oneself or the world (eg, “I am bad,” “The world is completely dangerous”)

(D3) Persistent distorted blame of self or others for causing the traumatic event or for resulting consequences

(D4) Persistent negative trauma-related emotions (eg, fear, horror, anger, guilt, or shame)

(D5) Markedly diminished interest in (pre-traumatic) significant activities

(D6) Feeling alienated from others (eg, detachment or estrangement)

(D7) Constricted affect: persistent inability to experience positive emotions
Evidence supporting PTSD/MDD comorbidity as a distinct trauma-related phenotype

An alternative view is that the comorbidity between PTSD and MDD represents a distinct phenotype, possibly even a subtype of PTSD. As discussed below, evidence to support this view can be inferred from the research literature examining risk factors and biological correlates of the two conditions. With respect to the phenomenology of the comorbidity, people with both PTSD and MDD report higher levels of distress and role impairment. They also show higher impairment in neurocognitive functioning and are at greater risk for suicide than people with PTSD only. Moreover, prognosis for people with both conditions is poorer than for either one alone. Finally, there are distinct biological profiles associated with PTSD versus MDD, as reviewed below.

Risk factors associated with PTSD/MDD comorbidity

The co-occurrence of psychiatric diagnoses is the rule rather than an exception, and the high rate has been attributed to fundamental underlying dimensions or latent factors, termed internalizing versus externalizing. The internalizing dimension is characterized by high levels of negative affectivity (also known as neuroticism) and low levels of positive affectivity (also known as extraversion) while the externalizing dimension is characterized by high levels of negative affectivity and low levels of constraint (also known as high impulsivity).
ity). In general, the internalizing dimension represents a latent or underlying trait vulnerability that explains co-occurrence among mood and anxiety disorders, while the externalizing dimension underlies substance use disorders, conduct disorder, and antisocial personality disorder. PTSD is a unique disorder in that it has been shown to be related to both internalizing and externalizing dimensions in large samples of people with a diverse range of psychiatric diagnoses, although see ref 27.

Research on the latent structure of PTSD comorbidity shows that people with PTSD who report high negative affectivity and low positive affectivity are more likely to have a comorbid diagnosis of depression. However, people with PTSD who report high negative affectivity and low constraint are more likely to have comorbid substance-use disorders, and report higher aggression scores. Thus, when PTSD and MDD co-occur this may be a manifestation of the underlying vulnerability to respond to trauma with the behavioral, affective, and cognitive symptoms that reflect the internalizing dimension. That is, people who report high levels of neuroticism are prone to react to everyday stressors and challenges with anxiety, worry, irritability and sadness (ie, negative affect). This style is particularly invoked when the challenge involves loss, threat, or frustration and reflects a long-standing personality dimension. Coupled with low extraversion, which refers to a tendency to seek out and enjoy social activities, the individual is less likely to ask for support from others when frustrated or upset and/or less capable of seeking novel and stimulating experiences that might be mood brightening.

Thus, when exposed to a traumatic experience, the person who develops PTSD and has an internalizing personality style is vulnerable to developing MDD. In support of this view, Spinhoven et al examined the influence of neuroticism and extraversion on rates of PTSD and MDD in a longitudinal study of more than 2400 adults. The results showed that high neuroticism and low extraversion assessed at baseline were associated with development of comorbid PTSD and MDD 4 years later. Interestingly, the traits were not associated with new-onset cases of either disorder by itself, suggesting that it is the combination of high neuroticism and low extraversion that leads to the comorbidity. In contrast, the person who develops PTSD but has the externalizing personality style characterized by impulsive thoughts and behaviors is not likely to develop MDD. In this instance, PTSD is more likely to be accompanied by substance abuse and aggression. Longitudinal research is needed to better understand the structure and etiology of PTSD epidemiology.

A prominent risk factor for both PTSD and MDD is childhood adversity and abuse and in the study described above, Spinhoven et al reported that the relationship between the high neuroticism/low extraversion and subsequent development of comorbid PTSD and MDD was fully accounted for by retrospective reports of childhood sexual and physical abuse in multivariate analyses. A similar result was reported by Hovens et al who found strong support for an association between retrospective reports of physical childhood abuse and comorbid mood and anxiety disorders in a large adult sample. In contrast, people with only an MDD diagnosis were more likely to report emotional neglect and psychological abuse in childhood. Thus, childhood maltreatment, especially physical abuse, may mediate the association between the internalizing dimension and development of MDD/PTSD. Other types of abuse may be associated with different adulthood outcomes.

In summary, epidemiological data indicate that rates of comorbidity in PTSD are higher than in other disorders, suggesting that the pertinent diagnostic query is not whether PTSD is accompanied by another diagnosis, but rather, which diagnoses are also present. The combination of high negative affect and low extraversion appears to represent a pre-existing trait that confers vulnerability for the development of comorbid PTSD/MDD, relative to other types of PTSD comorbidity. Childhood maltreatment is an important consideration in terms of understanding the etiology of PTSD comorbidity and may even mediate the association between the personality dimensions and the diagnoses. Further longitudinal research is needed to identify whether different types of childhood maltreatment are more likely to lead to internalizing versus externalizing styles of behavior, as this may provide insight into why some individuals develop PTSD/MDD while others do not.

**Biological factors that distinguish between PTSD and MDD**

In contrast to the risk factor research described above, biological studies that address PTSD/MDD comorbidity generally examine how PTSD and MDD have dis-
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tinct, and sometimes diverging, biological signals. This research includes studies that examine structural and functional neuroimaging, measures of the hypothalamic pituitary adrenal (HPA) axis, and more recently, DNA molecular markers (ie, epigenetics, gene expression).

Neuroimaging

A series of twin studies provide evidence of differences between PTSD and MDD in neuroimaging measures. In these studies, male monozygotic twin pairs were identified in which one twin was combat-exposed to the Vietnam War and developed PTSD and the cotwin was not exposed (and did not have PTSD). Twin pairs not exposed to war trauma were included as control comparison to identify vulnerability factors for the development of PTSD. In the first study, Gilbertson and colleagues reported that the monozygotic twin pairs who were discordant for trauma exposure had comparable and lower hippocampal volume relative to twin pairs not exposed to war trauma. These results suggest that lower hippocampal volume is a risk factor for the development of PTSD. Drawing from the same twin sample and using the same study design, Shin and colleagues have reported that higher resting metabolic activity in the dorsal anterior cingulate cortex (ACC) and midcingulate cortex and activation in the dorsal ACC during a cognitive interference task are similarly risk factors for PTSD, but not depression. In contrast, Kasai et al reported lower pregenual ACC gray matter in association with PTSD and MDD. Lower gray matter was not observed in cotwins, suggesting that this measure represents an acquired characteristic of both PTSD and MDD.

Several functional imaging studies have directly compared people with PTSD and MDD to those with PTSD alone. Kemp et al reported lower medial prefrontal cortex (mPFC) and amygdala activation to fearful faces in PTSD/MDD patients compared with those with only PTSD. Lanius et al reported similar results in a symptom provocation paradigm, but the PTSD/MDD versus PTSD group difference in mPFC activation did not persist after controlling for PTSD symptom severity. People in the PTSD/MDD group also had higher activation in anterior cingulate cortex and posterior cingulate cortex and lower activation in the left insula relative to the PTSD only group, and these differences were not attenuated by PTSD symptom severity. Kennis et al built upon these results by examining functional connectivity in these regions and reported higher connectivity between the subgenual ACC and perigenual ACC in patients with PTSD/MDD relative to the group with PTSD only. The PTSD/MDD group also showed lower functional connectivity between the insula and hippocampus compared with the PTSD only group. A recent review has shown that higher levels of neuroticism are related to functional activity in many of these same regions, using similar emotion-laden tasks (eg, faces).

Hypothalamic-pituitary-adrenal axis

Measures that characterize the functioning of the hypothalamic-pituitary-adrenal (HPA) axis also differ in their relationships to PTSD and MDD. Both PTSD and MDD are associated with greater hypothalamic CRF release relative to healthy controls, but in people with PTSD, peripheral cortisol levels are generally lower and in MDD they are higher (reviewed in refs 41,42). In a direct comparison of patients with PTSD and MDD using 24-hour sampling of cortisol and chronobiological analyses, Yehuda and colleagues reported that overall cortisol levels differed between the groups, but also that the patterns of cortisol release were distinct. In PTSD, there was a greater mean-to-amplitude ratio of cortisol, reflecting a greater range of cortisol release over the 24-hour cycle. In depression, the range of cortisol release was lower, relative to healthy controls. Furthermore, people with PTSD showed fewer ultradian pulses, while patients with MDD showed more ultradian pulses, re-
Reflecting a more chaotic or less well-regulated cortisol release. Importantly, these chronobiological changes reflected central processes rather than being controlled at the level of the adrenal gland.

This distinct pattern appears to reflect differences in glucocorticoid receptor (GR) sensitivity in the two disorders, which may be a function of distinct epigenetic and molecular drivers. Enhanced GR sensitivity in PTSD is inferred from results of the dexamethasone suppression test (DST), which show that people with PTSD have an exaggerated cortisol suppression response to dexamethasone (DEX). In contrast, MDD has been historically associated with cortisol non-suppression (reviewed in refs 42,44). Similar results have been observed on an in vitro measure of glucocorticoid sensitivity.

Enhanced GR sensitivity in PTSD is inferred from results of the dexamethasone suppression test (DST), which show that people with PTSD have an exaggerated cortisol suppression response to dexamethasone (DEX). In contrast, MDD has been historically associated with cortisol non-suppression (reviewed in refs 42,44). Similar results have been observed on an in vitro measure of glucocorticoid sensitivity. In this assay, 50% inhibition of lysozyme activity is determined by incubating cultured peripheral blood mononuclear cells (PBMCs) with varying doses of DEX. Taken together, these results indicate that in PTSD, the negative-feedback system of the HPA axis is overly sensitive. Relatively less research has examined GR sensitivity measures when PTSD and MDD co-occur, but generally, results suggest that people with PTSD/MDD resemble people with PTSD alone (eg, refs 21,43).

**Molecular processes**

These results can be interpreted in concert with a growing body of evidence suggesting that epigenetic processes mediate the relationship between environmental exposures and risk for psychopathology, including PTSD and MDD. Epigenetics refers to stable molecular changes, including DNA methylation and histone modification that regulate gene expression. With respect to psychopathology, it is thought that early-life adversity leads to such changes, which, in turn may cause life-long alterations in how genes are expressed. Thus, epigenetics represents a molecular manifestation of vulnerability for psychopathology. In a recent publication, Yehuda and colleagues reported that there was a unique biological signal associated with PTSD relative to trauma exposure reflecting epigenetic signaling. In this study of combat-exposed veterans, lower epigenetic methylation in the promoter region of the GR gene was associated with PTSD relative to combat-exposed veterans who did not develop PTSD, indicating that this is a marker associated with PTSD, but not exposure.

Approximately half of the veterans with PTSD also met DSM-IV diagnostic criteria for current MDD and results showed that GR gene methylation was lower in veterans with PTSD only, compared with veterans with PTSD and MDD.

Differences between PTSD and MDD with respect to FK506 binding protein 51 (FKBP5) activity have also been reported. FKBP5 is a functional regulator of the GR complex; when stimulated by GR and (and other steroid receptors), FKBP5 increases in transcription and translation are associated with lower GR sensitivity. Lower FKBP5 gene expression has been associated with PTSD, which is consistent with higher GR sensitivity observed in this disorder. Depressive symptoms are correlated with higher FKBP5 gene expression. Interestingly, the same functional variants in the FKBP5 gene interact with environmental stressors, including childhood abuse, to affect risk for adulthood PTSD and MDD (reviewed in ref 51). However, these “risk” alleles are associated with DNA methylation, gene expression, and neuroendocrine measures in directionally opposite ways in the context of PTSD and MDD. The opposing directionality of some of the functional and molecular findings for PTSD versus MDD suggests that studying these two genes in people with both disorders may help to understand why PTSD and MDD co-occur.

**Treatment considerations**

The question about why PTSD and MDD co-occur has significant implications for treatment. If the comorbidity is due to symptom overlap, then ostensibly the same treatment strategies that are effective with PTSD could be offered to people with both disorders. If the comorbidity represents a distinct phenotype or subtype of PTSD, then treatment approaches that target specific aspects of PTSD (eg, avoidance) may be less effective when the presentation includes depressive symptomatology.

**Pharmacological treatment**

This issue is complicated with respect to pharmacological treatment as there are no pharmacotherapies that specifically address PTSD, ie, the recommended medications are antidepressants; current guidelines for the treatment of PTSD recommend initiation of a selec-
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tive serotonin reuptake inhibitor (SSRI, eg, paroxetine, sertraline, or fluoxetine) or serotonin-norepinephrine reuptake inhibitor (SNRI, eg, venlafaxine). Prazosin may be added as adjunctive therapy if the presentation of PTSD includes nightmares. If the initial trial of an SSRI or SNRI is not effective after 4 to 8 weeks, consideration of another first-line SSR/SNRI or mirtazapine is warranted. Again, Prazosin can be added as an adjunctive medication when nightmares are present. A recent meta-analysis showed that the effect sizes for pharmacological treatments for PTSD are low (although comparable to effect sizes for MDD) and do not fare well relative to effect sizes for PTSD psychotherapies. With respect to PTSD/MDD comorbidity, and report that there is some evidence to suggest that people with PTSD and comorbid depression respond more poorly to antidepressants than people with PTSD alone. However, they posit that people with comorbid PTSD/MDD who also report suicidal ideation and childhood trauma exposure may account for poor response to treatment.

With respect to psychotherapies, treatment recommendations for PTSD and MDD are distinct and there are no clear guidelines for treating the comorbidity. Treatment for PTSD includes trauma-focused therapies, which if effective, will also be associated with change in symptoms of depression (reviewed in ref 56), particularly if the depression is mild in severity. Prolonged Exposure (PE) and Cognitive Processing Therapy target avoidance, now considered by DSM-5 to be essential for diagnosis. Dropout rates are high in trauma-focused treatments and are attributed to the initial increase in symptoms as patients begin describing the trauma memory, which activates an avoidance mechanism (ie, cancelling or no-showing for subsequent appointments). Dropout rates are even higher when PTSD is comorbid with depression, suggesting that strategies that specifically target depression (eg, ref 57) or increase retention may be useful in enhancing delivery of the trauma-focused interventions. Regarding retention in psychotherapy, recently reported that hydrocortisone augmentation of PE was associated with greater improvement compared with placebo, a finding that was explained by significantly greater patient retention in the hydrocortisone augmentation treatment condition. The mechanism for such an effect is not known, but the authors proposed that hydrocortisone administration prior to a therapy session diminished the fear response associated with activation of the traumatic memory during the session. Such a mechanism could potentially decrease avoidance, thereby increasing retention in treatment.

Summary

Treatment of PTSD and comorbid MDD is complex. People with both disorders show greater social, occupational, and cognitive impairment, report higher levels of distress, and are more likely to attempt suicide. Prognosis is poor when the two disorders co-occur and treatment dropout is more common. People who respond to challenges and trauma exposures with negative affect may be particularly prone to developing both disorders and also to report childhood maltreatment. Biological evidence is beginning to suggest that this trauma-related phenotype may represent a subtype of PTSD. Further examination of the GR and FKBP5 genes and related molecular processes is warranted. Finally, new treatment strategies that target the unique psychological and biological aspects of the comorbidity are needed.

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Comorbididad entre trastorno por estrés posttraumático y trastorno depresivo mayor: explicaciones alternativas y consideraciones terapéuticas

Aproximadamente la mitad de las personas con trastorno por estrés posttraumático (TEPT) también sufren de un trastorno depresivo mayor (TDM). Este artículo examina la evidencia para dos explicaciones de esta comorbilidad. Primero, que la comorbilidad refleja una sobreposición de síntomas en los dos trastornos. Segundo, que la ocurrencia simultánea de TEPT y TDM no es un artefacto, sino que representa un fenotipo relacionado con el trauma, posiblemente un subtipo de TEPT. El soporte para esta última explicación se infiere de la literatura que revisa el riesgo y los correlatos biológicos del TEPT y el TDM, incluyendo los procesos moleculares. También se consideran las repercusiones terapéuticas de esta comorbilidad.

Comorbidité entre le trouble stress post-traumatique et le trouble dépressif caractérisé: autres explications et considérations thérapeutiques

Environ la moitié des personnes qui présentent un trouble stress post-traumatique (TSPT) souffrent aussi d’un trouble dépressif caractérisé (majeur) (TDM). Cet article analyse les données relatives à deux explications de cette comorbilité. Premièrement, dans les deux troubles, la comorbilité révèle des symptômes de chevauchement. Deuxièmement, l’apparition concomitante d’un TSPT et d’un TDM n’est pas un artefact, mais représente un phénotype lié au traumatisme, probablement un sous-type de TSPT. La littérature, qui analyse le risque et les liens biologiques du TSPT et du TDM, y compris les processus moléculaires que s’y rapportent, est en faveur de cette dernière explication. Nous examinons attentivement les implications thérapeutiques de cette comorbilité.

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