



REVIEW ARTICLE

A memory-based neuronal substrate model of psychogenic non-epileptic seizure and posttraumatic stress disorder



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Memory

Abstract

Background and objectives: Unspecific and broad associations between adverse life events exposure and PNES and PTSD have been reported in the literature. This review aimed to explore the differences in the effect of psychogenic trauma or the cumulative effects of multi psychogenic traumas in PTSD and PNES on the memory neuronal subsystems (using evidence from functional neuroimaging studies and animal models), which could have consequences on the constellation of PNES and PTSD symptomatology.

Method: The author performed a non-systematic review of the literature. Midline was searched using relevant terms and list of references for certain articles were reviewed as well. Key articles and conclusion from systemic reviews and meta-analysis papers were included.

Results: Evidence from neuroimaging studies show that PNES patients exhibited increased resting-state functional activity and alterations in functional connectivity in tier 4–5 memory subsystems that are involved in appraising distant and complex contextual and social threats, such as the frontal cortex, sensorimotor cortex, cingulate gyrus, insula, and the default-mode network, while neuroimaging studies and animal models in PTSD revealed hypoactive tier 4–5 memory subsystems (volumetric reduction in the hippocampi and the anterior cingulate cortex, with hypoactive prefrontal areas) and hyperactive tier 1–3 memory subsystems (ventral tegmentum, dorsal and ventral striatum, and amygdala), which deals with close and imminent physical threats.

Conclusion: Inferences can be made that the effect of a psychogenic trauma will differ according to the way the brain analyses the trauma which might determine the cluster of PNES and PTSD symptomatology.

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Introduction

Despite the fact that ICD 10 and DSM 5^{1,2} recognize Post Traumatic Stress Disorder (PTSD) and Psychogenic Non-epileptic Seizure (PNES) as separate psychiatric disorders, they, in actuality, have many overarching similarities in aetiology and symptomatology. For example, a critical review found that PNES samples showed very high rates of trauma (44–100%) and abuse (23–77%), and a higher prevalence of PTSD than control groups.³ It eventually questioned the possibility that PNES may arise as a clinical expression of a hypothetical PTSD subtype.³ Treatment wise, trans-diagnoses psychotherapy proved to be effective for both disorders. A prolonged exposure therapy with discrete modifications was offered to 19 adult patients with a dual diagnosis of PNES and PTSD, which resulted in reduction in PNES frequency as well as improvement in PTSD symptoms.⁴ Additionally, the stress-related aetiological models have been increasingly challenged in PNES, as 10% or more of PNES patients have no history of exposure to psychological trauma.⁵ We do not have a clear answer to this clinical phenomenon.⁵ Thus the aim of this review is to answer an important question; why could the same stressful life events cause PTSD, PNES, or both in different individuals? The recent DSM-5 has theorized PTSD as trauma and stress-related disorder instead of being part of the anxiety disorders and positioned it before dissociative disorders. This is followed by somatic symptoms and related disorders, to highlight the closeness in between them.¹ Furthermore, DSM-5 necessitates explicit exposure to threat of death, serious injury, or sexual violence to diagnose PTSD. Likewise, ICD-10 considers extremely threatening life events as essential diagnostic criteria for PTSD, while points out that conversion disorders have a close relationship with psychological stresses and they occur within a context of insoluble social problems and marks the striking denials of such problems.^{1,2} Additionally, in regards their aetiology, studies showed that both PTSD and PNES could be caused by uncontrollable violent and terrifying life events, childhood sexual and physical abuse, psychogenic stresses, and socio-interpersonal stresses.^{6–8} While on the subject of the overlap in symptomatology, DSM-5 described dissociative symptoms in both PTSD and PNES and implement a dissociative subtype of PTSD.¹ Also, 22%–100% of patients with PNES fulfil the DSM-5 criteria for PTSD.³

This narrative review hypothesizes that variations in symptomatology could be the result of the appraisal of the same stressor differently by the memory sub-systems which could lead to different detrimental effects on the subsets of the neurobiological systems. It is widely accepted that there are multiple, anatomically and functionally distinct memory systems that support the brain computations and evaluations, which are required to respond to psychological stresses. The theory of conscious and unconscious memory subsystems was modified to a model which distinguishes different forms of memory by the type of neural computation they depend on.⁹ A complex multi-levels and parallel neurobiological memory system model has been proposed to explain the neurobiological mechanisms involved in threats and stresses responses. The described memory systems are functioning simultaneously on all levels and can

enhance or inhibit each other in a competitive or cooperative manner. It encompasses 2 major divisions, declarative and non-declarative memory systems.¹⁰ The non-declarative system includes four subtypes: (1) non-associative learning which operates through reflex pathways and is based in the midbrain; (2) procedural system which operates through a more complex automatic stereotyped habit like behaviours and is dependent on striatum; (3) conditioning memory system which is dependent on the amygdala and cerebellum; (4) lastly is more developed priming perceptual learning regulated by neocortex. The declarative memory system comprises semantic and episodic memory systems.¹⁰

The first tier of the above model is a fast instinct oriented system and its core neural substrate resides in midbrains structures like the hypothalamus and the periaqueductal grey matter (which can be divided into four structurally and functionally distinct neuronal columns; the dorsomedial, dorsolateral, lateral and ventrolateral aqueduct regions). It works immediately in response to imminent dangerous threat situations to produce: fight, flight and freezing behaviours.^{10,11} The quick, economic, habit-like automatic behavioural strategies represent the second level in the memory system and it is well known to be associated with the ventral and dorsal striatum. It is called the procedural stimulus-response (S-R) memory system and it is characterized by learning the association between a proximal cue/stimulus and a response.¹² The third tier stores information about swift conditioned behaviour and it is dominated by the amygdala which is generally known as a hub for emotional associative learning.^{13,14} Amygdala is widely recognized as a centralized hub for processing information that is critical for threat assessment. Anatomically, it is composed of numerous sub nuclei which are reciprocally connected with a wide swath of cortical and subcortical structures. The extended amygdala, the central nucleus of the amygdala (Ce) and the lateral bed nucleus of the stria terminalis directly influence the PAG to facilitate or inhibit the flight/fight and freeze responses. Fox et al. proposed that the central extended amygdala serves to link threat-related information with the appropriate behavioural and physiological outputs. He emphasized that the central extended amygdala, including the Ce, is thought to provide an interface between the basal regions of the amygdala and the downstream targets required to initiate physiological, behavioural, and emotional responses.^{13,14} In another word, the amygdala is the midway structure in evaluating threats joining the basic tier one and two with the more advanced tier four and five memory systems when the threat becomes closer and induces a mixture of fear and anxiety. The fourth tier will engage when there is an excess of different cues indicating more than one threat, with vague significances and changeable locations and characters. The orbitofrontal cortex is the coordinator for this system, and it integrates information from different sensory modalities to map the value of threats and assesses the rewards/punishments of actions.¹⁵ The declarative memory system is the fifth tier and it is a huge structure that involves monitoring environments and predicting threats even in their absence and in building cognitive maps of probabilities as well as watching complex threat cues simultaneously. The spatial memory system envisages the proximity and dynamics of threats

subsequently selecting important proximal ones to concentrate on and the semantic memory answers the question of (what if). This system encompasses the hippocampus, the frontal lobes, the insula, the cingulate, the premotor areas and their connections.^{10,15}

The process of valuation of a threat needs to retrieve all related and relevant information in all or part of this five tiers memory system. Neuroimaging studies, for example, showed physiological stress consistently activates insula, striatum, and the middle cingulate cortex (tier 2–4) while psychosocial stress consistently activates the right superior temporal gyrus (tier 5) with deactivation of the striatum (tier 2),^{15,16} This means physiological stress activates a basic motoric fight-or-flight reaction, while during psychosocial stress attention is shifted towards cognitive and emotional memory. It seems the proximity, the distance; the clearness and dangerousness of the threat determine which memory systems will engage in evaluation of the threat. Also, at each level, there is a threat specific neuro-circuit; for example, studies indicate that in animals social defeat and anti-predatory defence are mediated by distinct hypothalamic circuits.^{17,18} Putting all the above together, it is possible that the same stressful life events can generate different stress-related disorders as the stressor can stimulate different sets of brain memory subsystems depending on the meanings that the individual attaches to that event, or in other words, it depends on the cognitive-memory valuation that an individual assigns to stressors.

In PTSD and PNES, there has been a cumulative growth in neuroimaging studies which explore their possible neuro-anatomical based pathology. These techniques have provided valuable insight into the functional reorganization of network connections in these illnesses. The core of this narrative review is reliant on the findings of these studies and research on animals as they were the main sources available for a possible neuro-circuitry based biological abnormalities associated with these illnesses. However, we should consider the limitations of these techniques which could lead to potential pitfalls in interpretation. For example, these neuro-circuits changes might be caused by different pathological factors in addition to the psychological trauma. Yet it is advantageous to have a vision about the possible underlying dynamic of causativeness.

Neuroimaging studies:

1-Psychogenic Non-Epileptic Seizure (PNES)

Using Functional connectivity analysis on Resting state fMRI (rsfMRI), Van der Kruijs and colleagues reported that in comparison with healthy subjects, PNES patients showed stronger connectivity values between areas involved in emotion (insula), executive control (inferior frontal gyrus and parietal cortex) and movement (precentral sulcus), which were significantly associated with dissociation score.¹⁹

In another study, 21 patients with PNES, without psychiatric or neurologic comorbidities, and 27 healthy controls underwent resting-state functional MR imaging. PNES patients displayed an increased contribution of the orbitofrontal, insular and subcallosal cortex in the fronto-parietal network; the cingulate and insular cortex in the

executive control network; the cingulate gyrus, superior parietal lobe, pre- and postcentral gyri and supplementary motor cortex in the sensorimotor network; and the precuneus and (para-) cingulate gyri in the default-mode network.²⁰ However, these authors reported that their entire sample of 11 patients with PNES was free of any co-morbid psychopathology, which occurs in less than 5% of PNES populations.²¹

Furthermore, changes in brain functional connectivity in 18 patients with PNES and 20 healthy controls were investigated using functional connectivity density mapping (FCDM). It was found that patients with PNES showed abnormal FCD regions mainly in the frontal cortex, sensorimotor cortex, cingulate gyrus, insula and occipital cortex. They demonstrated bilateral differences in both long-range and short-range functional connectivity. Seed-voxel correlation analyses also showed disrupted functional connectivity between these regions. In addition, the occipital cortex FCD correlated with duration of disease. Three regions with increased long-range functional connectivity values correlated positively with illness duration, namely the right calcarine fissure, the left lingual gyrus, and the right lingual gyrus.²²

The functional connectivity (FC) of insular sub-regions in PNES was examined using the same data from the above study. Results showed a hyperlink pattern of insular sub-regions involved in abnormal emotion regulation, cognitive processes and motor function in PNES. Increased functional connectivity between the left ventral anterior insula and the left post-central gyrus and bilateral supplementary motor area (SMA) was reported. Both right dorsal Anterior Insula and Posterior Insula showed stronger functional connectivity values with the left superior parietal gyrus and left putamen in patients with PNES compared to healthy controls.²³

Analysis of the same data revealed that the PNES patients showed significantly increased fractional amplitude of low-frequency fluctuations (fALFF) mainly in the dorsolateral prefrontal cortex (DLPFC), parietal cortices, and motor areas, as well as decreased fALFF in the triangular inferior frontal gyrus. Also, PNES exhibited widespread inter-regional neural network deficits, including increased DLPFC, sensorimotor SMA, and limbic system and decreased ventrolateral prefrontal cortex indicating that changes in the regional cerebral function are related to remote inter-regional network deficits. Correlational analysis revealed that functional connectivity values between the Sensory Motor Area and the anterior cingulate cortex positively correlated with the frequency of PNES episodes.²⁴

Additionally, Perez and colleagues reported cingulo-insular volumetric alteration in functional neurological disorder in 18 women out of the twenty-three patients in their cohort (18 women, and 5 men, who were recruited from an integrated behavioural neurology-neuropsychiatry FND Clinic at the Massachusetts General Hospital). All patients met diagnostic criteria for at least one FND subtype including clinically-established Functional Movement Disorders documented or clinically-established non-epileptic seizures and/or exhibited positive examination findings for functional weakness. Specifically, their study showed significant associations between functional neurological symptoms and reduced left anterior insular grey matter volume. Similarly, a higher magnitude of experienced childhood abuse

was associated with decreased left anterior insular volume. However, there were no statistically significant associations between functional neurological symptoms, childhood abuse and left anterior insular volume in the mixed-gender FND cohort (controlling variables for age and gender).²⁵

Finally, a recent comprehensive review which examined the available PNES neuroimaging data, acknowledged that overall fMRI findings suggested altered functional connectivity within network regions involved in executive cognitive functions, which may notably be involved in generating and maintaining PNES. Comparably, MRI findings pointed to hemispheric asymmetry, and areas involved were right motor and premotor cortex, the uncinate fasciculus, insula, precentral and orbitofrontal regions. The study established that macroscopic abnormalities present in patients with PNES are multifocal, and are network based. However, it concluded that overall the quality of studies specific to PNES is low with small samples and variation in methodologies. It recommended conducting large studies that specifically controlled neuropsychiatric comorbidities, with a comparison to patients with epilepsy, to better delineate the network abnormalities.²¹

The limitations to the existing knowledge provided by these studies are also considered in this section. Many of the neuroimaging studies that have been conducted so far in PNES assumed they were studying homogenized group avoiding the critical question about the problem of comorbidity. A systemic review concluded that, although, all of the MRI and fMRI studies in PNES support the view that structural and functional brain changes may be present in patients with PNES, these results may be incidental and related to a third factor.²⁶ However, despite the inconclusive results of these neuroimaging studies in PNES,²⁶ the above findings suggest that PNES patients exhibit functional alterations in brain networks mediating emotion regulation and awareness (Anterior Cingulate Cortex, Orbito-Frontal Cortex, and Insula), executive/cognitive control (Inferior Frontal Gyrus, and ACC), attention (Posterior Parietal Cortex), self-referential processing (Default Mode Network, particularly the precuneus), and motor (SMA, Precentral Gyrus, Cerebellum) functions. In summation, it seems resting-state neuroimaging studies which have been conducted in PNES suggested disturbed activations of tier 5–4 of the memory systems.

2-Post-Traumatic Stress Disorder

A large-scale neuroimaging consortium study on PTSD conducted by the Psychiatric Genomics Consortium, which included data from 1868 subjects (794 PTSD patients), contributed by 16 cohorts, that showed significantly smaller hippocampi in subjects with PTSD compared with trauma-exposed control subjects.²⁷ Furthermore, smaller amygdalae were found in the meta-analysis but not to a significance level after counteracting the problem of multiple comparisons.²⁷ The study used T1-weighted magnetic resonance imaging scans to assess the volumes of eight subcortical structures (Nucleus Accumbens, Amygdala, Caudate, Hippocampus, Pallidum, Putamen, Thalamus, and Lateral Ventricle). Additionally, a meta-analysis of grey matter alterations in PTSD which explored volumetric

differences of three key structural brain regions (Hippocampus, Amygdala and Anterior Cingulate Cortex), showed: significant volume reduction bilaterally in the ACC; Hippocampal volume reduction mostly on the left side; and medium-size reduction in the bilateral amygdala in subjects with PTSD, when compared with findings in healthy controls. However, no significant differences in amygdala volume between PTSD subjects and trauma-exposed controls were found. The meta-analysis noted a problem with the homogeneity of the PTSD subjects across the selected studies.²⁸ A more recent meta-analysis and systemic review that looked into the structural white matter changes reached a comparable conclusion. It did suggest that changes in white matter microstructure which is associated with changes in brain circuits related to the higher level of working memory and the contextual processing of the environment.²⁹

In one functional neuroimaging study of PTSD that used either a non-trauma or trauma-exposed comparison control group in a meta-analysis, supported the notion that hyperactive amygdala and hypoactive medial prefrontal regions.³⁰ Another meta-analysis of resting-state functional neuroimaging studies of PTSD showed hyperactivity in the right anterior insula and bilateral cerebellum, and hypoactivity in the dorsal medial prefrontal cortex (mPFC). Moreover, compared with trauma-exposed control (TEC), PTSD showed hyperactivity in the ventral PFC. The pooled meta-analysis showed hypo-activity in the posterior insula, superior temporal, and Heschl's gyrus in PTSD.³¹

In 2016, DiGangi et al.'s findings concluded that the effect of a compact trauma on default mode network connectivity was evident in a veteran with or without PTSD, while it was absent in normal control. The effect of the trauma also included weaker connectivity within a network involving the precuneus, medial prefrontal cortex (mPFC) and right superior parietal lobule. The findings suggest that the experience of trauma, rather than the pathology of PTSD, may be related to (DMN) changes.³² In addition to this, in a trial to analyze brain networks connectivity between the central executive network (CEN), default mode network (DMN), and salience network (SN) in subjects with PTSD after an exposure to a single prolonged trauma (i.e. coal mining flood disaster) using Arterial Spin Labelling (ASL), a comparison was made with subjects without PTSD but had the same exposure to the trauma. Decreased connectivity was identified in the left middle frontal gyrus of (CEN), left precuneus and bilateral superior frontal gyrus of (DMN), and right anterior insula of (SN) in subjects with PTSD. The decreased connectivity in the left middle frontal gyrus of (CEN) was associated with clinical severity. The study suggested that decreased triple network connectivity is a possible cause for the cognitive dysfunction of this type of PTSD.³³

In another tactic, functional connectivity within the (DMN, CEN, and SN), as well as functional and effective connectivity between these resting-state networks, were examined with independent component analysis (ICA) and compared between 27 patients with typhoon-related PTSD, 33 trauma-exposed controls (TEC), and 30 healthy controls (HC), by conducting an analysis of variance. The PTSD group showed decreased functional connectivity in the supplementary motor area within the (SN) relative to both control groups. Moreover, PTSD patients showed increased excitatory influence from the (CEN) to the (DMN) compared

with both control groups.³⁴ Moving away from the seed-based fMRI connectivity analysis, which requires defining seed locations prior to the tests, a connectome-wide association approach was used to analyze resting-state functional connectivity for war veterans with and without PTSD compared to non-trauma-exposed healthy controls. The analysis revealed that PTSD patients had hypoconnectivity between the left lateral prefrontal regions and the salience network regions as well as hypoconnectivity between the parahippocampal gyrus and the visual cortex areas. Connectivity between the ventromedial prefrontal cortex and the middle frontal gyrus and between the parahippocampal gyrus and the anterior insula were negatively correlated with PTSD symptom severity. The decreased connectivity between the parahippocampal gyrus and visual cortex supported the dual representation theory of PTSD, which suggests a dissociation between sensory and contextual memory representations in PTSD.³⁵ In computability with the above, Periaqueductal Grey (PAG) sub-regions resting-state functional connectivity in three groups of people: PTSD patients without the dissociative subtype; PTSD patients with the dissociative subtype; and healthy controls, showed that all PTSD patients demonstrated DL-PAG functional connectivity with areas associated with initiation of active coping strategies and hyperarousal. Only dissociative PTSD patients exhibited greater VL-PAG functional connectivity with brain regions linked to passive coping strategies and increased levels of depersonalization.³⁶ Collectively the aforementioned findings are pointing to hyper-responsive tier 1–3 memory systems which are associated more with evaluation of basic needs and physical threats, with hypoactive 4–5 memory systems which are associated with appraisal of social and contextual challenges.

Animal models

Recent research on stress responses in animals including micro-dialysis of neurotransmitters in the brain after exposure of rats to stresses resulted in evidence that pointed to the involvement of tier one, two and three of the memory system to produce hard-wired repertoires of behaviours when danger is perceived as very close, uncontrollable, and unavoidable. Initially, active coping strategies will be initiated which involve confronting the source of threat or avoiding it, then a passive coping strategy, freezing behaviour, will follow if it is not possible to escape or overcome the threat.³⁷ This process is a complex and involves producing instrumental and habitual behaviours by the dorsal and ventral striatum (tier 2) guided by orchestrated activities of different cell groups in the ventral tegmental area (tier 1) which have different functions despite secreting the same, neurotransmitters.³⁷ When rodents were exposed to a series of inescapable foot shocks a stressful experience, they demonstrated: an increase of DA release in the Nucleus Accumbens Septi (NAS) if they have control over the shock experience, and a decrease of DA release in this brain area if they are not allowed to exert any control.³⁸ Dopamine secreting cells in the midbrain consist of a distinct group of cells located within discrete sub-regions of the ventral tegmental area (VTA). The heterogeneous structure of the VTA orchestrates the response of rewards or aversions. These

groups project to the brain in a non-overlapping mediolateral topography. Ikemoto described separated projections from the dopamine-rich cells in the VTA to corresponding zones of the accumbens core and medial shell. These neurons project to other brain areas like the prefrontal cortex also.^{39,40} Stresses and threats increase activity in particular groups of ventrally located dopamine cells in the VTA that projects to the NA, Amygdala, and mdPFC while inhibiting dopamine cells associated with reward in VTA. This activity facilitates the release of a subcortical accumbens related innate defence behaviours (fight or flight) or triggers a passive innate defence behaviour (freezing). The converging results in research document anatomical and temporal fluctuations in the level of dopamine secretion from the VTA associated specifically with the appraisal of whether a threat is escapable or not which determines the release of a specific innate defence behaviour.³⁷ In a trial on rats, it was found that behavioural changes resembling PTSD traits induced by an intense electrical foot shock can be ameliorated by a bilateral inactivation of the VTA dopamine by administering dopamine antagonist immediately before the traumatic event.⁴¹

The aforementioned descriptions for stress responses mean that tier one and two systems will take the lead in the response to a threat when the ventral subiculum (which represents an interface between the hippocampus proper and key cortical and subcortical structures and a key centre for analysis of threats contexts) as well as the mdPFC and the infralimbic cortex perceive a close and inevitable danger and trigger a safety behaviour by regulating the firing of the dopamine neurons in the ventral tegmental area, nucleus accumbens, and ventral Pallidum-VTA pathway. The hippocampus and the dorsal striatum memory systems operate in parallel to guide a spatial navigation goal-directed behaviour or cues directed behaviour respectively depending on the closeness of the target. However, when the threat becomes so close, the hippocampus will give the lead to the dorsal striatum memory system as the target is immediate, near and inescapable. The amygdaloid complex plays a pivotal role in conditional fear memory which scans the environment for stimuli that predict or are potential dangers and represent an intermediate stage between the hippocampal and the striatal memory systems.^{39,42–44} Furthermore, an over-modulation mediated by hyperactive midline prefrontal lobe inhibition to the limbic structures was proposed to explain the dissociative type of PTSD.⁴⁵

Discussion

The neurophysiology of adverse life events on the aetiology of PTSD and PNES remains a major question in psychiatry and neurology. This narrative review was a trial to conceptualize the effect of the psychological trauma in relation to partially independent hierarchical systems that decodes threats through consecutive levels of memory subsystems and contextualizing this effect in a disorder-specific manner. Different threats operate distinct brain circuits and pursue separate computational processes. Hopefully, this will facilitate the prediction, prevention, and management of those illnesses.

Yet, it is important to acknowledge and discuss that both PTSD and PNES have some similarities in symptomatology and comorbidity. In fact, some authors conceptualized PNES as manifestations of PTSD as both have intrusive symptomatology and dissociative experiences spread over the clinical features of PTSD and PNES.^{46–48} To explain this overlap, we might conceive that the five-tier memory system is based on multisensory convergence and previously encoded information towards the executive cognitive processing at the top of the hierarchy.⁴⁹ Nevertheless, within this hierarchy, there are anatomical loci and brain network hubs which are sub-specialized in analysis and evaluation of certain aspects of threats.⁵⁰ For examples, the basolateral amygdala is associated with anxiety and it distinguishes emotionally significant events via interactions with multiple perceptual association cortices, limbic-paralimbic affective systems, frontoparietal attentional network, and medial prefrontal cortex. While the central amygdala, in contrast, is essential for fear and freezing behaviours, through projections to the brainstem, cerebellum and sensorimotor system.⁵¹ Also, a social threat in shy people recruits a right dorsal anterior cingulate cortex (dACC) network encompassing nodes of the frontoparietal network.⁵² Another example for sub-regional specialization: specific anterior cingulate cortex (ACC) subregions are involved in social threat evaluation anterior midcingulate cortex (amCC), pregenual (pgACC) and subgenual (sgACC),⁵³ while the dorsal anterior cingulate and dorsal medial prefrontal cortex work together to evaluate aversive threats.⁵⁴ Moreover, we already know that distinct Insula sub-regions connections with the amygdala vary in-between PTSD – DS and PTSD + DS. PTSD – DS is characterized by failed cortical inhibition of the amygdala and limbic system.⁵⁵

Therefore studies suggest distinct resting-state functional connectivity among hippocampal sub-regions when investigating PTSD pathophysiology.⁵⁶ Which could be due to hippocampus subfield specialization in detecting different environmental patterns.⁵⁷ In a cross-sectional study that examined the relationship between PTSD symptomatology and structural shape of the hippocampus and amygdala using vertex-wise shape analysis in a group of combat-exposed US Veterans, results provided evidence of localized abnormalities in the anterior hippocampus and centromedial amygdala.

Stepwise regression suggested that among PTSD symptom clusters, arousal symptoms explain most of the variance in the hippocampal abnormalities, whereas re-experiencing symptoms explains most of the variances in the amygdala abnormalities.⁵⁸ This anatomical gradient and sub-specialization is a core concept in some models explaining the pathophysiology of PTSD, for example, distinct anatomical regions of the frontal lobe, the ACC, and the amygdala were conceived as part of the faulty contextual memory processing in PTSD.^{59,60}

In summary, inferences can be made that the effect of a psychogenic trauma or the cumulative effects of multi psychogenic traumas on the memories neuronal circuitry subsystems will differ according to the way the brain evaluates the trauma and that will determine the cluster of symptoms a patient will present. This review shows that there is evidence available suggesting adverse life events could result in different symptomatology according to their effect on certain neuro-circuits. This archetypal

model might prompt further research to understand not only the possible causation but also common comorbidities, shared symptomatology between these illnesses and farther. Accordingly, fMRI data analysis methods are needed that map patterns of neural activity. Multi-voxel pattern analysis is required more in the field of studying adverse life events in their emotional and cognitive meanings to discern the functional networks associated with trauma-related mental health problems.^{61–63} Ultimately, categorizing specific neuro-circuits will lead to identifying psychological factors associated with the aetiology of stress-related illness, and will pave the way to empower clinicians to develop and implement more effective psychological approaches for prevention and treatment. In anticipation, this model can improve communicating the diagnosis of PNES and PTSD to patients, assuaging PNES patient's scepticism about the frequently reported absence of temporal relationship between the trauma and the illness, cognizing the puzzling diversity of PTSD presentations, and understanding psychogenesis by relating symptomatology to certain brain circuits. Psychoeducation is extremely important and proper education for clients and their families will help minimize the stigma that is often associated with this condition.^{64–67} This model also provides an explanation for the comorbidity between PTSD and PNES, and the promising therapeutic effectiveness of certain types of cognitive behaviour therapies (CBT) cross PNES and PTSD.^{4,68,69} Furthermore, the general CBT model does not offer explanation of why PTSD & PNES patients have abnormal emotions processing or why they have memory and cognitive deficits, which ultimately would limit the CBT effectiveness.^{70–76} The anatomical functionality of hyperactive tier 4–5 memory subsystems in PNES patients could provide explanations to their intense emotional experiences, self-depreciation and bottling of their emotions.^{76–80,69,81} It also could open the horizon to extend the concept of emotional abnormality in PNES beyond anxiety; that is to include abnormalities in social emotions.⁸² Whereas the anatomical functionality of hypoactive tier 4–5 memory subsystems in PTSD explicated the deficit in regulation of their emotions.⁸³ Such a hypothetical approach can empower research and applications of psychotherapeutic interventions that focus on disturbed affect regulation and aim to enhance emotional awareness. This memory model also provides a base to validate the implementation of the Meta cognitive and the Meta memory models in the treatment of PTSD and PNES,^{84,85} reflecting the close link between emotions, memories, and cognitions.^{86,87}

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None.

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