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Comorbidity between somatic symptom disorder and dissociative amnesia is best explained by trauma-amnesia-pain theory

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Abstract

Dissociative amnesia is comorbid with somatic symptom disorder (SSD), yet this link is not well-understood. Clinical studies indicate that childhood trauma, especially sexual abuse and emotional abuse, are primary causal factors in the etiology of SSD. This paper provides evidence that dissociative amnesia is an explanatory variable between childhood trauma and SSD. As many or more trauma victims develop amnesia and somatic complaints as those who develop post-traumatic stress disorder (PTSD), but SSD and dissociative amnesia receive much less attention. This leaves clinicians and patients without effective intervention and sometimes causes misdiagnosis. PTSD's neuroendocrinological cascade, from peritraumatic perception to psychobehavioral endpoints is well-mapped, and it informs an opponent-process for dissociative amnesia and SSD, allowing a better conceptualization of a primary cause of SSD – trauma. The novel trauma-amnesia-pain (T-A-P) neuroendocrinological map presented here is a mirror process of the tonic immobility-PTSD pathway initiated by the hypothalamus-pituitary-adrenal (HPA) axis. Dissociative amnesia-SSD develops through the same HPA axis pathway, with PTSD essentially being a downregulated cortisol response and T-A-P an upregulated cortisol response. Copious evidence has now emerged from neurological, physiological, and clinical studies of animals and people regarding the role controllable stress/trauma plays in the etiology of both amnesia and analgesia. T-A-P also validates the decision to consolidate pain disorder, somatization disorder, and functional somatic disorder under one nosological category in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision. The implications of this theory are important for both prevention and effective intervention with trauma-induced SSD.

Keywords: Traumatic amnesia; Pain disorder; Functional somatic disorders; Somatic symptom disorder; Cortisol; Peritraumatic perception

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1. Introduction

Three primary causes of somatic symptom disorder (SSD) are reported in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR). The first is biological and the last two are environmental: increased pain sensitivity, caregiver/social-cultural conditioning and reinforcement of the sick role and somatic-only expressions of suffering, and early traumatic experiences.[1] This paper focuses on

the third, because recent research has identified childhood trauma, especially emotional abuse and sexual abuse, as explaining one-quarter of the variance in somatic symptoms and levels of daily physical discomfort in a large national sample of adults.[2] Furthermore, Eilers *et al.*[2] showed a moderate size effect (d = 0.30) of childhood trauma on later somatic symptoms, after controlling for gender, age, education level, and relationship status. Trauma specifically, not more general "early adversity," is a key variable in the etiology of SSD, but the neurodevelopmental mechanisms linking the effects of childhood trauma to long-term somatic complaints have not been well understood. Trauma-amnesia-pain (T-A-P) theory is presented as a novel conceptualization of the neuroendocrinological cascade that maps how trauma explains the comorbidity of dissociative amnesia and SSD. Clinicians need to understand the critical link for many patients between dissociative amnesia and SSD because treatment may not progress well without acknowledgment of trauma experiences, or trauma-informed intervention. It is difficult to address trauma history given the possibility of a patient's dissociative amnesia for trauma, but implications and intervention options are offered at the end of the paper.

In the DSM-5-TR under comorbidities of SSD, dissociative amnesia is not listed, but post-traumatic stress disorder (PTSD) is listed. Somewhat confusingly, in the DSM-5-TR under comorbidities of dissociative amnesia, SSD is listed.[1,p. 344] It could be an oversight to not have listed the comorbidities in both places, or it could be an indication that dissociative amnesia is presumed to be primary and casual of SSD, a secondary effect. The T-A-P model will address the primary nature of amnesia and the secondary effect of somatic symptoms, such as pain.

To diagnose SSD, at least one somatic symptom must be significantly disruptive or distressing to the sufferer, and the time, thoughts, or anxiety the sufferer spends dealing with the symptom(s) is abnormally high. Many sufferers have multiple somatic symptoms, such as neurological paralysis, numbness, tingling, and burning, but pain is most common.[3,4] Pain disorder, somatization disorder, and functional somatic disorder (FSD) are considered dimensions of SSD in the DSM-5-TR.[5,6] Sometimes the somatic symptom is medically unexplained, but excessive focus on determining whether symptoms are "psychogenic only" in earlier versions of the DSM led to the current recognition that the mind-body connection cannot and should not be dissected when diagnosing SSD.[1]

Van der Kolk[7] posited a triune trauma outcome based on his decades of case studies and experimental findings but admitted the underlying mechanisms contributing to each of the three trauma outcomes remained unknown. He argued that trauma led to either traumatic amnesia, resolution, or PTSD,[7] depending on the victim's peritraumatic perception. Importantly, he identified the connection between PTSD and analgesia. To explore whether there is also a connection between dissociative amnesia and SSD, this paper begins with the traumatic amnesia neurochemical literature, addresses the PTSD neurochemical literature, and ends with the clinical memory and somatization literature. Very quickly after sensory organs and the thalamus detect life-threatening situations, emotion, and memory systems are engaged, along with their relevant neurotransmitters.[8,9] Cortisol, acetylcholine (ACh), glutamate, adrenomedullin, and enzyme acetylcholinesterase will factor large in the model. Olff, Langeland, and Gersons' stress-coping model for PTSD informs one-half of T-A-P theory.[10]

The T-A-P pathway has five phases: Peritraumatic perception; trauma memory processing; sympathetic nervous system (SNS) response; acute somatic symptoms; and chronic somatic symptoms. After the groundwork is laid for the definition, prevalence, and clinical presentation of traumatic amnesia, each phase of the T-A-P pathway will be explained separately. Diagrams are provided that collectively distinguish and compare the triune trauma outcomes: traumatic amnesia/SSD, which is the focus of this research; PTSD/analgesia, which is the opponent process of T-A-P; and trauma integration/resolution, which is the non-clinical healthy resolution of trauma. It is important to note that although the cascade is robust in animal and human models for hours and days following trauma, the final phase of chronic psychobehavioral outcomes, such as dissociative amnesia, SSD, and PTSD can be altered by age, therapeutic intervention, social support, and cognitive reappraisal in the months following the trauma.[8,10,11]

2. Traumatic amnesia

Perhaps one reason traumatic amnesia has received little discussion in the literature in comparison to PTSD is because its behavioral consequences were generally unknown. If people cannot remember the trauma they experienced, why would they seek therapy? Large clinical populations were lacking. Furthermore, controversy swirled around how traumatic amnesia was defined and whether amnesia was an appropriate term for a condition in which trauma victims were unable to encode or consolidate key declarative memories of a trauma since the term amnesia often implies forgetting.[12] Nevertheless, most experts have settled on the term traumatic amnesia if it is defined as an absence of declarative memory, for one or more traumatic incidents, due to failure to encode or consolidate long-term memory at, or soon after, the time of

the trauma.[13-15] Given this definition, "recovering" trauma memories is impossible since they were never encoded. Importantly, this definition of traumatic amnesia does not assume that separate memory systems, such as procedural and emotional memory systems, have also failed. There is further confusion over the name dissociative amnesia because some research shows dissociation is a key determinant in PTSD etiology—PTSD's intrusive remembering being the opposite of amnesia. In the descriptions of dissociation for people with PTSD, it is an appraisal of "numbness" during and after the trauma, associated with the freeze response.[5] Yet the research below shows that dissociative amnesia is not caused by numbing/freezing, but instead by a very active response to the trauma: Fight or flight. The high cortisol generated to drive this high initial activity leads to memory blockade, and that leads to amnesia, not numbing. Dissociative amnesia falls in the DSM-5-TR category of dissociative disorders, linked by the amnesia and separation of memory systems common in dissociative identity disorder—leading to its name dissociative amnesia. However, the definition of dissociation—body separated from mind, or mind separated from present reality—is not salient in the initial creation of the disorder. The single diagnostic criteria in the DSM-5-TR for dissociative amnesia refers to amnesia for (inability to recall) autobiographical events (declarative memory) that are usually traumatic in nature. There is no symptom referring to unreality, depersonalization, or numbing of emotion or sensation. To reduce confusion, "traumatic amnesia" will be used in this review as a more general condition that encompasses dissociative amnesia.

It is helpful here also to briefly review the divergent natures and anatomy of declarative and procedural memory systems. Due to various factors, one can be impeded during encoding while the other remains intact.[16-21] Although partial impairment of recall for some aspects of trauma, and/or dissociation, and feelings of the "unreal" quality of trauma are fairly common in PTSD, PTSD sufferers are aware that they experienced a trauma, and can name it, as well as many aspects of what happened to them – when, where, and so on. In their comprehensive review, Bovin and Marx concluded that memory for trauma is stable over the course of PTSD.[8] In contrast, traumatic amnesia spares victims from intrusive, upsetting declarative memories, but preserves emotional and somatosensory memories. What at first appearance is a reprieve from the memory of a traumatic experience becomes an intrusive and painful re-living of the trauma in the form of somatic complaints.

3. Prevalence

The DSM-5-TR struggles to present a reliable prevalence rate for dissociative amnesia, listing it at 1.2%, due again, to a lack of large clinical samples.[1] We can determine prevalence rates for traumatic amnesia from population studies and unique prospective designs of documented trauma survivors, such as substantiated child sexual abuse victims or car accident victims. Six studies have been identified that share a compellingly similar prevalence rate. Three of the six reported 19% of victims, and three reported 36% of victims have no memory of the trauma event(s), immediately after a documented traumatic experience, and many of those have no memory of the trauma even months or years later.[22-28] The bimodal result seems to relate to the type of trauma; the three studies that contacted child sexual abuse victims years later found higher amnestic rates than the three studies that contacted medical/health crisis trauma victims or general population members about any kind of trauma and associated amnesia experienced. Young age and relationship to the perpetrator (betrayal trauma) affect memory.[29,30]

Traumatic amnesia is a more likely outcome of trauma exposure, yet is much less studied than PTSD. PTSD's prevalence rate is between 8% and 9%.[1,31] Has there been an assumption that what you can't remember can't hurt you? Sadly, the T-A-P theory indicates that what you can't remember does just that—it hurts you. Because of the difficulty in substantiating trauma history with many amnestic victims, if they seek any help at all, their symptoms can seem a mystery to themselves, their families, and their health providers. In the worst-case scenario, they may be labeled malingerers or hypochondriacs. In contrast, people with PTSD symptoms are more likely to be believed and treated. Van der Kolk sensitively describes how victims use fragments of recollection, external corroboration, and fuzzy intuitions to confirm that they experienced trauma.[7] They piece together the meaning behind their mental or physical dysfunction, having to trust emotional and body memory only. That delicate process has led to dead ends for some, reconstructed, potentially false memories for others, and denial for yet more (Alpert *et al.*,[29] Fredrickson,[30] Freyd,[32] and Herman[33] for discussions of how traumatic amnesia was often mischaracterized and mishandled as "repressed memory"). Traumatic amnesia complicates the detection, diagnosis, and treatment of trauma-related symptoms. However, patient progress is possible when information retained by emotional and procedural memory systems is included in clinical formulations, as somatic psychotherapists recommend.

4. Peritraumatic perception

Peritraumatic perception initiates divergent hypothalamus-pituitary-adrenal (HPA) axis responses to trauma.[34,35] Since Foa first suggested that perception of an event's potential threat might be more determinant of its impact on PTSD

than the event's manifest danger, it took over 10 years for laboratory results to prove her postulation.[9] Perception of trauma as either controllable or uncontrollable affects the HPA axis response to trauma. This review focuses on the consequences of peritraumatic perception of *control/escapability*, as opposed to peritraumatic perception of *inescapability*, or tonic immobility. For extensive coverage of the etiology of PTSD and perceived inescapability/tonic immobility (Bovin *et al*., Hagenaars and Putman, Lima *et al*., Marx *et al*., Olff *et al*., Rocha-Rego *et al*., and Volchan *et al*.[3,34-39]).

5. Defense cascade: Fight, flight, or freeze?

The defense cascade refers to a common series of physiological and behavioral events triggered by danger or perceived threat in animals and humans. Animals move through the cascade in a predictable fashion, from attentive stillness (hyperalert assessment) to fight, to flight, to freeze, depending on their species (*e.g.*, some animals are suited to fight more than flight).[38,39] Freeze, or in its extreme form, tonic immobility, is characterized by gross motor inhibition, a fixed stare, suppressed vocalization, lower body temperature, and even temporary paralysis. It is a last resort for the animal; "playing dead" is an attempt at self-preservation when no other escape seems possible.[9] In humans, as early as 1989, van der Kolk, Greenberg, Orr and Pitman hypothesized that the freeze response led to PTSD symptoms.[40] Others followed, documenting similarities between tonic immobility and symptoms observed in patients with dissociation, including some who were diagnosed with PTSD.[41] The peritraumatic dissociative experiences questionnaire was developed, with derealization and dissociation predicting PTSD symptoms.[42,43] Derealization is concerned with the perception of trauma, and dissociation is connected to a freeze response.

In humans, as dissociation increases, cortisol secretion decreases.[44] Forebrain areas engage if critical processing of the threatening situation occurs, which is a slower brain activity, whereas midbrain areas engage if immediate panic or tonic immobility occurs, which is a faster cortical reaction.[10,45] The assessment of how serious or imminent a danger or encroaching threat is, causes one cortical area to fire faster than another, determining the amount and type of neurochemicals that circulate. In the case of an inescapable threat, initial attentive stillness is followed immediately by tonic immobility, whereas when a threat is perceived as potentially escapable, an attempt to bargain, fight, or flee occurs.[9,10] The key neuroendocrinological player relevant to both these reactions is cortisol. For decades, we have known that cortisol secretion has dose-dependent, clinically relevant, differential effects on memory impairment. Newer research indicates that it also triggers nervous system effects related to pain perception and dysregulation of the parasympathetic nervous system (PNS).

6. Cortisol's central role in trauma outcomes

6.1. Memory

Perception of control is a determining factor in whether amnesia develops, or indelible memory of trauma develops, in both animal and human studies. In a seminal work by Drugan on rats exposed to trauma/stress, simply by varying 'controllability', he and his colleagues succeeded in inducing either long-term traumatic amnesia, or contrarily, tonic immobility and depression/PTSD. He defined controllable stress as "the subject is allowed to make an active behavioral response to alter the pattern, onset, duration, or intensity of stress".[46,p.246] In the escapable stress paradigm, the rats had subsequent amnesia for the experience. Postmortem, Drugan found elevated levels of corticosterone (rat cortisol) binding with nicotinic acetylcholine receptors (nAChRs) in the hippocampus, and elevated gamma-aminobutyric acid (GABA) in the amnestic rats. He concluded that a hypercorticosterone condition was created by the escapable stress paradigm, and either cortisol or GABA was responsible for the rats' traumatic amnesia.[46]

Perceiving trauma as controllable or escapable tends to have a protective amnestic effect on the mental health of people and animals, and may, in some cases, be useful for survival and species success. Moderate to high amounts of cortisol are also useful to an organism preparing for fight or flight because cortisol helps mobilize energy resources, increases cardiac activity, primes muscles for action, and potentiates the startle response.[10,47-49] However, because nearly every neurotransmitter system is affected by exposure to prolonged stress, escapable or otherwise, negative consequences are high as well.

Compelling prospective evidence in human's shows, like rats, our freeze/inescapable stress response leads to PTSD, whereas our fight/flight/escapable stress response leads to either amnesia or no PTSD[50] For example, many people who qualify for acute stress disorder in the early days following a trauma no longer meet symptom criteria after 30 days. They have resolved the trauma in some manner, and this is linked to moderate cortisol levels. Research on car accident victims is demonstrative. Delahanty found among 134 motor vehicle accident victims and 43 minor injury controls, the group who felt responsible for their vehicle crashes (peritraumatic perception of control) had significantly fewer or no PTSD symptoms, three and

6 months after trauma, compared to the accident victims who felt no control over the accident (because someone else was to blame). Delahanty's team realized they should follow up with victims of motor vehicle accidents who had amnesia for an accident (21 of 99) but had been initially excluded from the research. Those victims' urinary catecholamines (epinephrine, norepinephrine, dopamine) and cortisol levels were tested immediately after arrival to the hospital and 15 h later. Their cortisol levels were extremely high. Cortisol was the only neurochemical that significantly differentiated between motor vehicle accident victims who reported intrusive memory, and 1 month later, PTSD symptoms, and motor vehicle accident victims who had no intrusive memory or PTSD.[51]

We can now pinpoint exactly how long-term memories are consolidated or interrupted in humans. High levels of cortisol are associated with declarative memory impairment.[10,15,18,52] When there have been conflicting results about levels of cortisol and PTSD versus traumatic amnesia, it was due to comparison across studies that measured cortisol at the onset of the disorder versus cortisol levels over the duration of the disorder. T-A-P theory is concerned with cortisol levels at initiation, as opposed to maintenance during the course of traumatic amnesia or PTSD. Conflicting results are also born of measurement inconsistencies. A number of researchers have commented that salivary levels in one study have been compared to plasma or urinary levels in another study, or basal levels at different times of day have been compared, yet failed to take into account circadian rhythm effects.[51,53-56]

Below is a summary of the specific amounts of cortisol that affect memory. The lowest levels, between 9 and 120 mg, induce intrusive memory and PTSD; moderate levels, between 140 and 450 mg, stabilize the HPA axis and lead to normal memory and functioning; high levels of cortisol, between 450 and 650mg, create amnesia. The effects of cortisol can be reversed or increased within a few hours if a patient receives agonist or antagonist therapy. For example, in three human studies, administration of 25 mg of hydrocortisone (exogenous cortisol) immediately post-trauma decreased memory for trauma and prevented PTSD, but was not sufficient to induce traumatic amnesia.[56-58] In rats, plasma corticosterone levels are 400% higher after inescapable stress compared to controls (637.5 ± 99.8 ng/mL vs. 176.6 ± 50.6 ng/mL).[59] Furthermore, in accident victims with PTSD symptoms, 15 h after trauma, the average of their urinary cortisol level was 131 mg. The urinary cortisol level in accident victims without PTSD symptoms averaged 443 mg at 15 h after trauma.[51] Wahbeh and Oken [60] also found long-term lower cortisol in veterans with PTSD than in veterans without PTSD.

Although there is only one study directly controlling cortisol's role in the T-A-P pathway, Zohar *et al.*[61] successfully prevented PTSD in hospitalized trauma victims by administering a high dose of hydrocortisone immediately post-trauma. In their double-blind randomized controlled trial, they were able to facilitate a return to HPA axis homeostasis in both human and animal models and increase or facilitate normal hippocampal dendritic growth in animals. Their groundbreaking finding was that a 1-time, 100 – 140 mg weight-dependent dose of hydrocortisone administered within 6 h of trauma prevented PTSD symptoms and indelible, intrusive memory.

The inverted U-shaped relationship cortisol has with memory has been widely reported.[15,18,62-64] At very low and very high levels, cortisol is problematic in the hippocampus. At moderate levels, cortisol does not overly impede or facilitate memory. Yet, many studies have not measured cortisol in a systematic way or accounted for its nonlinear relationship. This may explain why some authors' findings conflict. Future studies of human models should report milligrams per volume unit of urine for cross-comparison. Furthermore, precise measurement of urinary cortisol levels of amnestic trauma victims needs to be included in future studies, so that exact dose ranges within which cortisol alters memory, such as the suggested guidelines above, can be confirmed.

6.2. Pain

The initiation and maintenance of pain in the body is a complex process that involves an interplay of both the SNS and PNS, simply put, tends to involve activation of the SNS first (which turns "on" the pain response), and then an activation of the PNS (which turns "off" the pain response), returning the system to allostasis. In actuality, the process involves many different neurotransmitters and the potentiation or depotentiation of both neuronal brain cells and afferent and efferent neurons in the spine and body.[47,65] Many of the neurotransmitters, receptors, and anatomical areas of the brain involved in pain perception are also involved in the body's response to trauma, particularly regarding the actions of the HPA axis and catecholamines. Catecholamines trigger cortisol production and release.[66,67]

Early PTSD researchers proposed that the freeze or tonic immobility response associated with PTSD involved sustained analgesia, an analgesia more potent and longer-lasting than stress-induced analgesia (SIA) usually seen in animals. SIA involves attentive stillness/immobility early in the defense cascade. Animal research overwhelmingly supported both a hypocortisol-analgesia connection and a hypercortisol-pain connection. In the only studies that refuted the hypercortisol-pain connection, SIA was

examined, rather than the longer-term tonic immobility-related analgesia.[67-71] Sometimes important differences in the intensity and duration of SIA, varying in response to escapability/inescapability, were not measured. For example, Pinto-Ribeiro *et al.*[69,70] reported long-term analgesia in rats exposed to chronic inescapable stress but may have mistakenly interpreted the effect as due to hypercorticosteronism. What is termed "elevated" or "high" glucocorticoid can vary depending on the study. Pinto-Ribeiro *et al.* exogenously administered 40 mg of corticosterone to rats in the 2009 study,[70] presumably to match the levels her team noted in the plasma of rats subjected to chronic inescapable stress in the 2004 study[69] (although those levels were not reported in the 2004 study). Forty milligrams would not be indicative of hypercorticosteronism but instead indicates that low corticosterone is linked both to memory for trauma and analgesia. Unfortunately, Pinto-Ribeiro overlooked Uki *et al.*'s results[72] in which plasma corticosterone levels indicating traumatic stress are 120 mg in rats.

Another critical difference is how long analgesia is measured. Drugan *et al.*[73] monitored SIA for more than 2 h. They found that SIA for rats in escapable stress paradigms rapidly declined over 2 h until there was no analgesia, whereas rats in inescapable stress paradigms experienced ongoing analgesia for over 24 h, indicating that a state of tonic immobility had also begun, although the authors did not assess that. They did note that rats in the inescapable stress condition had the benefit of endorphins, whereas the escapable stress rats did not.[73-76] By 1999, Drugan[46] determined that cortisol and GABA levels were significantly elevated in the escapable stress conditions and were linked to both amnesia and interrupted SIA.

This research begged the question: In light of the results in animal models, does traumatic amnesia interrupt analgesia and create susceptibility to chronic pain in humans as well? And, is the pain experience governed by peritraumatic perception if it is a byproduct of traumatic amnesia, neurochemically downstream from glucocorticoid (cortisol) effects? In animal models, one study[66] to date showed that cortisol differentiated pain perception along the same dose-dependent lines as it differentiated memory. Cortisol is critically tied to a fight/flight perception of trauma like it is tied to freeze/PTSD. Souza da Silva and Menescal-de-Oliveira[66] created chronic trauma-induced pain in guinea pigs using a controllable stress paradigm. Importantly, even if only exogenously administered (no stress/trauma paradigm), high levels of corticosterone caused ongoing pain.

6.3. Trauma-induced analgesia

In 2009, Janig[47] came close to mapping how peritraumatic perception dictates whether analgesia or pain is experienced in response to trauma in humans. Depending on the peritraumatic response, he said that either analgesia or pain is differentially regulated by either opioid or non-opioid mechanisms. In a fight/flight response to trauma, early rapid analgesia occurs through the prevention of SNS activation through epinephrine's action (non-opioid) at the trigeminal dorsal horn and its deactivation of ACh in the PNS. Alternately, in a freeze response, slower ongoing analgesia is maintained by ACh activation of the PNS, keeping the SNS "off" through endorphins opioid.[47] However, Janig was incorrect when he defined the initial attentive stillness phase of peritraumatic perception, which occurs in both fight/flight and freeze responses, as the complete fight/flight response. Instead, early SIA caused by attentive stillness is characterized by cholinergic-modulated analgesia, but later in the cascade, catecholamines produce hyperalgesia in the fight/flight reaction, according to many.[9,66,70,73,74] There is agreement with Janig's hypothesis that freeze/tonic immobility responses to trauma involve opioid-modulated analgesia.

For example, both Leite-Panissi *et al.*[74] and Souza da Silva and Menescal-de-Oliveira[66] substantiated that SIA is a cholinergic-modulated analgesia. However, others found that long-term analgesia caused by inescapable stress is opioid-modulated (endorphins bind with mas-related gene [$MrgX_2$] receptors) in the spinal horn.[66] Furthermore, Drugan *et al.*[73] discovered that naltrexone (an opiate antagonist) completely eliminated the analgesia in chronically inescapably shocked subjects but had no effect on the analgesic response of chronically escapably shocked subjects. In other words, in the case of inescapable stress and hypocortisol, after initial SIA in the nucleus raphe magnus, from there, projections into the spinal horn activate tonic immobility, stimulate endorphins, and thereby prevent the SNS from activating. In the case of hypercortisol and escapable stress, after initial SIA, beta-endorphins are inhibited and excessive glutamate triggers N-methyl-D-aspartic acid (NMDA) receptor activation of SNS pain while cortisol prevents ACh from calming the SNS.

From clinical studies of human beings, we know that hypercortisol also plays an important role in the onset of many types of somatization by causing misattribution and misperception of body signals.[71] Furthermore, patients with pain disorder, fibromyalgia, and chronic back pain show reduced gray matter density in cingulate-parahippocampal or fronto-limbic areas.[11,77,78] Hypercortisol has been implicated in brain matter loss in the hippocampus and surrounding areas.[55] We cannot assume that if chronic SSD patients present with ongoing hypercortisolism that it was also the cause of SSD, but there is strong evidence indicating that hypercortisolism is key to both onset and

maintenance of SSD. For example, in studies of patients with FSDs, some initially develop pain from increased SNS activity caused by hypercortisolism, yet almost all FSD patients present with a dysfunctional PNS, which disrupts allostasis and sustains pain.[71]

Methodology discrepancies explain the few examples that counter the hypercortisolism connection in pain patients. For example, women in Heim *et al.*'s study[79] revealed hypocortisol and PTSD symptomology (an expected correlation), but they also suffered with chronic pelvic pain. However, finding hypocortisolism in some of patients with pain should be cautiously evaluated because cortisol measurements were collected in vastly different ways, at different times of day, and calculated differently, so making conclusions regarding a trend toward hypocortisolism, hypercortisolism, or no effect, in maintenance of SSD is premature.[71,79] A hypercortisol condition is linked both to traumatic amnesia and initiation of SSD, through disruption of the PNS. During maintenance of the disorders, cortisol levels sometimes vary. The next section illustrates the chain of neurological events that connects amnesia and pain through the action of the HPA axis and provides a new formulation of the etiology of SSD. The model also indicates how procedural memories of trauma are cemented at the same time that declarative memories are prevented.

6.4. Cortisol and the HPA axis

Cortisol's role in the HPA axis as it responds to stress is mapped in Figure 1. Trauma and stress are first perceived by the sensory thalamus, which quickly sends input to the amygdala,[53] or possibly simultaneously to the amygdala and locus coeruleus, depending on the emotional content and level of arousal of the stressor.[5,67,80-83] The amygdala has been observed to release corticotropin-releasing hormone (CRH)/factor directly to the pituitary,[55] but in most HPA axis models, CRH release occurs after the amygdala is stimulated by the locus coeruleus. The action of catecholamines released directly from the locus coeruleus to the hypothalamus triggers CRH production.[67,82,83] Some hypothesize that fear-related stress would tend to trigger amygdala-mediated CRH release (and the less perceived control, the more fear, therefore the more CRH release), whereas physiological stress/trauma would tend to elicit hypothalamus-mediated CRH release.[55,81,83]

Once the catecholamines (epinephrine, norepinephrine, and dopamine) are triggered in the locus coeruleus, two relevant analog peptides in the traumatic-amnesia-pain equation are co-secreted: proadrenomedullin N terminal-20 peptide (PAMP) and mid-regional pro-adrenomedullin (MR-PAM), two of the four peptides made in the adrenal glands. PAMP downregulates further catecholamine release, likely as part of the HPA axis feedback loop, eventually returning the system to normal response.[84-87] MR-PAM has recently been shown to significantly reduce cortisol synthesis and secretion in both human infants and mice.[87] CRH then excites adrenocorticotropin hormone (ACTH) production in the pituitary gland. ACTH triggers the adrenal glands to produce cortisol.[80,88,89] Cortisol travels to numerous parts of the body. In the brain, it steroidally depotentiates ACh that has already bound with its receptors in the hippocampus, blocks further ACh from binding with ACh receptors and binds with glucocorticoid receptors.[59,89] The hippocampus contains more glucocorticoid binding sites than anywhere else in the brain, though the amygdala also contains many glucocorticoid receptors. Roozendaal *et al.*[81] discovered that high levels of cortisol binding with its receptors in the basolateral amygdala led to stronger emotional and kinesthetic memories of trauma, providing further evidence that while the hippocampus is the seat of declarative memory, the amygdala is the seat of emotional memory. It is very important to note that each is differentially affected by cortisol; the hippocampus has a curvilinear relationship with cortisol – failing to encode memory when cortisol levels are very low and very high, but indelibly or normally recording memory when levels are low to moderate. The amygdala has a linear relationship with cortisol – low levels lead to less emotional memory and high levels lead to more emotional memory.[10,52,81]

A complex algorithm dictates the normal storage of long-term declarative memories. Electrical theta and gamma oscillations that are potentiated by ACh as it binds with mAChRs and nAChRs are depotentiated by GABA and allow for continuous feedforward and feedback mechanisms between the hippocampus and other brain areas which store long-term memories, based on the strength and prior use of pathways.[82,88,90] The same neurotransmitters and receptors identified as affected during the HPA axis response to trauma – ACh and GABA, nAChRs, and muscarinic AChRs, respectively – influence how or whether any new memory is encoded.[91,92] If the delicate rhythm is interrupted, as in the case of hypercortisol, then memory is disrupted. Among nAChR inhibitors, cortisol shows moderate strength.[59] Furthermore, cortisol's blocking of nAChRs triggers GABAergic overstimulation,[72,88,93] as does cortisol's ability to bind with glutamate receptors, leaving more glutamate circulating. Excessive glutamate also overstimulates GABA's inhibitory role.[65] The hippocampus provides a feedback system for the HPA axis through the inhibition of further CRH production by both cortisol interference with hippocampus excitation, and overproduction of GABA.[80] GABA has a calming effect on

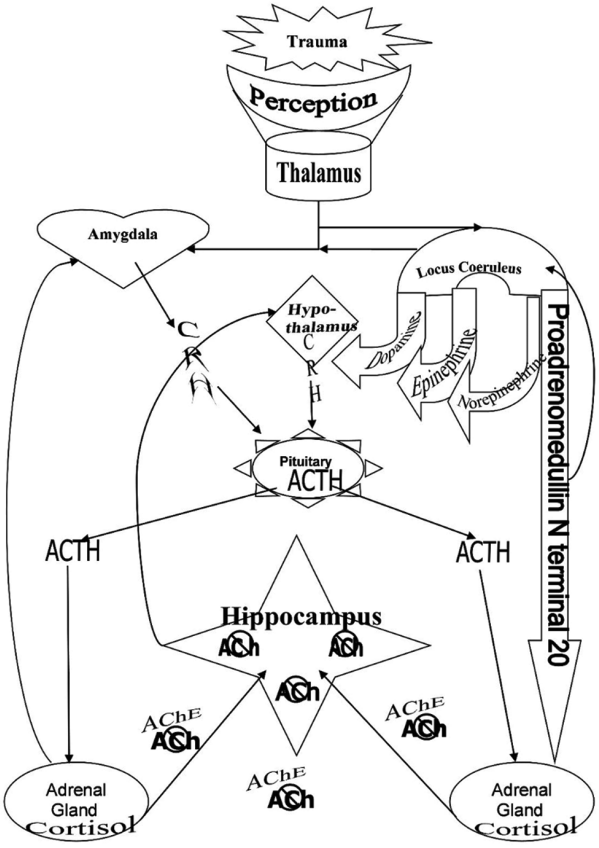

Figure 1. Hypothalamus-pituitary-adrenal axis involvement in traumatic amnesia and somatic symptom disorder
Abbreviations: ACh: Acetylcholine; ACTH: Adrenocorticotropin hormone; CRH: Corticotropin-releasing hormone/factor.

the hippocampus and other brain areas, helping the HPA axis return to normal functioning.[55,83]

It is hypothesized that PAMP (co-secreted with catecholamines) also begins working to return the HPA axis response to normal by downregulating any further catecholamine release, due to its high blocking affinity to nAChRs in the locus coeruleus (preventing catecholamine production, and downstream, further cortisol production.[87,94,95] PAMP is a high-affinity antagonist for nAChRs α9/10,[85,86] the receptors specifically implicated in amnesia,[96] so PAMP may further impair memory by blocking ACh binding, production, and secretion.[97] In rats, PAMP was observed entering the hippocampus from the locus coeruleus, but its action there was not understood.[94] The action of PAMP in humans and whether it is a co-contributor with cortisol in inducing traumatic amnesia needs validation.

6.5. Pain and the fight/flight response

As well as its primary role in memory, the hippocampus has more recently been implicated in pain perception and transmission. After testing the involvement of CA3 region hippocampal neurons in the pain perception of rats, Li *et al.* noted, "there is substantial evidence indicating that the hippocampal formation is involved in pain processing".[98,p.559] The authors suggest that hippocampal mAChR involvement in pain processing enhances organism survival because it facilitates learning and memory about how to avoid reinjury from noxious or dangerous situations. In a very recent study, Mueller *et al.*[82] identified ACh's role in allowing the PNS to remain over-activated, triggering inflammation. Along with nAChRs, mAChRs, and GABAergic receptors on neurons in the hippocampus are NMDA receptors[99] (Figure 2). Because of interactions between these four receptors, response to trauma affects not only memory but also pain perception.[46,59,82] When ACh binds with mAChRs, one result is that glutamate is released. Glutamate not only binds with its own receptors but also NMDA receptors.[100,101] NMDA receptors are the primary activators of neuropathic SNS pain activation.[59,70,82]

In the case of inescapable trauma, a hypocortisol condition allows normal ACh activation of mAChRs, preventing excessive glutamate release, so NMDA receptors and the SNS are not turned "on." Furthermore, early in any trauma response, SIA is triggered by catecholamines that stimulate both CRH production, and turn "on" mAChRs in the nucleus raphe magnus of the spine.[66] SIA in the nucleus raphe magnus benefits an organism by suppressing pain but still allows for motor movement if escape is possible. Within a couple of hours, however, peritraumatic perception of control begins to discriminate analgesic properties.[73,74] Hypercortisol in the hippocampus leads directly to the experience of pain because cortisol binds with its receptors in profusion, thereby depotentiating ACh's binding at mAChRs, both of which prevent the uptake of glutamate at the synapse. High levels of glutamate circulating causes more NMDA receptors to activate.[59,100] Cortisol travels further down in the spine as well, activating glucocorticoid receptors and NMDA receptors, turning on the SNS. Then cortisol also blocks ACh's ability to activate the PNS, which would normally shut down the SNS.[82,89,102]

The HPA axis connection to memory systems is firmly established, and the HPA axis connection to the autonomic nervous system is emerging, with the effects of ACh and cortisol on nAChRs and mAChRs figuring prominently in both memory formation and pain perception. For confirmation, there is one study of human beings regarding the pain trajectory through the HPA axis. In a large national study in Denmark, patients with chronic lower back pain had nearly 2 times higher cortisol levels within 30 min of awakening (cortisol awakening response) compared to controls with no lower back pain.[103] This is

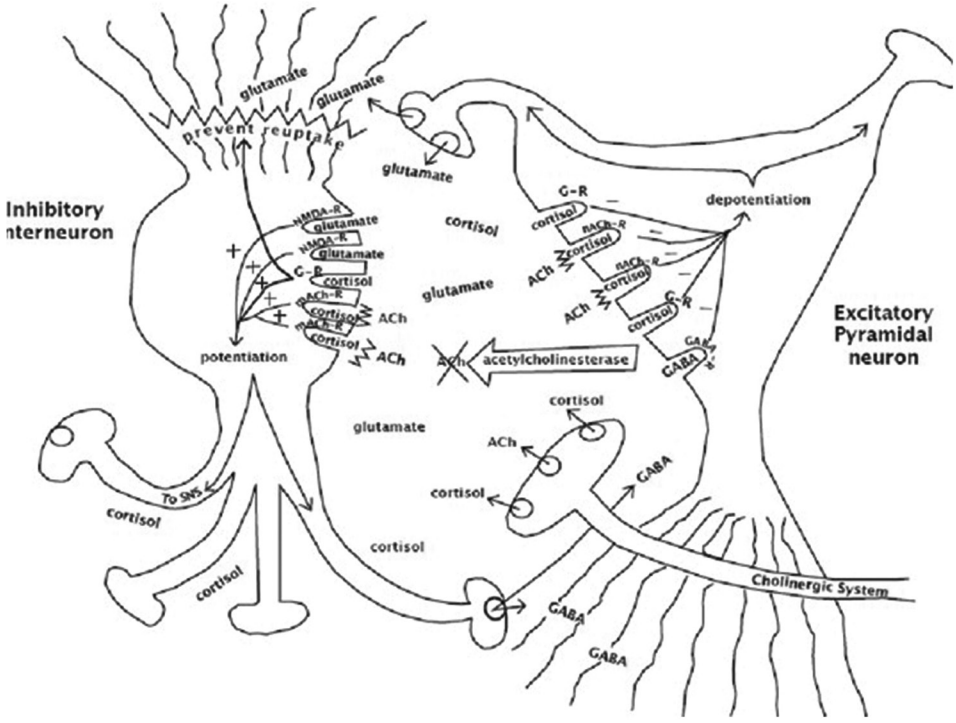

Figure 2. Hippocampal transmitters and receptors are affected by hypercortisol
Abbreviations: ACh: Acetylcholine; GABA: Gamma-aminobutyric acid; SNS: Sympathetic nervous system.

directly opposite what the researchers hypothesized, likely given the contradictory literature they found on cortisol, trauma, and pain, and the lack of this paper's map of the neurochemical cascade for trauma, memory, and pain.

7. Secondary contributors: Acetylcholinesterase and PAMP

7.1. Acetylcholinesterase

Acetylcholinesterase, the enzyme that hydrolyses or breaks down ACh at the synapse should also be considered as a possible player in the T-A-P connection. Increased activity of acetylcholinesterase is linked to memory impairment.[104,105] However, there is only one study to date that indicates acetylcholinesterase increases specifically in the wake of trauma perceived as controllable. Its results are important in that they support the cortisol findings above, as well as encourage researchers to consider interplay of HPA axis neurochemicals and receptors when it comes to understanding and treating traumatic amnesia and its consequences. In 2005, Das *et al.*[106] discovered memory impairment and higher levels of acetylcholinesterase in rats who were exposed to chronic unpredictable stress, compared to those exposed to chronic predictable stress, vs. only one episode of stress (control group). Replication of the study and confirmation of whether chronic unpredictable stress is equivalent to controllable stress is needed. It is logical that chronic unpredictable stress is perceived as controllable, unlike chronic predictable stress, which the subject comes to expect, knows the nature and length of, and therefore comes to believe there is no escaping.

As further evidence of aceytlcholinesterase's importance, there is limited literature verifying its increase in response to chronic stress when cortisol levels are high.[106-109] High levels of cortisol or exogenously administered hydrocortisone either stimulate the synthesis of acetylcholinesterase or speed up its degradation of ACh.[110] By degrading circulating ACh, high levels of acetylcholinesterase allow more glutamate release.[111] Acetylcholinesterase can also prevent ACh activation of the PNS, as discussed earlier, a key problem for chronic psychogenic pain and somatization sufferers.[82,102] Furthermore, elevated acetylcholinesterase is linked to other PNS problems, such as increased muscle fatigue and degeneration at neuromuscular junctions in mice[112] – the same complaints many fibromyalgia and chronic fatigue sufferers have. Finally, acetylcholinesterase is nearly an exact match of atropine's protein sequence (99%), and butyrylcholinesterase, a cholinesterase that also hydrolyses ACh and other choline esters, is in fact, an exact match (100%) of atropine's protein sequence according to the

National Institute of Health's open database, Genbank's B.L.A.S.T., which is a protein sequence matching tool (http://blast.ncbi.nlm.nih.gov/Blast.cgi).[113] It is hypothesized that acetylcholinesterase or butyrylcholinesterase, or both, are endogenous versions of atropine because atropine binds with high affinity to acetylcholinesterase enzymes.[114] Further, the research presented above indicates that they differentially affect memory systems in the way atropine does.[20,115] Parasympatholytics, or PNS inhibitors, such as atropine (https://pubchem.ncbi.nlm.nih.gov/compound/Atropine),[116] are a concern because PNS inhibition is a core problem for FSD sufferers. If acetylcholinesterase is endogenous atropine, then its profusion is likely causing or exacerbating FSD.

7.2. PAMP

The role PAMP has in the HPA axis as an antagonist of nAChRs and mAChRs should be considered, such as acetylcholinesterase, as also antagonizing the PNS. This paper argues that PAMP reinforces cortisol in the T-A-P pathway. High levels of PAMP (discussed above as associated with elevated catecholamines and hypercortisol in the controllable stress paradigm) could interfere with SIA and the beginning of tonic immobility in two ways. First, PAMP could prevent analgesia at the level of $MrgX_2$ receptors in the spinal dorsal horn,[67,117] because PAMP blocks $MrgX_2$ receptors with stronger affinity than six of that receptor's ligands, preventing analgesis that is normally associated with activation of $MrgX_2$ by endorphin or enkephalin.[85,117] Second, after hypercortisol activates the SNS by way of NMDA receptors,[70] the PNS' attempts to return the system to allostasis could be blocked by PAMP. If low ACh is circulating early in the controllable stress paradigm due to high catecholamines, since PAMP is an ACh receptor antagonist, it could prevent the little ACh that is circulating from activating the stabilizing effort of the PNS. If PAMP and cortisol bind with mAChRs in the PNS, then tonic immobility and analgesia are turned "off."

8. Conclusions

8.1. Chronic pain and somatic symptom sufferers

PD, FSD, and SSD patients experience a great deal of suffering and sometimes face huge costs for treatments and medications. They stand to lose functional ability at work, in relationships, and socially.[2,118-120] They are often told their symptoms have no clear explanation or origin, which is frightening or frustrating. Many patients feel their needs are not being served well by either medical doctors or mental health clinicians. In fact, only about 25% of patients with SSD ever seek psychotherapy, in part due to stigma.[121] Worse, without clear knowledge of underlying pathogenesis, their health providers may suggest inappropriate, ineffective, or even harmful treatments for the disorders. Pointedly, many treatment methods have been unsuccessful and PD/FSD patients are sometimes blamed for their lack of progress.[119] Dr. Jeffrey Staab of Minnesota's Mayo Clinic was a researcher involved in the field trials for the diagnostic criteria for SSD, and he acknowledged:

"Most psychiatrists assume that some sort of trauma, tragedy or conflict in the past is driving health-anxious fears and behaviors. Moreover, if we can't find it, and the patient can't find it, it can become a speculative wild goose chase for trauma. Trauma is more likely in these patients, but if we don't find a history of trauma, we can look at stress, and if we don't find that, we can still talk about exaggerated preoccupations with health and help patients reset and reframe that without digging around in the past."[122]

T-A-P theory posits not a completely new idea – the body keeps the score – but it is the first to delineate a neuroendocrinological sequelae between dissociative amnesia and SSD. In 2021, when looking at future directions, Mueller *et al.*[82] called for an answer to the question "does the hippocampus provide the anatomical substrate for the link between disorders of central inflammation, dysautonomia, and a dysregulated HPA axis?" T-A-P theory answers their question with a thorough map of the defense cascade that initiates and maintains SSD, locking trauma into the body for many patients. Importantly, the theory argues that somatic and emotional memory is what is persistently re-experienced in SSD, a parallel process to PTSD patients' persistent remembering of their trauma. The hippocampus' autobiographical memory is shut down by hypercortisol during traumatic amnesia, but amygdala-based memory, motor memory, and somatosensory memory systems are enhanced or unaffected by hypercortisol, encoding the trauma. When internal and external reminders or cues of the trauma occur, in the same way they frequently do with PTSD patients, SSD patients' neurochemistry is triggered into SNS activation without PNS deactivation, leading to unexplained pain and other neurological or somatic symptoms. Somatic symptoms could be considered flashbacks and treated as such in many patients. The defense cascade travels familiar neurological pathways to old injury sites or previously diagnosed medical problems (also known as "priors"), and sends signals there, or interprets signals from there, saying, "something is wrong. I still hurt!" The true message from the body may be, "something bad happened; you don't remember it; pain is our only voice to say the world is not safe; you may be under attack at any moment!" Relatedly, catastrophizing and alexithymia are primary traits associated with SSD.[123] Patients cannot voice how they feel, or it is greatly reduced

compared to normal controls, but they overvalue body messages.[3]

8.2. T-A-P model

Figure 3 displays a diagram that summarizes the T-A-P pathway. Cortisol plays the primary role in explaining how traumatic amnesia leads to PD/FSDs. Cortisol interrupts the action of ACh on nAChRs in the hippocampus, preventing declarative memory for trauma, but facilitating procedural memory for trauma in the amygdala. PAMP has fast access to hippocampal nAChRs since it is co-secreted with catecholamines before CRH and ACTH are secreted to trigger cortisol release. Elevated catecholamine secretion leads to elevated PAMP co-secretion, further preventing ACh binding with nAChRs in the hippocampus – augmenting amnesia. In the spinal dorsal root horn, PAMP competes with ACh to bind with mAChRs and competes with endorphins to bind with $MrgX_2$ receptors – augmenting and sustaining pain perception. Hypercortisol prevents tonic immobility and triggers prolonged activation of the SNS by depotentiating ACh in the spinal dorsal horn, and by increasing acetylcholinesterase which degrades ACh in the synaptic cleft there. Hypercortisol also prevents downregulation of the sympathetic response when it steroidally depotentiates ACh at nAChRs and increases acetylcholinesterase synthesis and activity in the PNS.

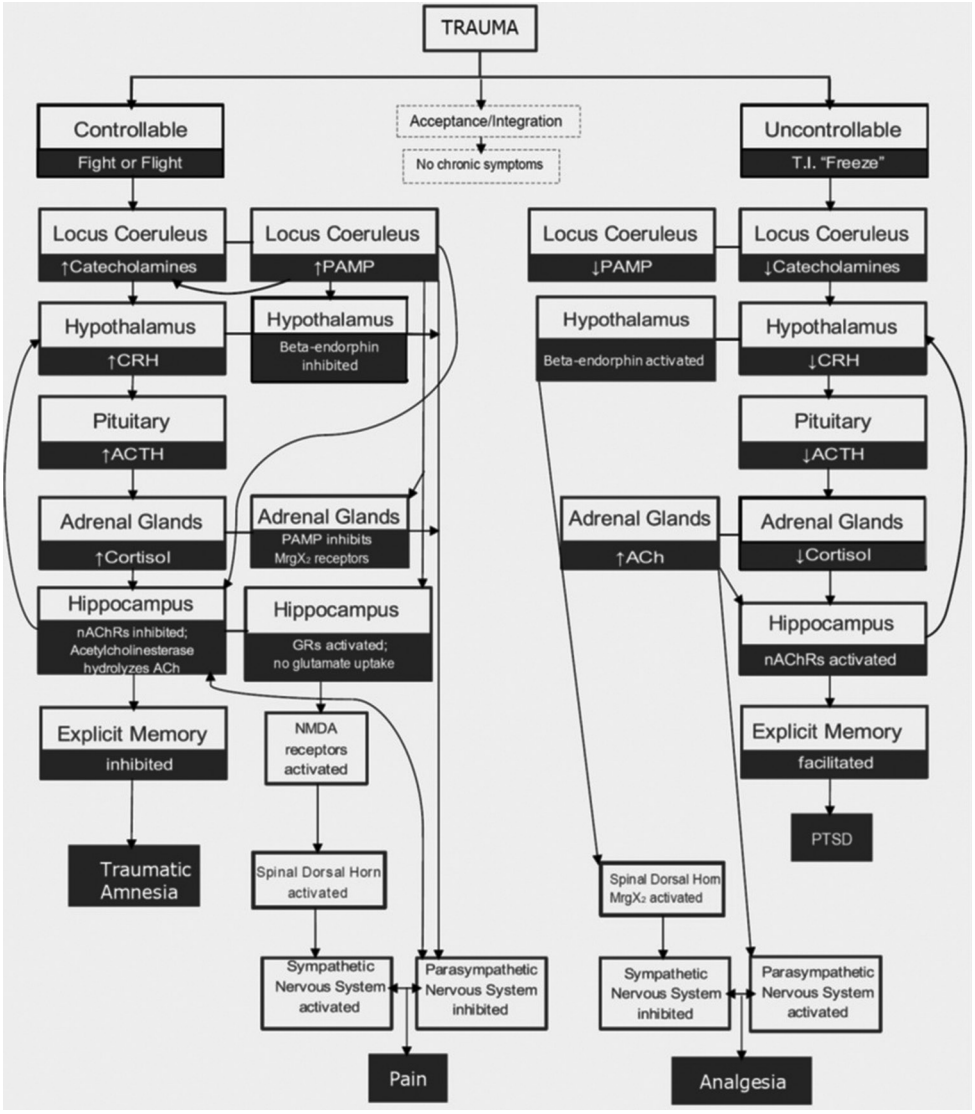

Figure 3. Trauma-amnesia-pain flow chart

Abbreviations: ACh: Acetylcholine; ACTH: Adrenocorticotropin hormone; CRH: Corticotropin-releasing hormone/factor; GRs: Glutamate receptors; nAChRs: Nicotinic acetylcholine receptors; NMDA: N-methyl-D-aspartic acid; PAMP: Proadrenomedullin N terminal-20; PTSD: Post-traumatic stress disorder; T.I.: Tonic immobility.

This novel conceptualization of the etiology of traumatic amnesia and SSD also explains why SSD is comorbid with dissociative amnesia. The findings are based on a large body of neurological, physiological, and clinical research, which converges to conclude that hypercortisol and peritraumatic perception of control are key factors in both disorders. The shared etiology of PD, somatization disorder, and FSD also legitimizes the DSM-5-TR move to unify the disorders under one umbrella, SSD. Considered as a whole for the 1st time, this comprehensive review provides definitive evidence that how trauma is perceived is the linchpin that explains the dose-dependent effects of cortisol (and its co-contributors, acetylcholinesterase, and PAMP) on both memory and somatic symptoms. It appears that traumatic amnesia affords individuals protection from excessive fear, anxiety, and intrusive explicit memories. However, the by-product of this escape route is either pain, extra sensitivity to pain, or unpleasant somatic symptoms.[3] Sufferers of dissociative amnesia and patients with SSD deserve a better understanding of their symptoms and challenges. T-A-P theory predicted what Vinkers' research found with the NESDA cohort: Remembered childhood trauma does not lead directly to dysregulations of the HPA axis and autonomic nervous system.[124] The people not captured in Vinkers' study were those who do not remember childhood trauma, yet are much more likely to experience HPA and PNS dysregulation. By taking into account the perception of trauma and its underlying neuroendocrinological processes, we will drive more effective clinical treatment methods and appropriate pharmacological interventions.

9. Recommendations

When screening for SSD, clinicians need to also screen for dissociative amnesia. If a history of cumulative traumatic effects, especially emotional abuse or sexual abuse can be informed by family or other sources, clinicians must treat underlying trauma alongside somatic symptoms. Cognitive-behavioral treatment strategies have shown some effectiveness with PD, SSD, and FSDs, such as fibromyalgia, chronic back pain, and irritable bowel syndrome.[1,11] As an adjunct to the core cognitive-behavioral strategies, clinicians can monitor whether patient pain experience is maintained by regular internal "procedural memory" triggers and intervene with each trigger either through avoidance, system-calming techniques, or experience validation and normalization.[1,125] We know memory is retrieved and influenced by pre-existing beliefs, expectations, and knowledge, but it is also influenced by the context of retrieval.[49,52] Recognition that SSD patients may have procedural memory fragments (well-preserved in the amygdala) that trigger elevated HPA axis responses, may assist clinicians in helping patients manage or prevent ongoing pain.[29,32,33,102,125] This type of experience has been termed a "body-loop feedback" for pain, or "top-down" pain signals by some authors,[1,11,47] and may be likened to a type of repetitive re-experiencing of the trauma, as in PTSD, but through the procedural memory systems. For the T-A-P theory to be fully substantiated, not only replication of some of the animal studies is needed, but human studies that control for peritraumatic perception are also required. The inclusion of amnestic trauma victims in clinical samples is a must.

Future studies should validate the T-A-P pathway using consistent glucocorticoid (cortisol) measurement, especially reporting and standardization of "high" versus "low" glucocorticoid amounts. Future research should also focus on determining how much predictive influence acetylcholinesterase and PAMP have relative to cortisol in the T-A-P pathway in both animal and human trials. Furthermore, future studies need to address the other two primary causes of SSD, reinforcement learning of the sick role due to social acceptability, and biological sensitivity to pain. Both of these conceivably strengthen T-A-P connections, but how so remains to be discovered. Furthermore, prevention and intervention with these factors were beyond the scope of this paper.

Treatment should explore the use of new pharmacotherapy options in SSD intervention, in light of research presented here regarding the neurochemicals and receptors involved in SSD. The effectiveness of nAChR agonists in the treatment of both neuropathic and psychogenic pain is emerging. In the same way that ACh—nAChR agonist – is the mind's natural way to enhance memory and provide analgesia, other nAChR agonists have shown initial effectiveness in treating pain. The effectiveness and lack of side effects of nAChR and mAChR agonists, such as acetyl-L-carnitine (ALCAR) and ABT-594, an epibatidine analog, has been established in the treatment of pain in animal models.[126,127] Future research with humans is needed and will contribute to further validation of the T-A-P connection. nAChR antagonists such as MK-801, atropine – and its isomers scopolamine and hyoscyamine – have also been used as pain relievers under the suspicion that an endogenous nAChR antagonist (like PAMP) was the primary culprit in displacing ACh and triggering pain.[128] Interestingly, the newest nAChR α9/10-specific antagonists RgIA and Vc1.1, are showing potential as analgesics,[102,129,130] and PAMP shares an exact protein match with nACh α9/10 receptor subtypes.

Acetylcholinesterase inhibitors like neostigmine have also been tested as possible analgesics (assuming acetylcholinesterase is the primary culprit in degrading

and preventing ACh from providing pain relief), but to be effective, it must be a high dose. Unfortunately, high doses come with dangerous side effects, such as respiratory failure.[102] Finally, research indicates that when combined with opioid drugs, nAChR agonists increase pain relief,[100,131] which is useful for patients who use opioids to manage pain, but must carefully avoid addiction and overdose. In contrast, nAChR agonists are not known to be addictive, so they should be explored more thoroughly.[130]

Finally, as mentioned earlier in this review, Zohar *et al.*'s study[61] provides hope that traumatic amnesia and SSD could be prevented altogether. In the same way that high doses of glucocorticoids have successfully prevented PTSD; traumatic amnesia and some SSD should be preventable by reducing glucocorticoids within 72 h post-trauma. It is concerning that little discussion of Zohar *et al.*'s study, or widespread implementation of their results, has occurred in the past 10 years. Another candidate for trauma intervention is neuropeptide Y, which calms the SNS and prevents PTSD, providing yet more validation of the link between memory and somatization. Neuropeptide Y has three benefits: (i) it can be taken nasally; (ii) it is safe at fairly high doses; and (iii) it prevents PTSD even if administered 1 week after trauma exposure.[132] We must take advantage of this current knowledge to offer victims of trauma to measure and regulate their cortisol output, up- or down-regulate glucocorticoids, or possibly take neuropeptide Y, and thereby prevent either amnesia and pain or PTSD. It is recommended that human trials continue until FDA approval is granted. In cases where prevention is not possible, pharmacological interventions with SSD and FSD need to consider nAChR agonists, acetylcholinesterase antagonists, and anti-adrenergic beta blockers.

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