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Toward staging differentiation for posttraumatic stress disorder treatment

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Abstract

Objectives: Several medical and psychiatric disorders have stage-based treatment decision-making methods. However, international treatment guidelines for posttraumatic stress disorder (PTSD) fail to give specific treatment recommendations based on chronicity or stage of the disorder. There is convincing evidence of a finite range of PTSD symptom trajectories, implying that different phenotypes of the disorder can be distinguished, which are highly relevant for a staging typology of PTSD.

Methods: State-of-the-art review building on prior work on staging models in other disorders as a mapping tool to identify and synthesize toward PTSD.

Results: We propose a four-stage model of PTSD ranging from stage 0: *trauma-exposed asymptomatic but at risk* to stage 4: *severe unremitting illness of increasing chronicity*. We favor a symptom description in various chronological characteristics based on neurobiological markers, information processing systems, stress reactivity, and consciousness dimensions. We also advocate for a separate phenomenology of treatment resistance since this can yield treatment recommendations.

Conclusion: A staging perspective in the field of PTSD is highly needed. This can facilitate the selection of interventions that are proportionate to patients' current needs and risk of illness progression and can also contribute to an efficient framework to organize biomarker data and guide service delivery. Therefore, we propose that a neurobiologically driven trajectory-based typology of PTSD can help deduct several treatment recommendations leading to a more personalized and refined grid to strategize, plan and evaluate treatment interventions.

KEYWORDS

assessment, neurobiology, PTSD, staging, stress, treatment

1 | INTRODUCTION

In physical disorders such as cancer and diabetes, clinical staging models are routinely used to enhance the disease process's early detection and systematic management. Staging approaches for somatic illnesses have primarily been based on morphology, but neurobiological and pathobiological characteristics of the different stages of the

disorder are among the most promising underpinnings for a typology of posttraumatic stress disorder (PTSD).

The DSM-5 diagnostic criteria for PTSD focus on the longitudinal course of the disorder as they recognize an acute, chronic, and delayed onset form of the disorder.[1] These trajectories for PTSD have been extensively documented, with the delayed onset form being substantially more common than initially anticipated. However, the diagnostic pattern of symptoms is assumed to be the same for each trajectory type of PTSD in DSM-5. This is despite the emerging evidence from network analyses that the internal structure, and linkage of symptoms changes with time.[2–6] This limitation of phenomenological definitions of psychiatric disorders has been raised as a significant deficiency as it does not address the fluidity of the phenomenology of a disorder across time, particularly as it changes in various stages of the disorder.[7] Symptoms may also evolve into more stable diagnosable syndromes, involving meaningful stepwise changes in clinical status.[8] Traditional psychiatric taxonomies also take no account of the secondary phenomena termed illness extension,[8] which represent adaptions or consequences of the symptoms beyond the primary clinical syndrome.

Another critical concept in current staging approaches is allostatic load, serving as a framework to describe up- and downregulation of different activating and inhibiting systems. The organization of domains of valence-based thinking is also recognized in the Research Domain Criteria (RDoC) of the National Institute for Mental Health,[9,10] which can provide a further valuable framework in thinking about a staging approach. Schmidt and Vermetten have added two additional clusters to better integrate trauma-related psychopathology in this system: 1. Maintenance of consciousness and 2. stress and emotion regulation.[11] The question also arises about how early life developmental processes impact all these phenomena (e.g., childhood trauma) and cumulative adult trauma as these also need to be accounted for by a staging approach as they modify symptom trajectories and adaptation. One of the challenges with the increasing interest in the development of biomarkers is determining whether these represent risk factors, are related to trauma exposure, the onset of symptoms, or the development of a full-blown disorder, that is, different stages of disease. Equally, activating neurobiological systems may have other consequences at different time points in the disorder's progression.[12]

Despite the extensive evidence about the importance of longitudinal course and time in the etiology of PTSD, international treatment guidelines for posttraumatic stress disorder[13–15] do not give specific treatment recommendations based on chronicity or stage of the disease. This lack of consideration of the impact of chronicity and different patterns of presentation and duration of illness is in contrast to the treatment guidelines for other disorders such as affective disorders.[16] Duration of disease, for example, is an essential determinant of treatment resistance in a range of psychiatric disorders such as depression and may be a more robust indicator than the number of episodes.[17,18]

In summary, the current treatment guideline recommendations are similar for individuals who have developed PTSD 1 month or 10 years after traumatic experiences, while there are indications that chronicity and complexity of the disorder affect treatment outcomes.[19,20] For example, there are no studies on the role of background inflammation as a predictor of antidepressant response, despite evidence for higher levels predicting treatment nonresponse to antidepressants in major depressive disorder.[21] Equally, there are no differential recommendations for the treatment of PTSD that was caused by single incident traumas as against cumulative exposures. Treatment for veterans with PTSD after combat-related trauma is similar to treatment for civilians with PTSD, while research shows different responses. A meta-analysis of the treatment of veteran populations who have had multiple trauma exposures showed that they have poorer outcomes with prolonged

Clinical recommendations

- Positioning an individual on each proposed staging axes (neurobiological markers, information processing systems, stress reactivity, and consciousness) may contribute to a proportionate personal treatment plan.
- Stage-based treatment recommendations range from short, neuroprotective interventions for early stages to trauma-focused or pharmacological interventions for middle stages and multimodal or rehabilitative interventions for late stages.
- Consensus in taking the medical and treatment history of patients with PTSD is the first step toward applying staging principles in clinical practice.

Limitations

- More research is required to optimally characterize the underpinnings of the disorder at each stage.
- States of disability or handicap have not been adopted into the staging model as they represent different axes of adaptation influenced by interventions and psychosocial circumstances.

exposure (PE) and cognitive processing therapy (CPT), and the majority, even with clinically meaningful improvement, are left suffering from PTSD.[22–24]

Against this background, we propose here that treatment guidelines for PTSD need to address the outcomes in a more nuanced manner to take into account the issue of differential effectiveness in different patient groups based on the staged manifestation of the disorder, as well as according to the severity of symptoms and the type of trauma exposures. We suggest that a staging approach is a key strategy to dissect the probabilities of recovery and effectiveness of treatment intervention. This approach then argues for different treatment approaches at different stages of a disorder. We propose that a staging approach to the diagnosis as well as to the treatment does service to the changing pathobiology of the disease. In this paper, we aim to provide a framework that informs the dissection of these relationships to assist in the development of more targeted treatment interventions and ultimately result in more refined recommendations to advise patients on which treatment would be efficacious for them.

2 | STATE-OF-THE-ART

In 2017, McFarlane et al.[25] proposed a neurobiologically based staging model for PTSD. Based on the body of research that has been published in recent years, we offer to extend this staging model for PTSD by distinguishing between trajectories of the disorder not only based on neurobiological markers but also on more complex information processing systems that are involved as well as on parameters involved in stress reactivity and consciousness dimensions.[11] Our proposed staging model aims to follow the international consensus statement on clinical staging.[8] In addition, we argue that it is important to develop a staging model based on the longitudinal course, the phenomenology of the disorder, and the shifts in multiple neurobiological systems rather than treatment response, which we aim to consider separately. This is a modification of the model proposed by McFarlane et al.,[25] which combined these perspectives.

The biological formulations of PTSD have posited that time is a critical dimension of the underlying processes, including kindling and sensitization.[26] The dynamics of inflammatory and neuro-hormonal responses to traumatic stressors have changed with time. High levels of inflammatory mediators in the aftermath of trauma appear to have a protective effect,[12] but at a later stage, background inflammation predicts the worsening of symptoms.[27] Phenomenological evidence of these underlying processes comes from symptoms such as an exaggerated startle response which takes up to 6 months to emerge after the trauma exposure.[28–30]

For the more chronic state that emerges after the acute challenges of adaptation, McEwen et al.[31] have highlighted the role of allostatic load as a critical biological dimension where there is a disruption of the normal homeostatic regulation of many neuro-hormonal systems. Furthermore, neuroimaging studies provide evidence of loss of neural tissue, which is a process that is underpinned by time course.[32,33] There are also thoughts about accelerated aging driven by telomere length impacted by stress and trauma. Such phenomenological and neurobiological evidence points to the phasic nature of the development of PTSD underpinned by conditioning/habituation, reinforcement, and extinction, which are time-dependent phenomena.[34] Repeated exposure to reminders drives the increasingly persistent paired associations between environmental triggers, the traumatic memories, and the reactivity of the individual.[35] Frequently cases pass through a subsyndromal phase rather than a rapid emergence of disorder, and the progression of symptom development is underpinned by the increasing strength of these paired associations. For delayed types of presentation, the drivers for the phenomenological manifestations are thought to be similar, yet these could also be regulated by different discrete sets of brain regulatory processes, possibly driven by higher cortical processes.

A range of dynamic processes and factors highlight the need for a phasic understanding of adapting to traumatic events. Memory consolidation, for example, is a process that occurs in the aftermath of trauma and has been postulated as a critical pathobiological construct that would lead to memory fragmentation and poor recall. A related neurobiological mechanism is progressive stimulus generalization that drives a lack of specificity of memory recall. There is also minimal information that allows predicting whether particular biomarkers of treatment response are found with C-reactive protein as in depression. Hence different phenotypes may predict treatment response, and as a consequence, these dimensions should be studied separately. Processes and factors such as these are essential to consider in a staging model for PTSD.

The development of a staging model for PTSD will assist in answering questions such as at what stage of the disorder and with which phenotype is treatment likely to be more or less effective. These are important when considering where emerging treatments such as cognitive vaccination,[36] stellate ganglion block,[37] neurofeedback,[38] high-intensity psychotherapeutic treatments,[39,40] ketamine,[41] and drug-augmented (e.g., MDMA) psychotherapy[42] should be offered for optimal therapeutic benefit. Furthermore, without this approach of staging both disease progression and treatment resistance, potentially useful treatments may fail

TABLE 1 Proposed staging model for PTSD incorporating progression and extension (in the left column, we aim to describe the progression of PTSD in terms of chronology, whereas the other columns to the right include important domains to which the disorder extends depending on the stage the individual is in)

Extension of the disorder →				
Progression in the chronological course of the disorder ↓		**Possible neurobiological markers of stage**	**Information processing systems**	**Psychophysiological stress and emotional reactivity, and consciousness**
Stage 0	*Trauma-exposed asymptomatic but at risk*	Downregulation of GR sensitivity, increased amygdala reactivity, 5FKH genotype, changed circadian cycle/melatonin	Transient attention bias to threat; consolidation of traumatic memories ongoing, deficits in extinction learning and habituation, enhanced contextual anxiety	Increased vigilance
Stage 1a	*Undifferentiated symptoms of mild anxiety and distress*	Inflammatory cytokine activation, decreasing response inhibition in frontal cognitive systems	Mild attention or memory difficulties	Heightened basic stress level and some disruption of normal sleeping pattern.
Stage 1b	*Subsyndromal distress with some behavioral and functional decline*	Increased physiological reactivity to trauma-related stimuli, prolonged autonomic arousal on provocation	Recurrent memories of trauma; increased attention bias to threat	Startle response; some reduction in task-oriented attention in the presence of distractors;
Stage 2	*First episode of full-threshold symptoms that has different trajectories*	Early and potentially reversible neurobiological disinhibition of frontolimbic circuitry.	Impairments in concentration and memory, changes in sleep architecture (more N1, less N3, REM alterations); spectrum from feeling briefly disconnected from reality to losing consciousness, amnesic spells/gaps in memory, poor recall of extinction and over-sensitization	Anxious avoidance; reduced task focus, nervousness, sleeping problems, jumpiness; anhedonia and emotional numbing; loss of interest and emotionality, emotional instability, sometimes with self-injury; spectrum reaching from brief periods of absentmindedness to seizure-like attacks (spectrum from intrusions to PNES)
Stage 3	*Persistent symptoms which may fluctuate with ongoing impairment*: *a. incomplete remission of first episode* *b. recurrence or relapse of PTSD & persistent impairments* *c. multiple relapses or worsening following incomplete remission*	Stronger PFC inhibition, decreased anterior cingulate and hippocampal volume, hypertension and metabolic syndrome; stimulus generalization	Similar to stage 2, but more severe or resistant to therapy; decreased cognitive flexibility leading to dysfunctional cognitions and rigidity; overregulation of (frontal) neuronal networks and disruption of default mode network.	Generalized avoidance leading to more pronounced isolation and limited task performance; decrease in synchronization in social conversation because to associative thinking, attenuated emotion recognition; loss of feeling connected to others; erosion of basic trust in oneself, others and/or the world; increasing influence of guilt and shame
Stage 4	*Severe unremitting illness of increasing chronicity*	High allostatic load, high levels of inflammation, medical comorbidities, entrenched sensitization of	Neurocognitive decay resulting in premature cognitive aging; moderate memory deficits; chronic dysregulated non-	Permanent limitations in task performance, strong isolation; extreme avoidance; survival mode;

TABLE 1 (Continued)

Extension of the disorder → / Progression in the chronological course of the disorder ↓	Possible neurobiological markers of stage	Information processing systems	Psychophysiological stress and emotional reactivity, and consciousness
	a range of neurobiological systems.	regenerative sleep architecture; thinking characterized by psychotic symptoms; persistent overregulation of (frontal) neuronal networks, increasing dysregulation of default mode network; possibly alterations in brain stem nuclei, hypothalamus (specifically in PTSD: abnormal supramarginal gyrus and superior parietal activation)	guilt/shame as drivers for behavior; loss of (self-)reflective capacity and empathic connection, retreating back into logical linear pattern of thinking, unstable self-image; persistent affect dysregulation (e.g., fear, guilt and shame)

to show benefit as they have been tested selectively in treatment-resistant patient groups.[43]

Table 1 shows the proposed staging model with the operationalization of progression and extension processes for PTSD. The model categorizes post-trauma responses from stage 0 ("trauma-exposed asymptomatic but at risk") to stage 4 ("severe unremitting illness of increasing chronicity"). The perspective of progression does not imply that all individuals move toward the end stage and allows for recovery from all stages except the final one. It does involve that manifesting symptoms that belong to a certain stage carries a risk to progress to a later stage. The staging model is based on biological and clinical concepts which need to be investigated further to be confirmed. In the paragraphs below, we summarize the evidence that is currently available from the literature for the elements we mentioned in the table.

2.1 | Chronological course of the disorder

It is well known that responses to potential trauma are heterogeneous and can be explained by a finite set of longitudinal trajectories,[44] including chronically elevated posttraumatic stress following the event, continuous symptom elevations that preceded the event and progress afterward, and elevated pre-deployment (baseline) symptoms followed by steady improvement. These long-term studies demonstrate long-term reactions to traumatic stress to be highly heterogeneous and labile. This research has also demonstrated resilient outcomes characterized by a stable trajectory of healthy adjustment (e.g., little or no symptoms pre- to post-event).[45] Longitudinal evaluations of PTSD symptoms in deployed military personnel have yielded essential information for mapping outcome heterogeneity and, thereby, the stages of the disorder. Similar patterns have been found across different trauma populations.

There are several perspectives regarding the longitudinal course of PTSD. Much can be learned from the trajectories of these studies. Bonanno et al.[46] explored three-year longitudinal trajectories using LGMM in active duty, reserve, and national guard personnel in relation to deployment. They found low-stable posttraumatic stress or resilience (83.1% single deployers, 84.9% multiple deployers), moderate-improving (8.0%, 8.5%), then worsening-chronic posttraumatic stress (6.7%, 4.5%), high-stable (2.2% single deployers only) and high-improving (2.2% multiple deployers only). Bryant et al.[47] mapped the distinctive long-term trajectories of PTSD responses over 6 years with LGMM in a sample of 1084 traumatic injury patients admitted to Australian hospitals and found five trajectories of PTSD response across the 6 years: resilient (73%), worsening (10%), worsening/recovery (8%), recovery (6%), and chronic (4%). Eekhout et al.[48] reported on PTSD symptoms and associated risk factors in a cohort of Dutch Afghanistan veterans 5 years after homecoming, followed up in the same cohort 10 years after homecoming.[49] In the 10-year follow-up sample of 963 servicemen, four trajectories of PTSD symptom development were identified: resilient (85%), improved (6%), severely elevated-recovering (2%), and delayed onset (7%). The longest study to date was on

164 Israeli ex-prisoners of war (POW) and 185 comparable combatants from the 1973 Yom Kippur War. Three follow-ups (1991, 2003, 2008) were conducted over 35 years. Solomon reported four trajectories of PTSD: chronic PTSD, delayed PTSD, recovery, and resilience. In her study, the majority of POWs reported delayed PTSD, while the majority of controls were classified as resilient.[50] The largest study using LGMM identifying trajectories was performed on 56,388 first responders who were part of the Japan Ground Self-Defense Force involved in the 2011 Great East Japan Earthquake. In a 7-year prospective cohort study, five symptom severity trajectories were identified: resilient (54.7%), recovery (24.5%), incomplete recovery (10.7%), late-onset (5.7%), and chronic (4.3%).[51]

In the overview above, several overlapping results have been reported regarding the longitudinal course of PTSD. This results in several perspectives. One is that over time, individuals with PTSD will partially or wholly recover.[52] An alternative view is that with time, PTSD will exacerbate because to worsening of the physical and psychological state of the individual, particularly during mid-life.[53,54] Yet another approach proposes that an initial improvement in PTSD symptoms will occur in the aftermath of the traumatic event, but beyond this, there are no precise predictions that can be made regarding the longitudinal course of the disorder.[55] Three possible courses of PTSD were already identified by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)[56]: acute, chronic, and delayed. In the early days, Blank also proposed intermittent and reactivated PTSD as additional courses.[57] It should be noted that the suggested courses of PTSD are not necessarily mutually exclusive, as one may, for example, present a delayed onset of the disorder, which subsequently becomes chronic.

In summary, the longitudinal course of PTSD represents a complex matrix of outcomes with patterns of recovery as well as increasing severity of symptoms. From a staging perspective, one issue that is not well described in the literature, is whether the individuals did or did not have a disorder prior to the event that is being studied.[58] Many of those who have a more chronic course had significant symptoms prior to the index trauma.[46,59,60] Hence the trajectories described in these studies are of individuals in different stages of the disorder. Furthermore, a recent systematic review found that delayed PTSD patterns are also preceded by mild symptoms in the early aftermath of trauma in most cases.[61] Progression is not inevitable but will be determined by a range of factors in the recovery environment such as other life stresses, as well as the vulnerability factors that the individual has brought to the event.[62,63] When environmental challenges exceed the individual's ability to cope, a state of allostatic overload[64–66] emerges, which is a multidimensional process with activation of various stress response systems having broad-ranging consequences for mental and physical health. Based on the accumulated evidence from trajectory studies and the work on allostatic load,[26] we think this broad-ranging progression is most strongly supported by the literature and highly relevant for a staging model. A challenge for staging models concerns how to capture the existence of other disorders, given the prevalence of comorbidity of other mental disorders with PTSD.[59,67] Hence the staging model requires further development in the future as to how to incorporate these other factors in the modeling of the range of possible trajectories following trauma exposure.

As indicated and incorporated in the DSM 5 diagnostic categories, studies on symptom trajectories in PTSD show that several phenotypes of the disorder can be distinguished.[68–70] As can be seen from recent LGMM studies, the most frequently identified phenotypes are immediate onset PTSD which recovers over time, immediate onset PTSD, which becomes chronic, and delayed onset PTSD, for which the onset is not until years after the traumatic experiences. These different phenotypes of the disorder may be distinguished by various characteristics.[71] A disorder with immediate onset may have an amygdalocentric, fear conditioning, and stress sensitization-based character, meaning that stress reactivity and hyperarousal play a considerable role in the onset and maintenance of the symptoms. Over time stimulus generalization may drive symptoms, and generalized anxiety and avoidance can start to occur. When the disorder surfaces years later, there are a series of possible mechanisms. As is found in disaster victims and accident survivors, delayed-onset PTSD is common and represents an increasing sensitization of stress reactivity and increasing allostatic load.[47,72] It may also characterize a moral injury subtype, indicating moral difficulties in coming to terms with the traumatic experiences which have shaped the person's thinking over the years. This could represent a less amygdalocentric but more prefrontal cortex (PFC)-based presentation of PTSD.

Delayed-onset PTSD is perhaps the most common course of PTSD development, and the majority of cases do not emerge within the first year after the trauma. Hence, these studies have identified sub-cohorts of those who develop symptoms of PTSD in the first year after the index traumatic event to offer them early interventions in order to arrest progression over time. So most studies of PTSD trajectories have identified four significant trajectories following traumatic experience: (a) resilient class with consistently few PTSD symptoms (also referred to as "resistant" by some researchers), (b) recovery with initial distress, then gradual remission over time, (c) delayed

reaction with worsening symptoms over time, and (d) chronic distress with consistently high PTSD levels. By early intervention, we mean interventions that are implemented in the initial hours, days, or weeks after trauma exposure. The goals of these approaches (so-called Golden Hours approaches)[73] are variably to reduce the acute stress or achieve secondary prevention to avert subsequent PTSD.

2.2 | Neurobiological markers of stage

A set of proposed markers for the different stages of PTSD is set out in the previous paper by McFarlane et al.[25] In addition, a body of subsequent research has provided some directions on how this might be refined.

One of the challenges that need to be addressed in future research is to better characterize the progression of the neurobiological changes between those with no trauma exposure, those with trauma exposure but no symptoms, subsyndromal symptoms, early PTSD, and the chronic form of the disorder. At present, the substantial body of the current literature does not allow these differentiations to be made. There is a need to map the longitudinal dynamic changes in a range of biological systems, including inflammatory cytokines, glucocorticoid production, receptor functioning, opioid systems, autonomic regulation, noradrenergic and adrenergic reactivity, and neural network structure and connectivity.

The findings of the changes in the reactivity of inflammatory systems and their relationship to PTSD exemplify how the loss of reactivity of systems underpins the disorder rather than simply considering the levels of inflammatory mediators.[74] The inflammatory systems, when acutely activated, can have protective effects in contrast to the negative effects of chronic low-grade inflammation.[75] This highlights that a staging model needs to consider the dynamics of these systems in response to challenges and study their steady-state. This is akin to mapping the model of allostatic load, which considers the balance between the mechanisms that upregulate systems and the inhibitory controls and where dysregulation is characterized by the loss of flexible homeostatic reactivity.[31] In particular, inflammation can predict the risk of PTSD but also emerge as part of the disorder and have a role in linking PTSD with medical comorbidities,[76] which should be considered in a staging model.

Similarly, recent studies of the volume of brain regions that underpin PTSD have concluded that these differ according to the stage of the disorder. This body of research has been driven by the finding that there are subtypes of PTSD based on cognitive impairments and the underlying neural networks in the maintenance of symptoms.[77] In particular, the uncoupling of the frontal–parietal control and limbic networks is important.[78] These findings highlighted the role of the central executive network as a domain of interest in a staging model. In addition, how changes in other biological systems underpin these changes is relevant in developing a staging model.

A further issue that needs to be considered is the increasing literature about the genetic profile that underpins PTSD. The degree of methylation of the regions of interest and the extent of the genetic risk are likely to underpin the progression of PTSD and, hence, the disorder's stage.[79] A recent study highlighted the existence of different genetic profiles of subtypes of PTSD observed in US combat veterans, where a dysphoric profile had a higher polygenic risk for major depressive disorder and more life stresses.[80] Findings such as these indicate the role of genetic risk and the degree of methylation as another dimension that should be considered in a staging model.

In summary, a complex matrix of systems characterizes the nature and progression of PTSD.[81] It is beyond the scope of this paper to summarize this literature and all the possible systems that could contribute to a staging model of PTSD. However, an understanding of the longitudinal course, prognosis, and treatment response in PTSD can only be understood by taking a multidimensional and interactional perspective of the multiple systems that have been identified to play a role in PTSD.

2.3 | Information processing systems

Much research has been performed in the past decades investigating information processing systems in PTSD, which have a clear neurobiological basis. These can be described from various perspectives, including learning principles, neurocognitive performance, sleep dysregulations, and neural networks involved. In addition, some work has been done to identify pre-trauma vulnerability and compare trauma-exposed populations with and without PTSD in this domain. However, similar to the state of evidence regarding biomarkers, the relative contribution of especially subsyndromal symptoms, development of the full disorder in its acute form, or the chronic form of the disorder remains unclear at this point.

Summarizing the evidence on learning principles, Lissek and van Meurs[35] stated deficits in original extinction learning and habituation and enhanced contextual anxiety to be premorbid risk factors for PTSD. On the other hand, poor recall of extinction and over-sensitization are termed acquired markers of PTSD. Furthermore, the

increasing generalization to stimuli is a marker relevant to the progression between stages. These information-processing phenomena can be presumed to be at the basis of the neurocognitive dysfunctions individuals with PTSD cope with daily and contribute to strengthening dysfunctional cognitions as the disorder progresses. Bias for threat-related material, for instance, in sexual victimization survivors, was stronger for individuals with PTSD than trauma-exposed individuals.[82] A similar amplification of reactivity to threat is manifest in the development of the startle response in the months following trauma exposure.[28–30]

Looking at neurocognitive functioning pre-trauma, there is evidence that poorer neuropsychological performance, for instance, measures of word recall, digit span, coding speed, and verbal intelligence[83] and visual recall,[84] may be vulnerability factors for developing PTSD symptoms later on. A twin study further supports the premorbid risk factor perspective,[85] and a study in accident survivors showed that select neuropsychological measures shortly posttrauma predict later PTSD symptoms.[86] Based on the literature, accumulation of traumatic experiences, the development of subsyndromal PTSD symptoms, and the emergence of the full disorder can all be presumed to contribute to the further pronunciation of these phenomena.[84,87–89] Meta-analyses have found neuropsychological dysfunctions to be in the small- to the medium-sized range for individuals with a PTSD diagnosis,[90,91] with the strongest dysfunctions in verbal learning, working memory, and processing speed. Importantly, these relate to information processing of neutral stimuli,[92] and verbal memory dysfunction has been related to the persistence of PTSD after trauma-focused psychotherapy.[93–95]

Sleep dysregulations constitute another cognitive perspective that has been related to the severity of the disorder and its longitudinal course. Subjective sleep problems before or early after trauma predict the later development of PTSD symptoms in various trauma-exposed populations.[96,97] A meta-analysis of polysomnographic studies has shown a pattern of more N1 and less N3 sleep as well as greater REM density in PTSD populations,[98] making sleep in PTSD, in general, more superficial and less regenerative. In addition, there are indications that several aspects of sleep, such as sleep-disordered breathing, worsen with longer duration of the disorder[99] and, together with obesity, contribute to premature cognitive aging.[100]

In summary, a range of information processing systems are involved, and most have both a vulnerability component as well as a component related to the development of PTSD. In terms of neural networks, the central executive network and the dorsal/ventral attention network are most relevant to the observed neurocognitive alterations for neutral information. In contrast, the salience network is connected with biases in attention, for instance, for threat-related information.[101] As described above, especially the central executive network has been linked to increased chronicity and treatment-resistant forms of the disorder.[77] Challenges in these areas have significant task-oriented and interpersonal impacts.

2.4 | Psychophysiological stress reactivity and consciousness

The default mode network is activated in case of no explicit task-oriented demands. One presumed function of this network is to maintain a state of readiness to respond to environmental stimuli[102] and drive activity in task-positive brain areas when cognitive demands come into play,[103] which bears relevance to the stepwise increase in vigilance and stress responsivity at the various stages we describe here. In addition, self-referential processes, such as gaining insight and drawing inferences from one's own and others' emotional state, experiencing an embodied sense of self, and a continued experience of the self across time, have also been attributed mainly to the default mode network.[104]

Resting-state functional connectivity within this network is reduced in PTSD compared with healthy controls, with stronger reductions related to more severe PTSD symptom severity.[105] In PTSD, this reduced resting-state connectivity is concentrated primarily in the medial-temporal subsystem, which correlates with avoidance and numbing symptom severity.[106] In terms of clinical presentation, this may be represented as increased guilt and shame as well as alterations in bodily awareness, depersonalization, and derealization. We hypothesize guilt, shame, and dissociative phenomena to become increasingly more severe and debilitating as the disorder progresses to its later stages. Further reductions in default mode networks likely underpin these changes. In patients' daily lives, this may ultimately lead to retreating to a logical, linear manner of thinking, loss of reflective capacity, and no longer feeling as oneself. When presented with threat-related information, stronger default mode network connectivity with the midbrain periaqueductal gray as initiator has been demonstrated in PTSD compared with healthy controls.[107] According to Terpou et al.,[108] this may present clinically as stronger hyperarousal to possible threats and stronger related survival responses (fight, flight, and freeze). This may also induce more generalized avoidance, for instance, of unknown

TABLE 2 Proposed grades of therapy resistance

Grade of therapy resistance	
Grade 0	No history of failure to respond to a therapeutic trial
Grade 1	Failure to respond to at least 1 adequate trauma-focused psychological intervention trial
Grade 2	Failure to respond to at least 2 adequate trauma-focused psychological intervention trials
Grade 3	Failure to respond to at least 3 adequate therapeutic trials, of which two trauma-focused psychological intervention trials and one pharmacological intervention trial
Grade 4	Failure to respond to at least 3 or more adequate therapeutic trials (psychological or pharmacological intervention, of which at least 1 psychotherapy/pharmacotherapy combination) AND one intensified psychological intervention (massed/augmented/multi-component treatment).

situations and an increase in various types of safety behavior.

Processing of negatively valenced emotion by neural circuitry, either related to negative emotions or trauma, is another domain relevant to stress reactivity and self-referential processes. In a meta-analysis of negative emotional processing, Etkin and Wager[109] showed increased activity in the amygdala and insula as well as hypoactivation in the dorsal and rostral anterior cingulate cortices and the ventromedial prefrontal cortex in PTSD. Amygdala activity to negative emotional material proved to be determined by a ventral anterior hyperactive cluster and a dorsal posterior hypoactive cluster. The former may be relevant for acquired fear responses, while the latter may relate to emotional numbing and dissociative responses in PTSD. The pattern of hypoactivation in the rostral anterior cingulate cortex and the ventromedial prefrontal cortex in PTSD is proposed to be related to a deficit in reflexive emotion regulation in the absence of self-reflection about emotion or deliberate attempts at emotional control. The hypoactivation in the dorsomedial prefrontal cortex and dorsal anterior cingulate cortex may relate to decreased experience or impact of negative emotions. Etkin and Wager argue that this may lead to various forms of emotional dysregulation and anxiety generalization in the clinical presentation. The strength and progression of these patterns of connectivity are likely to change with the increasing stages of PTSD.

Altogether, studies on the default network show clear relationships with symptom severity in a number of PTSD domains. However, it has not yet been investigated whether the reduced resting-state connectivity within the network and the stronger threat-related connectivity also progress with a longer duration or chronicity of the disorder. As these patterns have been related to (early) trauma history as well, it could also be the case that these are predisposing or vulnerability factors for the development of PTSD after trauma,[104] which further strengthen as the disorder progresses. It can be assumed that negative emotional processing patterns are strengthened in the brain with increasing chronicity of PTSD, but relative contributions of the various stages remain to be studied.

2.5 | Grades of therapy resistance

We propose that a separate staging model of treatment be developed that addresses the response to treatment interventions and how these may change at different stages of the disorder, which is a different issue from the staging of the disease progression. Hence a staged model of treatment resistance has been proposed for depression and other psychiatric disorders and should be equally developed in PTSD. However, a staging model of the progression and extension of the disorder needs to be separated from a staged model of treatment resistance as these are different but related phenomena.[110]

It may be useful to define *grades* of therapy resistance as opposed to the *stages* in the chronological course of the disorder as they are two different phenomena. Table 2 shows how therapy resistance could be graded once PTSD is fully developed. Earlier propositions described a staged approach in which stage one TR-PTSD is defined as nonresponse to a full course of two evidence-based treatments and stage two TR-PTSD as nonresponse to a full course of at least three evidence-based treatments.[111] In the current paper, however, we propose to define treatment resistance by distinguishing four grades in line with operationalizations of treatment resistance in other disorders.[112]

3 | FROM RESEARCH TO CLINICAL PRACTICE

The approach above could lead to a set of graded treatment recommendations for every stage of the disorder considering its inherent neurobiological markers, information processing systems, and stress reactivity and consciousness dimensions. It is important to always include psychoeducation in line with the individual's stage.

TABLE 3 Possible intervention modalities and innovations per stage

Stage	Proposed intervention modality
Stage 0: Trauma-exposed asymptomatic but at risk	Watchful waiting (monitoring of symptoms over time)
Stage 1a. Undifferentiated symptoms of mild anxiety and distress	Cortisol, working memory task, attention training, ACE inhibitor, corticosteroids.
Stage 1b. Subsyndromal distress with some behavioral and functional decline	Short interventions: *i*. Interaction-based: limited number of PE sessions, writing therapy, neurofeedback. *ii*. Non-interaction based interventions, such as (mindful) relaxation.
Stage 2: first episode of full-threshold symptoms that has different trajectories	Relatively straightforward symptom-focused interventions, such as PE, EMDR, CT, CPT.
Stage 3: persistent symptoms which may fluctuate with ongoing impairment	
a. incomplete remission of first episode	*i*. Psychotherapeutic interventions that address multiple aspects of traumatization or sequential traumatization such as Brief Eclectic Psychotherapy for PTSD or Narrative Exposure therapy *ii*. Range of pharmacotherapeutic options regulating stress reactivity: SSRI's, SNRI's, mood stabilizers, prazosin, stellate ganglion block, *or* targeting emotional dysregulation, such as ACT, mindfulness, medicinal cannabis.
b. recurrence or relapse of PTSD and persistent impairments	Psychotherapeutic interventions that address the person in his/her context, such as interpersonal psychotherapy, schema therapy
c. multiple relapses or worsening following incomplete treatment response	Intensified treatment by means of *i*. "massed" interventions such as highly intensive 1- to 3-week trauma-focused treatments *ii*. interventions with emerging evidence of effect for treatment-resistant populations: 3MDR, MDMA-assisted psychotherapy, DBS, rTMS.
Stage 4: Severe unremitting illness of increasing chronicity	*i*. Physical: effective medical management of comorbidities *ii*. Specific interventions on social and vocational assistance *iii*. Treatment focused on moral injury, in case of a "moral injury subtype" of PTSD. *iv*. Interventions focused on maintenance and preventing further comorbidity: nonverbal therapy, service dog, equine therapy, day treatment, and stabilization.

Consistent with other staging models, we think early interventions and neuroprotective strategies should be provided in earlier stages, whereas more rehabilitative and multi-modal treatments dealing with the disabilities are more suitable in later stages.[8,113] The purpose of staged treatment recommendations would be to provide prevention and treatment aimed at full recovery from the stage the individual presents with to prevent further progression and extension.[8] Table 3 provides a hypothesis how stage-based treatment recommendations for PTSD could be formulated. Although some treatments have been investigated specifically in the acute phase after trauma or in treatment-resistant populations and have shown to be efficacious in those studies, the evidence for linking distinct treatments to a specific stage is limited for the majority of the interventions and points to the need for further studies in this area.

Broad adoption of the concept of staging in clinical care for PTSD has yet to occur. Regarding the characteristics of the model, high clinical utility[8] and a concise formulation[17] seem to be necessary prerequisites for successful dissemination. A first step toward working with staging in practice is consensus in taking the medical and treatment history of the patients. Pre-trauma risk factors, time since index trauma, start of the symptoms, remission of the symptoms in relation to received treatments, and stage are important variables. In addition, it is important to assess previous treatments and their relative success in a structured manner (e.g., Emory Treatment Resistance Interview for PTSD; E-TRIP).[114] The clinical utility of the proposed definitions of treatment resistance in the current paper requires further investigation.

Furthermore, tailoring interventions to provide a good fit with specific subtypes of PTSD seems important, although the relative influence of subtypes on treatment outcome and progression of the disorder is not yet clear from the current literature and deserves further study. Despite decades of documentation, it is remiss of the field that the underlying neurobiological dysfunction in patients plays no role in planning the nature of the optimal treatment. Identifying if a patient has a "moral injury

subtype," "dissociative subtype," or meets criteria for complex PTSD, as short interview addenda to a structured interview for PTSD, may prove helpful in the context of future application of staging in clinical practice.

More longitudinal studies are needed, and some of the described concepts we mention in the staging model, such as self-referential thinking and the stability of self, could be elaborated much further. This is essential to learn more about the neurobiological underpinnings of the clinical picture at each stage. Testable hypotheses are necessary to refute or confirm certain assumptions regarding the various stages and determine the proposed dimensions' reliability and validity. With this knowledge, profiling could be based on someone's position on each of the axes of the proposed model in the future. More evidence is also needed to refer patients in a particular stage of the disorder to one or more treatments for which they have a high probability of responding. Machine learning approaches and computational psychiatry are helpful approaches to predict which patient will benefit from a certain approach and can provide us with models demonstrating specificity with regard to underlying mechanisms.[115,116] Staging approaches like the current one may provide a critical dimension with explanatory power to machine learning and artificial intelligence solutions. This may increase their transparency and understandability.

If staging is recognized, there may be a better efficacy of various treatment approaches, as these need to be tailored to the stage the disease is manifesting itself. In addition, it is important to differentiate the overlapping or discrete phases in the disorder and develop more knowledge on the timing of interventions. Therefore, stratified approaches that consider these important clinical characteristics using machine learning algorithms may be more (cost)effective than the standard stepped care approaches.[117]

There is now evidence that some of the following examples should be considered in addressing the progression of PTSD through its stages to chronicity and which treatments may have benefits.

i. Studies of the treatment of depression have shown that increasing CRP levels in the context of life events stressors predict non-remission. Is this similarly the case in PTSD, and does this warrant the addition of other anti-inflammatory medications to augment the antidepressants' impact on inflammation?[118]
ii. The disengagement of default mode networks in PTSD underpins the loss of associative thinking in the disorder. Is the degree of the disengagement of these networks a biomarker for improving outcomes with psychedelic-assisted psychotherapy?[119]
iii. Are there particular markers of entrenched psychophysiological reactivity in PTSD in the more advanced stages of PTSD that point to the role of stellate ganglion blockade as a beneficial adjunct to treatment?[37]
iv. With ketamine, to what extent are its benefits predicted by its modulation of BDNF and disrupted connectivity of the frontal cortex and the default mode network? Ketamine has been found to normalize dysconnectivity of the prefrontal cortex and default mode network with other brain regions in patients with major depressive disorder.[120]
v. When strong cognitive and behavioral avoidance is an important component of the clinical picture in the advanced stages of PTSD, is it helpful to intensify trauma-focused treatment by adding virtual reality exposure[40] or 1- to 3-week highly intense exposure-based interventions?

These are only examples but point to how matching the stages of PTSD and particular symptom clusters to the mechanism of a particular treatment may lead to better outcomes using a staging model.

4 | LIMITATIONS

Current frameworks for classification and treatment of PTSD lack a stage orientation. As others have clearly outlined, staging models aim to clarify mechanisms underlying the progression of the disorder.[113] Important goals regarding treatment are tailoring clinical interventions and working toward more personalized medicine, thereby making treatment more effective. To move the concept of staging forward and to change PTSD treatment guidelines in this respect, the underpinnings of the disorder must be optimally characterized at each stage which requires additional research efforts. We support the perspective expressed by the international consensus statement for staging in youth mental health that staging models should incorporate and differentiate between illness progression and illness extension and lead to clinical indications for intensified interventions in case of illness progression versus broadened interventions in case of illness extension.[8] The intention is to address the disorder at the current stage and arrest its progression or elaboration to further stages. We describe four stages of PTSD that need to be incorporated into clinical care and neurobiological research.

We have not included states of disability or levels of occupational functioning in our model. Although there is a clear association between disease progression and reductions or limitations in social, behavioral, and occupational functioning, functioning levels may not be linked to the clinical stage of the disorder and may

change or be reversed with successful interventions. Impairments, disabilities, and handicap are different axes of adaptation that are impacted by other factors, including personality, the social environment, and resources. It is important to consider them as a separate domain of outcomes as they are not necessarily highly correlated to the severity of the underlying disorder. However, they are central concepts to take into account in the clinical management of the disorder. The ICF functioning and disability codes,[121] delineating a continuum of impairments, limitations, restrictions, and barriers, can provide a helpful perspective in defining a personalized treatment plan.

Staging in PTSD: principles and operationalization (see also Shah et al.[8]):

i. Staging should be fundamentally integrated the course of clinical presentation (including disease progression and extension) into comprehensive assessments, which would facilitate an assignment of stage. Multidimensional assessments should take into account core presenting phenomena (symptom type, severity, and frequency, along with functioning) as well as components of extension: severity of distress, substance use, neurocognition, physical and mental health comorbidities, and other clinically apparent features;
ii. begins with an initial stage (stage 0) comprised of known risk factors (e.g., prior history of childhood trauma, deployment, lifetime trauma exposures);
iii. should be designed to assist the earliest provision of specific early intervention and secondary prevention efforts that offer a better risk/benefit ratio and target the underlying pathophysiology (so-called Golden Hour interventions).[73,122] Consequently, this approach has the potential to prevent the development of chronic illness states (neurobiologically and psychosocially);
iv. although the proposed staging model has a disorder-specific approach, it has similarities with transdiagnostic staging models by describing a range of posttraumatic psychopathology that could also be framed under different psychiatric disorders for which trauma is an important etiological factor.
v. pre-trauma risk factors known to influence the course of the disorder have not been integrated in the proposed version of the staging model as it starts at the point of trauma exposure. Distinct subtypes of the disorder have not been coupled to specific stages either, as the clinical and neurobiological correlates of the subtypes need to be defined more specifically. These factors could provide opportunities to further refine the staging model in the future.
vi. treatment duration may also relate to stage of the disorder; clinicians mostly deem it necessary to refer to more specialized and longer-lasting treatment for later stages of the disorder, but this does not necessarily lead to treatment gains for the individual;
vii. suggested guidelines for treatment should be based on a stage-based approach and are therefore more in terms of type of treatment in line with the clinical progression, complexities, and comorbidities that accompany a certain stage than duration. We chose to express these in the model in terms of clinical phenomena attached to stage rather than in terms of comorbid ICD or DSM 5 diagnoses. The model promotes the measurement-based tracking of individual trajectories. However, individual trajectories need to be differentiated from the broader concept of clinical stages, with the stepwise nature of the latter being quite distinct;
viii. staging itself is unidirectional. Thus, while an individual may remit or recover fully at any stage, he/she still retains the original stage classification—but can be assigned a further designation regarding current state, such as "in remission" or "responded to treatment";
ix. staging is dynamic; understanding of an individual's clinical trajectory should change as more clinical and neurobiological information is acquired. This implies that the adoption and application of staging should encourage more individualized assessment and systematic longitudinal tracking over time.

Finally, the implementation of a staging differentiation requires the creation of collaborative and international clinical research processes to create, refine and test the validity of the proposed criteria used to define stages and distinguish between successive stages. It is hoped that this will lead to improved treatment outcomes for this intriguing but therapeutically challenging disorder.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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