FORUM – THE EVOLVING CONCEPTUALIZATION AND EVIDENCE BASE OF POST-TRAUMATIC STRESS DISORDER(S)

Accepted manuscript published in *World Psychiatry*, 2025, *24*, 52–80. doi: 10.1002/wps.21269

Post-traumatic stress disorder: evolving conceptualization and evidence, and future research directions

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The understanding of responses to traumatic events has been greatly influenced by the introduction of the diagnosis of post-traumatic stress disorder (PTSD). In this paper we review the initial versions of the diagnostic criteria for this condition and the associated epidemiological findings, including sociocultural differences. We consider evidence for post-traumatic reactions occurring in multiple contexts not previously defined as traumatic, and the implications that these observations have for the diagnosis. More recent developments such as the DSM-5 dissociative subtype and the ICD-11 diagnosis of complex PTSD are reviewed, adding to evidence that there are several distinct PTSD phenotypes. We describe the psychological foundations of PTSD, involving disturbances to memory as well as to identity. A broader focus on identity may be able to accommodate group and communal influences on the experience of trauma and PTSD, as well as the impact of resource loss. We then summarize current evidence concerning the biological foundations of PTSD, with a particular focus on genetic and neuroimaging studies. Whereas progress in prevention has been disappointing, there is now an extensive evidence supporting the efficacy of a variety of psychological treatments for established PTSD, including trauma-focused interventions – such as cognitive-behavior therapy with a trauma focus (CBT-TF) and eye movement desensitization and reprocessing (EMDR) – and non-trauma-focused therapies, which also include some emerging identity-based approaches such as present-centered and compassion-focused therapies. Additionally, there are promising interventions that are neither psychological nor pharmacological, or that combine a pharmacological and a psychological approach, such as 3,4-methylenedioxy-methamphetamine (MDMA)-assisted psychotherapy. We review advances in the priority areas of adapting interventions in resource-limited settings and across cultural contexts, and of community-based approaches. We conclude by identifying future directions for work on trauma and mental health.

Key words: Post-traumatic stress disorder, trauma, complex PTSD, identity, genetics, neuroimaging, prevention, psychological interventions, pharmacotherapy, community-based interventions

The world is currently experiencing the highest number of state-based conflicts (i.e., conflicts in which one of the actors is a government or state) since the Second World War, as well as a very high number of non-state-based conflicts (i.e., conflicts between formally or informally organized groups)[1]. Approximately 468 million children are currently living within a conflict zone, often in areas where armed groups or forces recruit and use them in those conflicts[2]. A variety of individual, relationship, community and societal factors are being associated with increased levels of gender-based violence[3]. Childhood and domestic abuse as well as exposure to traumatic events at work are on the rise[4,5], and recent health-related events have had a huge traumatic impact at various levels of population worldwide[6]. In the coming years, climate change is likely to further exacerbate the frequency of traumatic events, and their direct and indirect impact on adults and children[7].

Since 1980, the management of psychological trauma has become inextricably bound up with the diagnosis of post-traumatic stress disorder (PTSD). Although there were initially numerous skeptics, this diagnosis has since established itself and has become an extremely effective vehicle for publicizing the effects of all kinds of traumatic events. Not only has knowledge of trauma and its effects grown enormously as a result, but in many countries there is now an infrastructure to support these developments, and a high visibility of trauma-related conditions in the planning of governments and non-governmental organizations (NGOs).

With increasing knowledge has come a greater appreciation of the complexities of understanding people's response to traumatic events. First, what is a traumatic event? Initially this was conceptualized as an event that would have an overwhelming effect on anyone, while now it is understood as an event that has a potential overwhelming effect on some people. This effect can take forms other than PTSD – for example, depression or prolonged grief. Thus, the definition of a traumatic event cannot be considered solely in the context of PTSD.

Views were initially shaped by the lists of traumatic events contained in standard survey instruments, but greater recognition of the symptoms has led to trauma reactions being acknowledged in many other contexts, such as after a very difficult childbirth or a psychotic breakdown. Moreover, there is increasing appreciation that events may impact whole families and communities, and that the relation of persons to their community may affect their individual response.

The effective management of psychological trauma requires that new knowledge is constantly reviewed, evaluated and reflected upon. In this paper, we start by discussing the current understanding of what constitutes a traumatic event in different contexts. We continue by summarizing how PTSD has been diagnosed for most of the time since its introduction in 1980, and what has been discovered about its epidemiology using the relevant diagnostic criteria. Subsequent sections address changes and controversies in the definition of a traumatic event, and more recent developments in diagnosis, including the introduction of

complex PTSD in ICD-11. We then review some of the most important psychological and biological processes involved in PTSD. Later sections summarize how this condition can most effectively be prevented and treated, and identify trends and avenues for research and practice that are likely to be important in the future.

WHAT IS A TRAUMATIC EVENT AND WHAT MAY BE ITS EFFECTS?

A traumatic event is one with a potential to severely challenge the ability of an individual or a community to adapt, requiring major changes to ways of living or thinking.

Exposure to this category of events is a universal aspect of the human experience. In the health literature, we use to focus on the adverse effects that traumatic events can have on the lives of individuals and communities[8]. However, it is worth noting at the outset that the effects of exposure to traumatic events are complex and varied, and that they may elicit strong reactions without leading to maladaptive responses[9].

Normal reactions to traumatic events are often linked to the specific circumstances of the occurrence. For example, ongoing threat is associated with anxiety; loss is associated with grief and depression; negligence by others, injustice and betrayal are associated with anger; and abandonment is associated with despair[10,11]. If the traumatic exposure is time-limited, these reactions are typically brief, and may be adaptive and occasionally lead to personal growth[12]. However, traumatic events can have a significant and sometimes widespread and devastating negative impact.

Many factors help explain the substantial variation in the impact of trauma. Some of them depend on the characteristics of the traumatic event itself[13,14]. For example, the course of untreated PTSD arising from events that are considered intentional (e.g., domestic violence) has more frequently a worsening trajectory and shows a greater tendency to chronicity than that of untreated PTSD after unintentional events (e.g., natural disasters)[15].

Moreover, individuals' psychological, genetic and neurobiological characteristics can predispose them to maladaptive reactions to trauma[16-18], and act in combination with their sociocultural and societal-structural context. For example, exposure to traumatic events, urbanicity, ethnoracial discrimination, socioeconomic deprivation, and limited opportunities as a migrant all act in concert with genetic and other forms of vulnerability to enhance the risk of psychotic symptoms and disorders[19,20].

These interactions affect all aspects of traumatic exposure and its consequences, including the probability of exposure to psychosocial trauma[21]; the range of emotional reactions to traumatic exposure[22]; variations in risk, symptoms and course of resulting trauma-

related conditions[22,23]; the availability and type of supports that people can engage[24]; the availability and effectiveness of mental health interventions[23]; and the process of recovery[25].

The sociocultural and societal-structural context exerts its influence by shaping people's life circumstances and risks, their interpretation of events, the coping and healing options that they have access to and use, and community reactions that influence their experience.

The impact of trauma can also be transmitted across generations, as in the case of children of survivors of the Second World War Holocaust[26] and of the Cambodian genocide[27]. These community-level traumas have been argued to influence recurring cycles of mass violence. "Historical trauma", a term coined by Native American researchers to describe the impact of European and Anglo-American colonization, is thought to be a significant factor contributing to elevated rates of alcohol dependence and abuse, PTSD, suicide, violence and depression in Native communities[28,29].

In more sociocentric or collectivistic societies, communal elements may exert a larger influence on trauma reactions than they do in more individualistic societies. In many parts of Africa, for example, the predominant *Ubuntu* worldview ("I am because we are") holds that an individual's fate and well-being are closely tied to those of others in his/her social network[30,31]. A person can then experience PTSD symptoms due to an event happening to another member of the community.

Data from the World Mental Health Surveys have shown that, in societies that tend to be collectivistic (such as in South Africa and Japan), traumatic events occurring to others within a person's social network are associated with a high conditional prevalence of PTSD[32]. Among North Korean defectors, PTSD severity was more strongly associated with witnessing trauma events involving family members than with exposure to physical abuse or political-ideological trauma (e.g., being a political detainee)[33].

How do communal risk factors exert this influence on a person's reactions to traumatic events? Several mechanisms are currently being examined. One involves the impact of contextual factors on individual experience. Even when traumatic events affect entire communities, sociocultural/structural factors apportion risk differently, including by neighborhood characteristics and resources available to the person's support systems[34]. For example, among residents affected by Hurricane Andrew in Florida, Latinxs were significantly more likely to experience PTSD symptoms than non-Latinx Whites, a vulnerability partly mediated by Latinxs' acculturative stress as immigrants[35]. Specific living circumstances can also pattern trauma-related reactions. For instance, living among unpunished perpetrators in settings of mass violence can result in long-standing anger and frustration, complicating trauma-related psychopathology[36,37].

Another mechanism of communal effects involves meaning traditions that become part of personal identity, and shape collective reality. For example, among Tibetan refugees fleeing

Chinese government rule, religious persecution – e.g., witnessing the destruction of monasteries or being forced to publicly renounce the Dalai Lama – was more strongly associated with PTSD symptoms than torture or imprisonment[38]. Forced interruption of these meaning traditions can foster the onset and/or persistence of traumatic grief states, such as during the Rwandan genocide, when the grief of survivors was magnified by traditional beliefs about the precarious spiritual status of deceased relatives who had not been properly buried[39].

Individual transgressions of collective moral codes can also have a greater pathogenic effect than other severe traumatic exposures. Among US veterans in the National Vietnam Veterans Readjustment Study, harming civilians and prisoners was associated with higher odds of PTSD onset than either combat exposure or vulnerability factors preceding military service (e.g., childhood physical abuse)[40].

A further mechanism of communal effects involves the patterning of trauma reactions by cultural syndromes and other idioms of distress[41,42]. These are culturally specific forms of expressing emotional distress that arise in local contexts in response to specific culturally-based attributions[43]. Examples relevant to trauma reactions include *ataques de nervios* (attacks of nerves) in Latinx populations, *khyâl* attacks among Cambodians, *ihahamuka* (literally, lungs without breath) among Rwandan genocide survivors, and "thinking too much" in many cultural settings[41,44,45]. These patterned behavioral responses may be evoked as an embodied reaction by traumatic events, if they are linked to a traumatic etiology by the cultural group[46].

Despite this variability in the contexts where potentially traumatic events occur and in the range of their effects, the literature has focused overwhelmingly on one specific type of psychopathology, i.e. PTSD. However, issues raised in this section about the nature of traumatic events continue to be central in the remainder of the paper, whether it be how PTSD should be diagnosed, what are its psychological foundations, or how it can be treated.

DIAGNOSIS OF PTSD

DSM-III to DSM-IV-TR

Although many argue that post-traumatic stress syndromes have been described at least as far back as Homer's Iliad[47], PTSD was not codified as an official mental disorder diagnosis until publication of the DSM-III[48]. Earlier versions of the DSM had included combat-stress reaction as a syndrome, reflecting a long history of research documenting the psychological effects of war on soldiers, including large-scale empirical studies of First World War veterans conducted in the UK and elsewhere[49].

The inclusion of PTSD in the DSM-III has been credited to the convergence of several social movements in the US in the 1960s and 1970s. These included veterans' advocates recognizing the impact of the Vietnam war on those who served; feminists raising awareness of the prevalence and consequences of violence against women; and psychiatrists treating Holocaust survivors[50].

From its introduction, PTSD has been unique in the DSM in requiring a specific environmental stressor for its diagnosis. This component of PTSD has been one of the most debated aspects of its diagnostic criteria. Actually, it plays a gatekeeper role in focusing the disorder on reactions to events involving very high levels of physical threat. The intention has been to prevent a diagnosis of PTSD being applied following events that are regarded as more everyday stressors, such as financial problems.

Up to and including the publication of the DSM-IV-TR in 2000, four sets of symptoms have been consistently part of the PTSD diagnosis: re-experiencing of the traumatic event, avoidance of reminders of the event, numbing in the form of restricted affect or detachment from others, and symptoms of hyperarousal such as sleep disturbance and exaggerated startle response[51]. These have been distributed among three symptom groups, with the allocation of symptoms to groups changing somewhat with successive editions of the DSM. Survival guilt featured in the DSM-III only. Memory impairment for significant aspects of the event has remained in all editions, although it is the symptom most weakly associated with the others[52]. The total number of PTSD symptoms has increased from 12 in the DSM-III to 17 in the DSM-III-R.

Since the DSM-III-R, symptoms have been required to be present for a minimum of one month prior to diagnosis, and since the DSM-IV there has been an additional requirement for them to be accompanied by clinically significant distress or impairment in functioning. These changes have reflected the prevailing view that the symptoms do not indicate pathology in themselves. Pathology is indicated by the failure of the symptoms to remit of their own accord, and by their impact on everyday life.

ICD-10

PTSD was first recognized by the World Health Organization (WHO) as a diagnosis in the ICD-10[53], over a decade after the DSM-III publication. A key difference between the ICD-10 and the DSM-III/IV was that the former used a descriptive text and "diagnostic guidelines" rather than requiring the presence of specific diagnostic criteria. Although potentially helpful in terms of facilitating clinician judgment and applicability in very diverse clinical and cultural settings, the ICD-10 approach has not been easily translated into specific research

instruments. This has likely contributed to the use of structured measures of the DSM construct of PTSD, rather than the ICD guidelines, in most research before 2013.

The ICD-10 stressor description was “a stressful event or situation (either short- or long-lasting) of an exceptionally threatening or catastrophic nature, which is likely to cause pervasive distress in almost anyone”. Symptom descriptions included the following phrases: “Commonly there is fear and avoidance of cues that remind sufferers of the original trauma” and “There is usually a state of autonomic hyperarousal with hypervigilance, an enhanced startle reaction, and insomnia”. The diagnostic guidelines stated: “In addition to evidence of trauma, there must be a repetitive, intrusive recollection or re-enactment of the event in memories, daytime imagery, or dreams. Conspicuous emotional detachment, numbing of feeling, and avoidance of stimuli that might arouse recollection of the trauma are often present but are not essential for the diagnosis. The autonomic disturbances, mood disorder, and behavioural abnormalities all contribute to the diagnosis but are not of prime importance”.

These extracts highlight the many similarities between the two diagnostic systems, but also some differences. In the ICD-10, there was also no requirement for symptoms to last a minimum length of time or to be accompanied by distress or functional impairment. In one large-scale study, agreement between the ICD-10 and the DSM-IV was found to be moderate, with higher rates for the ICD-10 being mainly attributable to the requirement for significant distress or functional impairment in the DSM-IV[54].

DSM-5 and DSM-5-TR

In the DSM-5[55], PTSD was moved from Anxiety Disorders to a new diagnostic section named “Trauma- and Stressor-Related Disorders”, and the definition of trauma was narrowed to events requiring “actual or threatened death, serious injury or sexual violence”.

Significant restructuring of the symptom criteria also occurred. The symptom clusters were expanded from three to four, and the number of symptoms was increased from 17 to 20. To meet diagnostic criteria in the DSM-5, the individual must have one re-experiencing symptom, one avoidance symptom, two symptoms reflecting negative alterations in cognition or mood, and two symptoms reflecting alterations in arousal or reactivity. These changes resulted in a lower PTSD prevalence using the DSM-5 criteria, as compared to the DSM-IV ones. For example, Kilpatrick et al[56] found a lifetime prevalence of 9.8% using the DSM-IV and 8.3% with the DSM-5, when assessing PTSD symptoms in relation to the same event.

The DSM-5 criteria as described above apply to children over 6 years of age, with some qualifications to the re-experiencing symptoms to ensure that they are developmentally appropriate. For example, children may re-enact aspects of the trauma in play rather than explicitly describe recurrent intrusive memories of the trauma.

Following research that found under-diagnosis in pre-school children and tested the validity of alternative criteria[57-59], diagnostic criteria were added in the DSM-5 for children aged 6 and under. These include specifying that the child could develop PTSD if he/she witnessed or heard about a traumatic event happening to a parent or caregiver. There are only three symptom clusters: re-experiencing (one symptom required), avoidance and negative alterations in cognition or mood (one symptom required), and alterations in arousal or reactivity (two symptoms required). Moreover, the descriptions of specific symptoms have been changed to be developmentally appropriate. For example, the adult symptom of irritability or aggression includes “extreme temper tantrums” in children.

The criteria for PTSD remained unchanged in the DSM-5-TR[60]. The description of the disorder in the text was expanded in many areas, including more detailed discussion of what constitutes a traumatic event, the prevalence of PTSD from the World Mental Health Surveys and in conflict-affected populations, and the role of cultural factors and sex- and gender-related issues in the development and clinical expression of the disorder.

Delayed-onset PTSD

There has been an explicit recognition within successive editions of the DSM that PTSD does not always begin directly, or even soon, after the traumatic event. The “delayed-onset” form of PTSD (“with delayed expression” in the DSM-5) is defined as occurring at least 6 months after the traumatic event.

This claim has been controversial in some quarters, because it appears to contradict the commonsense notion that traumatic events overwhelm physical, emotional and psychological defenses. This assumption would imply that PTSD will almost always have an immediate onset. The ICD-10 in fact suggested that onset almost always occurred within 6 months of the traumatic event. As we will see below, however, there is robust epidemiological evidence for a distinct type of PTSD with delayed presentation.

Critiques of the PTSD diagnosis

One initial critique argued that PTSD was a Western construct of limited utility to other cultures and belief systems. However, subsequent research has determined the cross-cultural relevance of the diagnosis, while identifying culturally specific forms of trauma-related distress[41].

Other initial critiques suggested that PTSD did not offer anything additional to, and was not distinguishable from, existing diagnoses of anxiety and depressive disorders. However, PTSD did include symptoms that were not part of other disorders. Although some of these

symptoms, such as intrusive memories and the avoidance of such memories, turned out to be present in other disorders[61], other symptoms did discriminate. Following a traumatic event, flashbacks and dissociative amnesia were found to be present in cases of PTSD but not in cases of non-PTSD psychiatric disorders[62].

Longitudinal studies have successfully discriminated individuals who developed PTSD following trauma from those who developed different psychiatric disorders, identifying separate risk factors for each trajectory[63-65]. However, prospective work which followed people who had no history of depression before trauma exposure showed that depression only developed in those with PTSD[66]. High levels of comorbid depression remain a feature of PTSD, with some twin and molecular genetic studies reporting a high genetic correlation between PTSD and major depression. How best to understand this comorbidity remains a matter of debate, given the limitations in all research designs. One possibility is that individuals with both disorders constitute a distinct phenotype from those with PTSD alone[67].

A persistent critique focuses on the heterogeneity of PTSD, with more than 600,000 combinations of DSM-5 symptoms theoretically able to lead to the diagnosis[68]. The analysis of a large military cohort confirmed that, in practice, over half of the participants who met criteria for PTSD had a unique pattern of symptoms, emphasizing that a DSM-5 PTSD diagnosis does not reflect a uniform phenotype[69]. Some responses to this problem are described in a following section of this paper.

EPIDEMIOLOGY OF PTSD

Prevalence

Due to the ubiquity of trauma exposures globally, PTSD is among the most prevalent mental disorders in the community. Strong evidence for the global burden of PTSD comes from the World Mental Health Surveys, a series of studies conducted using the same measures across multiple countries, allowing for cross-country comparison. A study conducted in 24 countries, with 71,083 respondents, found that the overall lifetime PTSD prevalence in the general population was 3.9%, and varied across high-income (5.0%), upper-middle-income (2.3%), and low- to lower-middle-income (2.1%) countries[70].

Several country-specific population-based studies, and systematic reviews of these studies, confirm the cross-national – and even intra-national – heterogeneity in the prevalence of PTSD. Studies based on World Mental Health Surveys report lifetime prevalences ranging from as low as 1.3% in Japan[71], through 2.2% in Spain[72], and 2.3% in South Africa[73], to the relatively high prevalence of 8.8% in Northern Ireland[74]. The first nationwide mental health

survey in China reported a lifetime prevalence of 0.4%[75]. In the US general population, most studies find a lifetime prevalence around 5% in men and 10% in women, with an overall prevalence of about 8%[76].

Studies of current or one-year prevalence of PTSD highlight the worldwide variation. An analysis of the Adult Psychiatric Morbidity Survey in England reported a prevalence rate for current PTSD of 2.9%[77], similar to the 2.4% reported for Canada[78] and Italy[79]. The Australian National Survey of Mental Health and Well-Being found a 12-month prevalence of PTSD of 1.3%[80]. In contrast, a systematic review and meta-analysis of sub-Saharan African countries reported an overall prevalence during periods from the past week to the past year of 22%. There was substantial heterogeneity in the sample, with the pooled prevalence being 8% in conflict-unexposed and 30% in conflict-exposed regions[81].

The prevalence of PTSD thus appears to vary widely. This is partly due to the population studied, but also to variation in reporting of and exposure to traumatic events. For example, if specific trauma events that are associated with a high risk of PTSD, such as sexual assault, are not reported due to stigma, this will lead to underestimates of PTSD prevalence at the population level.

Another source of variation is methodological. The World Mental Health Surveys tend to report lower lifetime prevalence rates than other studies due to a key difference in assessing for PTSD. Most other studies have employed the “worst trauma” method, in which participants describe PTSD symptoms attributable to the worst traumatic event that they have ever experienced. This tends to overestimate the community prevalence of PTSD because “worst traumas” are not the most prevalent in any community, and less severe traumas may have a different conditional risk for developing PTSD[82]. The World Mental Health Surveys, in contrast, use the “random event” method, in which a random event is selected from the list endorsed by a participant, and PTSD symptoms are assessed in relation to it. Random events might more accurately reflect occurrence of traumatic events in the community, so the PTSD prevalence based on these events might be more representative of the actual burden in the community[32]. Surveys can also vary in numerous other ways, including their sampling frames, the use of interviews or self-administered questionnaires, and the choice of the survey instrument with its associated skip-outs, thresholds, or cut-off scores.

However, methodological standardization does not guarantee that diagnostic instruments are identifying equivalent conceptualizations and experiences of mental disorder. People endorse symptom queries within particular contexts of professional diagnostic practice; there are various levels of public awareness of nosologically defined forms of psychopathology across societies; and local variation affects response sets to survey instruments (e.g., different experiential thresholds at which a symptom is endorsed). All these factors may affect diagnosable rates of disorder[41].

Conditional risk

Whereas the overall prevalence of PTSD reflects the number of cases of the disorder in a population – with a number of factors likely contributing to different cross-national estimates – *conditional risk* refers to the prevalence of PTSD among those exposed to specific traumatic events, focusing on the variation by event type[73]. Overall prevalence is comparable to prevalence estimates for other psychiatric disorders, whereas conditional risk (which may be referred to as "prevalence" in some papers) is not. Conditional risks for trauma-exposed populations are higher than overall prevalences documented in population-wide surveys[32].

Most studies have shown that the conditional risk of PTSD varies depending upon the type of traumatic event, although the ordering of risk across specific events tends to be different across studies. For example, a representative sample of US adults under the age of 45 found the highest conditional risk of PTSD after assaultive violence (20.9%)[83]. In a European study, the highest conditional risks for PTSD were found after having a child with serious illness, being raped, being beaten by partner, being stalked, and being beaten by caregiver[84]. A study of a Brazilian urban population found the highest conditional risks after war-related trauma, childhood sexual abuse, adult sexual violence, and interpersonal violence[85].

In a range of studies, cumulative traumatic events have been found to be associated with greater subsequent risk of PTSD and greater severity of PTSD symptoms[86].

Demographic differences

Women are reported to have a 2-3 times higher risk of developing PTSD than men[87]. While men are more likely to experience traumatic events, women are about twice as likely to have PTSD after most of them. However, the conditional risk of PTSD is reported to be similar for men and women after childhood sexual abuse and sexual assault[88]. Importantly, traumatic events experienced by men and women tend to differ, with women experiencing more sexual assault and childhood sexual abuse, two of the traumatic events with the highest conditional risk for PTSD.

Evidence also suggests that gender non-binary and transgender persons have a prevalence of PTSD three to ten times higher than that reported in general population studies[89]. Although further research is needed, this higher prevalence is likely to reflect the higher burden of violence faced by LGBTQ+ populations as well as the additional impact of discrimination[90].

Age differences in PTSD are unclear. Findings from a German community-based study did not find substantial differences in PTSD reports by age[91], consistent with a review of

available studies[92]. In Northern Ireland, being younger than 65 was associated with increased PTSD risk[74]. Some smaller studies have noted differences by age, including, for example, a longitudinal study of survivors of motor vehicle accidents, which found higher PTSD reports among middle-aged vs. younger or older-aged women[93].

Several individual-level markers of social and economic status have been documented to be linked to PTSD[94]. These include low education[79], lower household income[70], and being retired or unemployed[70,74].

Sociocultural differences

The risk of PTSD differs by ethnoracial background, likely due to socio-structural factors, cultural interpretations, and/or trauma-exposure-related characteristics that covary with race/ethnicity in unequal societies[41,95].

For example, a higher prevalence of PTSD has been reported among Latinx vs. non-Latinx White individuals in several circumstances, including as combat veterans of the Vietnam War (after adjusting for degree of exposure and other demographic characteristics); as residents of lower Manhattan after the September 11, 2001 attacks; as police officers exposed to line-of-duty trauma; and as survivors of a devastating hurricane (adjusting for trauma exposure)[95].

The risk of PTSD also varies according to cultural interpretations and social contexts that influence the perceived severity of a stressor[41]. Among these are the relative severity of traumatic events affecting family members vs. the individual[33], the impact of religious persecution over other stressors[38], or the effect of being unable to conduct burial rituals beyond the impact of the death itself[39].

Among the covariates that likely influence the relation between traumatic event exposure and risk of PTSD according to ethnoracial background are the availability of social support and other social resources that tend to facilitate recovery from traumatic events[96], as well as the exposure to discrimination and persistent inequality (e.g., in wealth and other assets)[97,98].

There are probably important cross-cultural differences in PTSD symptomatology, although they are incompletely documented. For instance, numbing-avoidance reactions vary cross-culturally, as noted in studies with Vietnamese refugees and Kalahari bushmen, while somatic complaints are prototypical features of PTSD in some cultural groups and less common in others[46,99]. Some PTSD symptoms tend to be especially salient in certain groups, such as nightmares among Cambodians[100] and American Indians/Alaskan Natives[101]. These variations in PTSD symptoms are often influenced by the idioms of distress that are considered culturally normative responses to traumatic exposures. Nevertheless, despite these local variations, there is considerable cross-cultural validity of PTSD as a construct[41].

Some of the previously mentioned demographic differences vary across cultural and ethnoracial groups. For example, in a large US community-based epidemiological study, gender differences were found for non-Latinx White, African American and Afro-Caribbean women, but not for Latinx or Asian-origin women[102]. Also, little association between PTSD and gender has been found in South Africa[73]. These differences have been attributed, among other factors, to variation in types of trauma exposure (e.g., similar exposure across genders to state-sponsored violence during the apartheid regime in South Africa), to shared socio-structural factors such as discrimination among US Latinx, and to cultural variations in gender-based expectations of what constitutes abuse[73,102].

Mass traumatic events

There is a substantial literature suggesting that the population burden of PTSD can be high after mass traumatic events. For example, a systematic review and meta-analysis of the global burden of PTSD in war-affected countries found an overall population prevalence of 26.5%[103]. However, variability in the mass traumatic events studied, the exposure among persons in samples, the methods of measurement, and the assessment tools used – in studies that are often conducted quickly after unexpected events – make generalization about the consequences of these mass traumatic events difficult.

It is probably not useful to provide single estimates of PTSD prevalence in the aftermath of mass traumatic events, given the diverse populations that likely experience the event differently from one another. For instance, a review that synthesized the available literature estimated the prevalence of PTSD after mass traumatic events at 30-40% among direct victims, 10-20% among rescue workers, and 5-10% in the general population[104]. The prevalence of PTSD has been documented to be particularly high among children directly exposed to mass traumatic events[105].

In recent years, several studies have documented the burden of PTSD in the context of global traumas such as the COVID-19 pandemic. A meta-analysis of 63 COVID-related studies found an overall PTSD prevalence of 17.5% at the population level[106].

Trajectories after trauma and course of PTSD

After a traumatic event, four main trajectories have been usually reported: resilient (or resistant), in which persons have stable long-term healthy functioning and no (or few) PTSD symptoms; chronic, indicating long-lasting PTSD symptoms; recovered, with early onset of PTSD symptoms and subsequent remission; and delayed-onset, in which PTSD develops sometime after trauma exposure[107-109]. There is little consistency across studies about the

relative prevalence of these trajectories. Among 54 studies reviewed, however, the resilience trajectory was the modal response (average of 65.7% across populations), followed by recovery (20.8%), chronicity (10.6%), and delayed onset (8.9%)[108].

The majority of research has been concerned with the course of established PTSD. A systematic review found that, after a mean observation period of 40 months, an average of 44.0% of individuals with PTSD at baseline no longer met disorder criteria. There was wide inter-study variation in remission rates from 8 to 89%, with rates being higher the sooner PTSD was measured after the traumatic event[110]. Among patients assessed in clinical settings, 18-50% experienced recovery within 3-7 years, while the remainder had a recurrent or more chronic course[111].

Most of the evidence suggests a dose-response effect of traumatic load on the probability of long-term spontaneous remission of PTSD: a higher cumulative exposure to traumatic events is associated with a lower probability of remission[112]. The type of the experienced traumatic event(s) also contributes to the course of PTSD. One systematic review of untreated PTSD suggested that the perceived intentionality of traumatic events – such as domestic abuse (intentional) vs. natural disasters (unintentional) – was associated with worsening as opposed to improving trajectories, respectively. In five studies of exposure to intentional trauma, about one-third of persons with PTSD remitted after 3 months, while another third had chronic PTSD lasting more than 6 months[15].

PTSD course may also be affected by social disadvantage, via the link between resources and access to treatment. The World Mental Health Surveys highlight substantial differences in treatment seeking[70], with the proportion of people with PTSD accessing treatment in the previous 12 months being 53.5% in high-income countries, 28.7% in upper-middle-income countries, and 22.8% in low- and lower-middle-income countries. A subsequent analysis of data from 17 surveys[113] across 15 countries found that 43% of people with PTSD received any mental health services, including 50.6% in high-income countries vs. 19.8% in low- and middle-income countries.

Of special interest has been delayed-onset PTSD. Meta-analyses of prospective studies report that around a quarter of PTSD cases have their onset at least 6 months after the traumatic event[114,115]. Factors associated with delayed-onset PTSD are found to be encountering trauma in a professional capacity (e.g., military personnel, firefighters, rescue workers, police) and “Western” cultural background (defined by country of origin).

A systematic review found that delayed-onset PTSD in the absence of any prior symptoms was rare[116,117]. Delayed onsets that represented exacerbations or reactivations of prior symptoms accounted for 38.2% of military and 15.3% of civilian cases[116].

ROLE OF THE TRAUMATIC EVENT

With the introduction of PTSD in the DSM-III[48], traumatic events were conceptualized as being so extreme as to produce "significant symptoms of distress in almost anyone". This claim helped to justify the need for PTSD as a disorder that, most unusually for a psychiatric diagnosis, was primarily caused by environmental factors. The DSM-III-R[118] further specified such events as being "outside the realm of normal experience" and added a list of characteristics, including serious threat or actual injury, destruction of one's home or community, and witnessing mutilation or violent death. There was also a recognition that the events included serious threat or harm to one's children, spouse, or other close relatives and friends.

The DSM-IV[119] expanded the range of qualifying stressors affecting family and close friends to include learning about their sudden and unexpected death from any cause, and learning about traumatic events that they experienced. Furthermore, it included the person him/herself being sexually abused in childhood or diagnosed with a life-threatening illness. It recognized that traumatic events were not outside normal human experience but were relatively common.

The DSM-IV also acknowledged a subjective component in how individuals responded, with events not having to be "markedly distressing to almost anyone" but instead requiring that the "person's response involved intense fear, helplessness, or horror". Whether this response had to be present at the time of the trauma itself or could arise later, for example with the development of delayed-onset PTSD, was not specified. Compared to the DSM-III-R, most of the additional PTSD cases brought about by expanding the list of qualifying events were attributable to learning about the sudden unexpected death of a close relative or friend[120], emphasizing the importance of social attachments in PTSD.

The subjective requirement introduced in the DSM-IV was argued to add little diagnostic specificity. In fact, in surveys, events that did not involve intense fear, helplessness or horror were unlikely to meet the remaining criteria for the diagnosis. This finding was partly responsible for the requirement being dropped in the DSM-5, with a consequent reduction in the role of subjectivity[55]. The DSM-5 clarified that the diagnosis required exposure to actual or threatened death, serious injury, or sexual violence, either through direct experience, or witnessing in person the event happening to someone else, or learning that it occurred to close relatives or friends.

In cases of the actual or threatened death of a family member or friend, the event was required to be violent or accidental. This eliminated many events considered traumatic under the DSM-IV, such as non-immediate, non-catastrophic, but nevertheless life-threatening medical events with natural causes. An extensive body of research documents that after such

events, for example receiving a cancer diagnosis or having a heart attack, people may present symptoms of traumatic stress and meet other criteria for PTSD[121-123].

A fourth type of exposure new in the DSM-5 involved repeated or extreme encounters with aversive details of a traumatic event, e.g., first responders collecting human remains. Such exposure was excluded if it occurred solely via electronic media, unless this was work-related, for example police officers examining Internet sites for evidence of child abuse.

This persistent expansion of qualifying traumatic events led to concerns about "criterion creep", whereby PTSD would become trivialized and associated with stressors such as divorce, financial problems, and verbal bullying[124,125]. This tendency has been evident in the proliferation of the term "trauma" in colloquial language and social media. However, concerns about criterion creep were mainly raised in the context of litigation and claims for damages, rather than arising in the clinic. We are unaware of any substantiated claims of PTSD being formally diagnosed after such events in the absence of a history of more serious trauma.

An opposite concern lies in the growing recognition that the voices of various relevant groups have been marginalized in the discussions and decisions made on what qualifies as a traumatic event. The diagnostic formulation has reflected the views of influential clinicians and researchers, but has not considered the input of people with lived experience of trauma in different contexts.

The approach taken by the DSM in specifying the objective nature of traumatic events is designed to prevent the inappropriate use of the diagnosis and its application to non-traumatic stressors. There is an assumption that traumatic events involving life threat or risk to the integrity of one's person are qualitatively different from other stressful life events, so that the PTSD trauma definition should be limited to events meeting this high bar of exposure severity[126]. Survey evidence, however, suggests that relaxing the criteria so that a broad range of events can potentially qualify as traumatic makes little difference to prevalence rates of PTSD as defined by the DSM-IV[127,128].

Since even catastrophic events are generally followed by PTSD in some individuals but not others, there are likely to be complex interactions between individual risk factors and the harmfulness of a given stressful event[129]. The implication is that, in the presence of the relevant risk factors, events not included in the DSM definition might be followed by a syndrome with the characteristics of PTSD. Consistent with this, there are least three categories of events not considered by the DSM that are empirically associated with high levels of PTSD symptoms. These include: a) repeated, cumulative aversive experiences such as stalking, bullying, emotional abuse, neglect and harassment, sometimes exacerbated by systemic discrimination[130-132]; b) terrifying hallucinations experienced by patients with psychosis or undergoing sedation in intensive care[133,134]; and c) stressors encountered by non-neurotypical groups such as people with autism[135]. Such cases have not been prominent in

general population surveys, but may account for significant degrees of morbidity in more specific groups.

In the DSM-5, the majority of these presentations would currently have to be diagnosed as adjustment disorders, a situation that has been acknowledged as possibly incongruous if the same symptoms lead to two different diagnoses[129]. However, reports of PTSD diagnoses in response to events not considered in the DSM might instead be indicative of psychometric deficiencies in the measures used, particularly if these rely upon self-report. In the case of an individual experiencing terrifying hallucinations of events that did not occur in reality, the hallucination would not be considered a traumatic event by the DSM-5, but would be accounted for by the primary psychotic diagnosis and the associated impairment in reality testing.

We will see later on that the ICD-11 allows a diagnosis of PTSD in a wide variety of traumatic situations, as it only requires exposure to an event or series of events judged by the clinician to be extremely threatening or horrific. An alternative proposal[136,137] is to acknowledge the poor validity of attempts to define traumatic events by dispensing with this altogether, relying instead on the pattern of symptoms and resulting disability to diagnose PTSD.

A related view is that PTSD is often an outcome of specific peri-traumatic and post-traumatic responses. These responses are usually associated with the objective circumstances identified in the DSM-5, but may also occur in other situations. The responses may reflect a specific phenotype associated with a failure to recover from the normal effects of trauma[18], or be related to prior exposure to childhood adversity, or to different patterns of environmental exposure such as overwhelming or cumulative trauma, or to specific types of appraisal, or to the use of certain coping strategies.

Peri-traumatic responses that increase the risk of PTSD can reflect both previous history and psychological or biological susceptibility. They typically involve the subjective experience of fear, helplessness or horror, but may have additional components that mark them out from everyday stress responses. To date, psychological variables appear to be stronger markers of these responses than biological ones. They are characterized by cognitive overload (being unable to reflect or plan normally), mental defeat or resignation, and dissociative symptoms such as changes to visual and body perception[138-140].

A frequent pattern of PTSD development takes place when these peri-traumatic responses are followed by negative appraisals and maladaptive post-traumatic behaviors such as thought suppression and rumination[141], or by negative social reactions such as criticism and rejection[142-144]. The occurrence of subsequent stressors, not necessarily of a traumatic kind, is also an important contributor to onset[94].

The adoption of fixed and objective versus more flexible criteria for what constitutes a traumatic event primarily reflects strategic priorities. The former approach helps to exclude

invalid cases of PTSD, whereas the latter is designed to include all valid cases of the disorder. In moving forward, what is needed are more data on how PTSD presents following more "objectively" and more "subjectively" traumatic events. It is important to establish, for example, whether PTSD following repeated low-impact or hallucinated events, or occurring in non-neurotypical groups, is different in any respect from more conventionally recognized cases of PTSD, either in the way it develops, its symptom pattern, or its chronicity. Studies may lead to the identification of additional conditions within a "family" of post-traumatic stress disorders.

A separate, but equally important, issue is whether the different situations in which PTSD manifests require similar, or dissimilar, treatment approaches. The expansion of potentially traumatic stressors may offer an important opportunity to better understand the nature of the condition, and to more appropriately tailor its management.

DEVELOPMENTS IN DIAGNOSIS

The DSM-5 dissociative subtype

The DSM-5 introduced a dissociative subtype of PTSD characterized by meeting full criteria for the disorder and exhibiting ongoing symptoms of depersonalization and/or derealization. This addition was based, in part, on the results of latent class and latent profile analyses which showed that a small subset of individuals with PTSD (from 10 to 30%) exhibited prominent symptoms of derealization and depersonalization, and that PTSD severity alone did not predict who would manifest these symptoms[145].

Close to 20 studies have used latent class or profile analysis across a range of cohorts differing in age, geographic location, civilian status, and primary trauma exposure type, and provided support for this unique presentation of PTSD[146-149]. A recent study compared the fit of class models (which directly support the unique group of individuals with the dissociative subtype) to confirmatory factor models (which would account for the dissociative symptoms dimensionally by virtue of their correlation with PTSD symptom severity) and factor mixture models (a mix of factors and classes) among trauma-exposed veterans. The results indicated that, of these three types of models, the subtype structure provided the best fit to the data[150].

Consistent with this, there is preliminary evidence that the dissociative subtype may be associated with unique biological correlates relative to the core symptoms of PTSD. These include genotypes that are predictive of the dissociative symptoms after covarying for PTSD severity[150], and alterations in brain morphology and function[150-154]. However, the implicated brain regions and the nature of these alterations have varied greatly across studies[150,152,155,156]. It is also important to note that these studies have generally focused on trait dissociation (as

opposed to a state of active dissociation), so that these alterations may reflect a vulnerability or proclivity to dissociative experiences rather than the neurobiology of an active dissociative experience. In addition to potential biological differences, there is also evidence that individuals with the dissociative subtype may respond less well to psychotherapy for PTSD[157] and to pharmacological treatment[158].

Collectively, these differences in symptom presentation, biology and treatment response highlight the importance of delineating the dissociative subtype for both research and clinical purposes.

ICD-11 PTSD and complex PTSD

The ICD-11 set out to achieve several goals in its definition of stress-related disorders. These included maximizing clinical utility, by making the diagnoses simpler and more focused on core features to distinguish them from other disorders; raising the threshold for PTSD relative to the ICD-10 by including consideration of functional impairment; integrating PTSD more successfully with the ICD-10 "enduring personality change after catastrophic experience" diagnosis; and addressing the perceived need for a diagnosis of complex PTSD. The Working Group who developed the proposals included trauma experts from many parts of the globe[159].

Attempts to establish the core features of PTSD have most commonly identified nightmares, flashbacks, exaggerated startle response, and hypervigilance[62,136,160-162]. Avoidance has been suggested as another essential component of PTSD (even though one shared with other anxiety disorders and depression)[136]. In line with these observations, PTSD is defined in the ICD-11 by three sets of symptoms, with one indicator of each being required: a) re-experiencing of the event in the here-and-now (presence of flashbacks or nightmares); b) avoidance of traumatic reminders (avoidance of thoughts and memories or external situations and reminders); and c) a sense of current threat (presence of either hypervigilance or exaggerated startle response). Symptoms must follow an extremely threatening or horrific event or series of events, last for several weeks, and be accompanied by functional impairment[159].

Although those symptoms also appear in the DSM-5, the ICD-11 formulation is narrower and more specific. This is particularly true for the re-experiencing cluster. Intrusive thoughts and memories are found in many disorders. What characterizes PTSD is that the intrusive memories have strong sensory elements and are experienced as happening again in the present[61]. Like the DSM-5, the ICD-11 describes flashbacks as existing on a continuum, from intrusive memories with a fleeting sense of "nowness" to complete absorption in the traumatic memory and loss of awareness of the current environment.

The ICD-11 also introduced a separate diagnosis of complex PTSD, a more severe condition. This differs in several respects from previous formulations of complex PTSD[163] and from the ICD-10 "enduring personality change after catastrophic experience"[164]. Unlike them, it requires the presence of ICD-11 PTSD symptoms. Another difference is that exposure to chronic or repeated trauma is conceptualized as a risk factor, likely to be present but not required for the diagnosis.

In addition to the three PTSD symptom clusters, the ICD-11 diagnosis of complex PTSD is defined by three further sets of symptoms that emerge or intensify following the traumatic event, i.e. affective dysregulation, negative self-concept, and disturbances in relationships. These symptoms are collectively labelled "disturbances in self-organization". Symptoms were selected because they were frequently reported by participants in the DSM-IV field trials of a complex form of PTSD[165], and were identified by expert clinicians as the most common and impairing in clinical practice[166].

In the ICD-11, individuals may be diagnosed with PTSD or complex PTSD, but not both. A PTSD diagnosis implies that the requirements for complex PTSD are not met. The requirements for ICD-11 PTSD or complex PTSD are markedly harder to be met than those for ICD-10 PTSD, and somewhat harder to be fulfilled than the DSM-IV or DSM-5 criteria for PTSD[167]. Comorbid depression, while still frequent, appears to be less common in PTSD diagnosed according to ICD-11 than DSM-IV or DSM-5[167]. Individuals who qualify for the diagnosis of PTSD according to ICD-10 or DSM-5, but not for the ICD-11 diagnosis of PTSD or complex PTSD, may meet requirements for alternative diagnoses such as major depressive disorder.

The distinction between ICD-11 PTSD and complex PTSD has been extensively tested by research[167-170]. Confirmatory factor analysis carried out in many different cultures has found that complex PTSD includes six correlated first-order factors in line with the six symptom clusters, and two correlated second-order factors in line with the dimensions of PTSD and disturbances in self-organization. Distinct groups with symptom profiles corresponding to PTSD and complex PTSD have been repeatedly identified in mixture-modeling studies with disparate groups such as children and adolescents, military veterans, refugees, and asylum seekers. Those in the complex PTSD class typically report more functional impairment than those in the PTSD class.

It is sometimes suggested that complex PTSD is simply a more severe form of PTSD[171]. This possibility is addressed by factor-mixture modeling, a technique that combines dimensional and categorical analysis. An early study[172] reported factor-mixture models in two cohorts and found that, after controlling for a gradient of symptom severity, the PTSD and complex PTSD classes differed quantitatively but not qualitatively. In contrast, a study of refugees found evidence for qualitatively distinct PTSD and complex PTSD classes[173].

However, both these studies were performed before tailored instruments for the assessment of ICD-11 complex PTSD symptoms were available.

Two recent studies utilized the International Trauma Questionnaire[174], specifically developed for ICD-11 PTSD and complex PTSD, to assess symptom structure in a sample of young people and one of adults from the general population. Both studies found that ICD-11 PTSD and complex PTSD formed distinct latent classes and did not simply differ on a severity dimension[175,176]. Additional research employing factor-mixture modeling in large and diverse cohorts is needed to further address this question.

The evidence base for ICD-11 PTSD and complex PTSD now includes research, predominantly psychometric, carried out in five continents. It is not yet known whether these diagnoses will fulfil the WHO's intention of improving the recognition of trauma-related disorders. Studies are required that evaluate the relevance and practical utility of these diagnoses in different cultural settings, as exemplified by research among young people in violent neighborhoods in Brazil[177].

Another important issue is to understand why some people receive a PTSD diagnosis with the DSM-5 but not with the ICD-11. This could shed valuable light both on the nature of PTSD and on the strengths and weaknesses of both systems.

Comparing ICD-11 and DSM-5

The ICD-11 and DSM-5 approaches to representing post-traumatic psychopathology diverge in important ways. While the ICD-11 reduced the number of PTSD symptoms (relative to the ICD-10) to three core features of the disorder, and encompassed other enduring post-traumatic responses in the diagnosis of complex PTSD, the DSM-5 increased the number of symptom clusters (to 4) and symptoms (to 20) under the PTSD criteria.

Both approaches have advantages and disadvantages. The DSM-5 attempts to represent a greater breadth of symptoms under one diagnosis, and includes more items per symptom cluster, which allows for greater reliability[178]. However, the inclusion of more non-specific diagnostic criteria that are characteristic of generalized distress (e.g., chronic mood disturbance, distorted negative cognitions, sleep and concentration difficulties) may artificially inflate diagnostic comorbidity and introduce redundancy into the diagnostic taxonomy across a variety of mood and anxiety disorders.

In contrast, the ICD-11 approach is streamlined in its focus on the core and perhaps defining features of PTSD, but may fail to identify some individuals who experience alternative manifestations of post-traumatic psychopathology. For example, there may be some intrusive traumatic memories that do not meet the definition of flashbacks or nightmares. Given the transdiagnostic nature of intrusive memories, and the need for accurate assessment to

differentiate them from rumination about the causes or consequences of a traumatic experience, additional research is needed to determine whether such manifestations are best considered as indicative of PTSD or as part of other disorders such as major depression.

In contrast to the DSM-5, the ICD-11 does not include a dissociative subtype of PTSD or complex PTSD. However, one of the two ways by which an individual can meet the ICD-11 re-experiencing criterion is by having flashbacks, which are generally regarded as dissociative experiences. Further, affective dysregulation can be manifested as emotional numbing, which can be an expression of dissociation wherein an individual is separated from his/her own emotional experience. Thus, dissociation is actually represented in the current ICD-11 criteria. There is also evidence that individuals with complex PTSD may be particularly prone to dissociation[179,180], perhaps in relation to childhood trauma exposure[181].

Additional research is needed to determine if dissociative experiences are a core component of PTSD or complex PTSD, or are evident only in a unique subgroup of individuals with these conditions. The definition of dissociation employed will impact the results of research addressing this question, as some forms of dissociation (such as reduction in awareness of experience) are common and appear to covary linearly with PTSD symptom severity, while other forms (such as derealization and depersonalization) are far less common and are not strongly correlated with PTSD severity[145].

PSYCHOLOGICAL FOUNDATIONS OF PTSD

PTSD involves many different psychological processes, including attention, causal and other beliefs, affective reactions, coping strategies, and social interactions[182]. However, psychological theories of PTSD have mostly focused on disturbances to memory for the traumatic event and on the impact of the event on the survivors' identity, in particular the way in which they conceptualize and experience the self.

Trauma memory disturbance

Many different aspects of memory are affected in PTSD. When it comes to non-trauma-related material, people with this disorder have difficulty learning and remembering new items, particularly verbal items; their working memory functions less well; when given the task of recalling specific personal experiences to cue words, they tend to retrieve examples that are overgeneral in that they are repeated or last more than one day; they are also more prone to associative memory illusions[183]. However, more pertinent is the way in which memory for the

person's traumatic experiences functions – this is central to psychological theories of PTSD and to the aims of psychological therapy.

Enhanced re-experiencing

The most distressing and disruptive form of re-experiencing of the traumatic event in PTSD consists of flashbacks. These are usually brief and involve a few specific scenes, although they may involve a series of scenes that are experienced as like a videotape[184,185]. They contain very prominent sensory elements, as well as emotions and bodily sensations – such as heat, cold or pain – that were part of the traumatic event[186], and cannot be retrieved deliberately as ordinary autobiographical memories can. Another way in which they differ from ordinary memories is that there is a distortion in the sense of time, whereby they are to a greater or lesser degree re-experienced in the present or here-and-now[187-189] rather than as belonging to the past.

Re-experiencing trauma memories in this way is predictive of the course of the disorder over and above the overall symptom severity[190,191]. With treatment, intrusive memories of the traumatic event become less vivid, less distressing, and have less of a sense of being relived in the present[192,193].

Less commonly, there may be intrusive images that are partly based on the traumatic event but contain fantasy elements such as "what could have happened", as well as images that are entirely based on imagination[194,195]. There may also be involuntary autobiographical memories of aspects of the traumatic event that are experienced as belonging wholly to the past. Compared to flashbacks, much less is known about the significance of these intrusions and how best to treat them.

Impaired voluntary recall

Trauma clinicians are familiar with PTSD patients reporting puzzling gaps in their memories for the index event(s) or, more frequently, difficulty in constructing a coherent and ordered narrative. It is not uncommon for significant details to be recalled, apparently for the first time, during the course of psychological therapy[196]. Moreover, impairments in voluntary trauma memory have been found consistently to be related to self-reported dissociation, either during or after the traumatic event, and to predict the course of PTSD[197].

Studies of coherence and disorganization in trauma memories have mostly used three types of measurement. First, respondents rate the overall amount of fragmentation or disorganization in their own memories, or write trauma narratives that are rated by themselves or independent judges. Second, similar overall measures assess narrative coherence, on the

assumption that this is the opposite of fragmentation and disorganization. Third, trauma narratives are divided into individual utterance units, and raters assess linguistic markers of disorganization and fragmentation such as repetition and non-consecutive chunks.

There has been disagreement over whether these studies do[197] or do not[198] provide evidence for greater fragmentation or disorganization in the trauma narratives of PTSD patients compared to healthy controls. A recent meta-analysis[199] found that there is a significant association of moderate size between PTSD and fragmented trauma narratives. However, this is qualified by the methods used. Measures that assess disorganization and fragmentation directly, whether by self-ratings or judge ratings, show a strong association, but measures that define them as an absence of coherence show little if any association. This indicates that a narrative may be clearly disorganized in parts, perhaps during the most terrifying moments, without necessarily affecting elements of coherence such as having an overall story with a logical structure that makes sense.

Theoretical perspectives

Encoding of context

Some cognitive accounts of PTSD see the condition as reflecting the operation of normal episodic, or more specifically autobiographical, memory[200,201]. These accounts propose that – after traumatic events – factors such as the memory's emotional intensity, its tendency to come repeatedly to mind, and its salience all strengthen the accessibility of a memory, the links with its associated context, and its ease of retrieval. Although these theories can account for many aspects of PTSD, the evidence for memory fragmentation and disorganization is counter to their predictions.

In contrast, clinical theories of PTSD have often incorporated the idea that contextual information is less strongly, not more strongly, associated with the traumatic stimuli. In conditioning theories, a process of stimulus generalization is thought to affect elements of the traumatic situation, such that similar stimuli encountered in dissimilar contexts act as reminders and lead to the return of the fear memory[202]. According to another model, the traumatic event alters the way in which contextual information is represented. For example, following an unexpected attack, many situations previously regarded as safe now become unsafe, so that a wide range of environmental cues can potentially trigger a fear memory[203].

Other clinical theories emphasize that, in PTSD, frightening or horrific moments are poorly elaborated, not fully situated in time and place, and inadequately integrated into the person's general autobiographical knowledge[61,204]. These clinical theories have much in common with biological models that also associate PTSD with impairments in the learning of context[205,206].

Single versus multiple representational formats

Several authors have attributed the symptoms of PTSD to an exceptionally strongly encoded trauma memory in a single representational format. An influential perspective[203,207] holds that the trauma memory representations take the form of highly associated networks containing stimulus, response and meaning elements. The activation of any element, for example by encountering a trauma reminder, then activates all the elements in the network, leading to a re-experiencing of the event.

Although these theories explain many aspects of PTSD, they cannot readily account for the subjective distinction that people with PTSD make between involuntary phenomena, such as flashbacks, and ordinary memories that are easily retrieved, reflected upon, and communicated to others[208]. In contrast, dual representation theory[61] explicitly posits that traumatic events are encoded separately in a lower-level, image-based memory system governed by associative principles, and in a fully contextualized episodic memory system. Under normal conditions these systems are well integrated, but extreme fear, helplessness or horror causes the balance to shift, so that sensation-near images are strongly encoded while contextualized representations are weakened, failing to provide a context for re-experiencing. This model accounts for the fact that people with PTSD can appraise and provide linguistic accounts of many aspects of their trauma, while being unable to control the re-experiencing of specific moments.

Similarly, the cognitive model of PTSD[204] refers to the existence of parallel data-driven and conceptual processing during traumatic events. Data-driven processing is a lower-level form of processing and is associated with automatic, cue-driven retrieval of trauma memories and enhanced perceptual priming, defined as a reduced perceptual threshold for trauma-related sensory stimuli. Conceptual processing is language-based and is associated with the conscious appraisal of traumatic events and their sequelae.

Although differing in their emphasis on representations versus processes, both the cognitive model and the dual representation theory posit lower-level associative memories and higher-order, language-based memories of traumatic events[141].

Identity disturbance

Identity is a construct that spans past and future, summarizing previous experience but also projecting into the years that remain to be lived. Objective identity, or the Me-self, consists of a person's perception of his/her own traits and characteristics. Subjective identity, or the I-self, consists of the person's experience, including the emotional and bodily states that accompany feelings such as pride, shame or guilt.

The way in which people have been treated, and are being treated, by family, friends, teachers, colleagues, employers, and the wider community shapes their perceptions of who they are and what they can expect from social relationships. Not surprisingly, the quality of social relationships post-trauma is one of the strongest predictors of PTSD, with criticism or verbal attack being particularly detrimental[94,142,209].

Identity is multi-faceted, deriving from each person's physical and mental attributes, from the many different experiences in the multiple roles that the person plays (e.g., child, sibling, student, employee) and the situations that he/she encounters (work, family, school, interactions within own community, interactions with different communities), and from his/her goals and aspirations. Individuals differ in the degree to which these different facets are perceived to be integrated into a whole, with early childhood trauma making this process harder[210]. Some of these facets will correspond to identities that attract social stigma, whether or not this is observable to others[211]. Internalized stigma is the process by which people apply negative stereotypes to themselves, and expect to be rejected by others[212]. It is normal to try to manage one's identity by strengthening the positive, desired aspects and avoiding the negative or feared aspects coming to mind[213].

The impact of the traumatic event on the Me-self of the individual with PTSD has been regarded as a major feature of the condition from the very beginning. The event is frequently seen as bringing about drastic negative changes in the person's perception of him/herself, other people, and his/her future, that are often viewed as permanent[214,215], and can become a central turning point in the person's autobiographical narrative[216].

The event can cause disruptions in beliefs about core social expectations of safety, trust, power, esteem and intimacy[217]. It can be seen as challenging long-held assumptions that the self is basically worthy and that other people have benevolent intentions[218]. Alternatively, it may strongly reinforce existing concerns about the self and others, created by processes such as self-stigmatization and previous exposure to adversity[207].

It has been argued that survivors respond to these challenges in a number of different ways[219]. The situation may be reinterpreted in a distorted way, so that it can be assimilated into existing beliefs. For example, someone with a prior belief that bad things only happen to bad people may conclude that he/she must have done something wrong for the traumatic event to have occurred. Over-accommodation takes place when the event is followed by a complete abandonment of the pre-existing belief and the adoption of a new, extreme variant. For example, after an unexpected assault, someone may adopt the belief that nowhere is safe for him/her and no one is to be trusted.

Identity-related perceptions in PTSD, such as self-blame and holding others to be untrustworthy, have been suggested to derive from deep-seated beliefs of the form "I am totally incompetent" or "The world is completely dangerous"[207]. People already holding such

rigid negative views may have them confirmed by negative appraisals of the traumatic event, of symptoms that developed afterwards, of interference with successful functioning, and of others' responses.

A focus on negative beliefs and cognitions plays a central role in the cognitive theory of PTSD[204]. Individuals may blame themselves for the event happening, for their reactions or behaviors during or after the event, or for the symptoms that they develop subsequently. They may perceive that the event has led to a permanent change for the worse[220]. These appraisals predict the course of the disorder, often over and above initial symptoms[190,221,222], as well as driving symptom change in PTSD therapy[223,224]. Identity-protective responses such as thought suppression, rumination, and safety behaviors (i.e., actions aimed to prevent the occurrence of a feared outcome or reduce associated distress) appear to maintain the disorder[141].

In PTSD, changes to the I-self are also routinely observed. It is common for people to experience their body differently, for example with areas of medically unexplained pain[179,225,226]; to feel that their character or body is worthless or shameful[227,228]; to experience themselves as defeated, empty or even dead[204,229]; and to feel alienated from others[230].

Veterans with PTSD also frequently report the experience of shame[231], as well as feelings of disconnection from the civilian world[232]. One factor that is sometimes involved is moral injury, an experience of powerful negative emotions arising from the person's sense of having violated his/her own moral standards, or of having been betrayed by others[233]. Moral injury is common to a wide range of professions, including emergency services and health care workers[234], and is an important predictor of PTSD symptoms in former military samples[235].

The Memory and Identity theory[168] proposes that alterations in both the Me-self and the I-self are central to complex PTSD. Traumatic events confirm and prompt the reactivation of prior negative identities emerging due to childhood adversity, leading to a more pervasive and negative sense of self. The re-enactment of situations in which the self was experienced as worthless or inferior is linked to pervasive negative self-concept symptoms. Re-enactment of the self being abandoned, betrayed and/or alienated from others is linked to the disturbed relationship symptoms. Re-enactment of all these selves, and of experiencing being fragmented or non-existent, may foster the development of emotion regulation problems.

The theory further posits that chronic or repeated traumatic events may also create new negative identities, even in the absence of childhood adversity. For example, exposure to extreme situations such as torture can result not only in pain and suffering, but in dehumanization, degradation, and emotional isolation[236]. The repeated humiliation, criticism, and body shaming that are frequently part of intimate partner violence have been argued to be attempts to destroy positive identities and replace them with a sense of worthlessness[237,238]. War and genocide may also involve the conscious attempt to destroy the cultural identity of an entire population[239].

Identity is also an important element of Conservation of Resources Theory, a general theory holding that stress emerges in response to actual, or threatened, loss of resources[240,241]. Among the many types of resources, some of the most important are the physical (e.g., housing), the social (e.g., family and community support), and the structural (e.g., employment) ones. Numerous studies have found an increased occurrence of PTSD to be associated with traumatic events producing greater resource loss[242,243], and recovery to be predicted by resource gains[244]. This theory makes the important point that resource loss is critical to survival, social attachments, and social status. It thus generally threatens core aspects of the individual's Me-self and I-self, and often the identity of the family and wider group in which the individual is embedded.

Delayed-onset PTSD

The mnemonic model of PTSD suggests that the disorder arises not from the traumatic event itself but from the memory of that event[52]. Delayed-onset PTSD illustrates that in some cases the traumatic memory does indeed appear to change over time, for example becoming more distressing and intrusive.

There has been little investigation of the foundations of this form of PTSD. One study that compared immediate and delayed onsets in military veterans[245] found that the number of respondents reporting depression and alcohol abuse before the main trauma in service was significantly greater in the delayed-onset group. The two groups described similar amounts of military trauma exposure, but those in the delayed-onset group reported significantly less peri-traumatic dissociation, anger and shame. The delayed-onset group also reported a gradual accumulation of symptoms that continued throughout their military career, with an excess of other stressors unrelated to their traumatic event occurring in the year preceding their onset.

If replicated, these findings suggest that many delayed onsets involve a more general stress sensitivity and a progressive failure to adapt to continued stress exposure, rather than an experience of being overwhelmed by reactions to a specific event. It may be useful to consider biological processes that could explain the gradual build-up of cumulative stress effects, such as kindling or sensitization.

A small group of delayed onsets appears to occur in the absence of previous symptoms. These may reflect new circumstances that prevent reminders of a traumatic event being avoided, changes in the meaning of individual traumatic events over time, or the development of a neurological or cognitive impairment that prevents unwanted memories being inhibited.

Implications

Of the two most central disturbances in PTSD, one involves excessive intrusion and fragmentation in traumatic memories, so that the person experiences a marked lack of control over when they come to mind, and over the emotional and physiological consequences of this occurring. The other involves sometimes profound experiences of the self as being defeated, morally reprehensible, divorced from others, and sometimes as barely existing. Both disturbances often involve experiences, such as psychic and somatic dissociation, that are not integrated with the sense of self. These disturbances, and the compensatory behaviors adopted to mitigate them, are the main focus of psychological therapies, but are as yet poorly understood.

There is an urgent need for more phenomenological research to describe these core experiences in more detail. For example, little if anything is known about the extent to which intrusive memories during an episode of PTSD include images of prior traumas as well as the index event, or how repeated events are represented. Biological research, especially neuroimaging, also has an important role to play, and has produced preliminary findings supporting the theoretical position that traumatic memories are fundamentally different from ordinary episodic memories[246,247]. Disturbances in the sense of self, such as feeling the self to be fragmented or non-existent, have been linked to altered functioning in the default mode network[248].

BIOLOGICAL FOUNDATIONS OF PTSD

Biological research on PTSD has expanded significantly in the past decade[249]. Several reviews on specific aspects of PTSD biology have been published in the last five years, including on inflammation[250], the immune system[251], neural circuits[252], biomarkers[253], and the microbiome[254]. In this section, we touch on a few areas that have been recently the subject of meta-analysis, and then summarize more deeply key findings in the fields of genomics and neuroimaging, which have advanced exponentially over the past decade through large multi-site studies producing robust and replicable findings. Preliminary findings in the areas of epigenomics and other “omics” are also considered.

Motivated by clinical observations of some of the core features of PTSD, such as exaggerated startle response and reactivity to trauma-related reminders, many of the early rigorous empirical studies on PTSD biology were focused on the autonomic nervous system. These included key findings of increased heart rate and skin conductance, as well as facial electromyography reactivity, during traumatic script-driven imagery and during exposure to

trauma-related stimuli in persons with PTSD[249]. A recent meta-analysis[255] reinforced these findings, concluding that PTSD is associated with autonomic nervous system dysregulation. Persons with PTSD were found to have significantly higher heart rate and lower heart rate variability (i.e., variation in time between heartbeats), both at rest and during stress paradigms.

The role of hypothalamic-pituitary-adrenal (HPA) axis alterations in PTSD has also been an active area of research for many decades. Early findings suggested a differentiation in findings between PTSD and depression, with the former characterized by over-sensitization, and the latter by dysregulation of the axis[256]. However, findings from individual studies have been inconsistent. A recent meta-analysis reported that morning and 24-hour cortisol levels were lower, while evening dehydroepiandrosterone (DHEA) levels were higher, in PTSD subjects than controls, but concluded that there was not a consistent pattern of HPA axis alteration in PTSD[257].

The robust association of PTSD with chronic diseases – including cardiovascular diseases, diabetes, and autoimmune conditions – has motivated studies of the role of inflammation and oxidative stress in PTSD biology. A recent systematic review and meta-analysis[258] found that C-reactive protein, interleukin 6, and tumor necrosis factor-alpha were elevated in persons with PTSD versus controls. In contrast, oxidative stress markers were not associated with the disorder. The association between PTSD and inflammation appears to be bi-directional. Thus, it may be a mechanism through which PTSD increases risk of chronic diseases, while at the same time inflammation may increase risk of PTSD[258,259].

The findings concerning inflammation raise a key question relevant to many areas of PTSD biological research: most studies are cross-sectional, and it is not clear whether the observed findings – be they related to inflammation, cortisol secretion, or autonomic nervous system dysfunction – reflect a vulnerability for PTSD, are acquired because of developing PTSD, or perhaps both.

Genomics

Genetic factors are appealing for biological research on PTSD due to temporality. That is, an individual's DNA sequence is established at conception and therefore must precede the development of PTSD. Unlike many other biomarkers, a DNA sequence cannot be a consequence of developing the disorder. Genetic factors may increase the risk for PTSD through at least two pathways: increasing the likelihood of experiencing a traumatic event and increasing the risk of developing PTSD following trauma. Twin studies have shown that both the experience of trauma and PTSD are heritable, meaning that both are influenced by genetic factors[260,261].

Genetic risk for experiencing trauma and/or developing PTSD is not limited to a handful of genetic variants but is highly polygenic, with thousands of single nucleotide polymorphisms (SNPs) contributing to risk[262]. Here we focus on major findings related to PTSD risk. The role of genetic factors in trauma exposure[263] and how trauma influences genetic risk for PTSD[264] are discussed elsewhere.

Identifying causal SNPs requires the use of genome-wide association studies (GWAS) while accounting for genetic influences on trauma exposure[265]. Very large sample sizes are necessary to conduct GWAS in complex disorders such as PTSD, which led to the creation of the Psychiatric Genomics Consortium - PTSD Working Group (PGC-PTSD). This combined studies of PTSD with genetic data from around the world[266]. Understanding of the genetics of PTSD has also advanced through the Million Veterans Program (MVP). Together, the PGC-PTSD and the MVP have produced four robust genetic findings for PTSD.

First, the most recent GWAS, which combined data from the PGC-PTSD and MVP, included over 1.2 million participants and 150,000 PTSD cases. They identified 95 loci associated with PTSD, in genes related to neurotransmitter and ion channel synaptic plasticity modulators; developmental, axon guidance and transcription factors; synaptic structure and function; and endocrine and immune regulators[267].

Second, SNP-based heritability of PTSD from PGC-PTSD and MVP ranges from 0.053 to 0.092[267,268]. No significant differences in the SNP-based heritability of PTSD were found between male and female subsets.

Third, PGC-PTSD and MVP analyses produced a robust polygenic risk score for PTSD. This score is created by summing the number of risk alleles for a participant weighted by the alleles' effect estimates. Participants in the highest quintile of polygenic risk scores for PTSD were found to have 2.4 times the relative risk for PTSD compared to individuals in the lowest quintile[267]. Overall, the polygenic risk score explained 6.6% of the variance in PTSD[267].

Fourth, PTSD was found to be genetically correlated with attention-deficit/hyperactivity disorder, alcohol dependence, anorexia nervosa, autism, bipolar disorder, major depressive disorder, obsessive-compulsive disorder, schizophrenia, and Tourette's syndrome[267]. As found in previous studies[268-270], PTSD and major depressive disorder were highly correlated. However, their genetic correlation varied with the population and method of assessment of PTSD. Genetic correlations between PTSD and major depression from a military cohort were around one-third lower than from an electronic health records-based cohort[267].

There are several limitations to our current genetic knowledge of PTSD. Addressing these limitations is necessary to translate genetic associations to causal biology, which remains an ongoing effort[252,271,272].

First, the latest PGC-PTSD results were not conditional on lifetime trauma exposure, which previous analyses have found to alter SNP-PTSD associations, as the genetic loci may

increase risk for trauma exposure rather than PTSD[270]. This makes it difficult to disentangle risk for experiencing trauma and risk for PTSD.

Second, current GWAS combine cohorts that assess lifetime and current PTSD, thus losing the ability to determine if the identified genes are relevant to onset or course. Moreover, the latest and largest GWAS of PTSD used a simple case-control definition of PTSD based on ICD codes from electronic health records for around two-thirds of participants, rather than a validated scale measuring each PTSD symptom[267,268,273]. Including participants with less-validated diagnoses is necessary for GWAS, as large numbers of participants are needed[274]. However, this also further increases the heterogeneity of PTSD case status. Lack of precision in PTSD diagnosis also likely inflates genetic correlation with other mental disorders such as major depression.

Third, GWAS of PTSD have focused primarily on participants of European ancestry. Recent work on polygenic risk scores in PTSD[275-277] shows limited cross-population transferability and, by extension, poorer performance in populations from other parts of the world. Until this inequity is corrected, there is also a significant risk that the recent advances in PTSD genetics will result in a widening of the massive research and treatment disparities. This inequity is particularly troubling given the disproportionately high burden of trauma and PTSD faced by under-represented populations. For example, African Americans face a higher burden of PTSD driven by higher levels of exposure to violence at younger ages[278].

Epigenomics

While a person's DNA sequence is established at conception, how genes work can be influenced by many epigenetic factors. The most commonly studied measure of epigenetics in PTSD research has been DNA methylation, which modifies gene expression by binding a methyl group to DNA, usually at cytosine-guanine dinucleotides[279-285]. Epigenome-wide association studies of blood have found changes in DNA methylation in the genes *NRG1, AHRR, MAD1L1*, and *TBXAS1* to be associated with PTSD[279-281,286].

PTSD has also been associated with two epigenetic markers of accelerated biological age: shorter telomere length and older DNA methylation estimated age.

Telomeres are repeating patterns of DNA at the end of chromosomes that protect DNA during cell division and whose shortening leads to apoptosis of cells[287,288]. Shorter telomere length is considered a marker of biological age[289], as it has been associated with mortality[290]. Recent meta-analyses have found PTSD to be associated with shorter telomere length[291,292].

DNA methylation has also been used to estimate biological age. Older estimated biological age is associated with mortality and chronic diseases[293-296]. PTSD has been

associated with accelerated DNA methylation age[297], although these studies have primarily been conducted in cross-sectional military samples[298-305].

Finally, building on efforts in depression[306], the PGC-PTSD Working Group is creating methylation risk scores to predict risk for PTSD by combining DNA methylation associations from across the genome, as is done with polygenic risk scores[307].

Other "omics"

Other "omic" methods focus on the downstream products of genetic and epigenetic factors to identify biological pathways that differentiate PTSD cases from controls. In the largest meta-analysis to date, differential gene expression has been observed for interleukin-1 beta (a pro-inflammatory cytokine previously associated with PTSD) and integrin-linked kinase (which is expressed in the brain and associated with dysregulation of the hippocampus)[308]. Another study had also found differential expression in another hippocampus-related gene (*DSCAM*)[309]. Beyond elucidating biological pathways, differential gene expression profiles (i.e., combinations of differentially expressed genes) have been used to predict PTSD, and have been reported to be a potential screening tool for the disorder[310].

Proteomic studies, which focus on identifying and quantifying proteins that are critical for every aspect of cellular life, have detected biological pathways associated with PTSD including immune response and cardiovascular and metabolic disorders. They have been used to create composite risk scores predictive of PTSD[311,312]. Finally, an emerging area for PTSD biological research is metabolomics, although to date studies have focused on a small number of candidate metabolites, with inconsistent patterns of association[313].

Neuroimaging

Many studies have examined structural and functional neural alterations associated with PTSD, primarily using magnetic resonance imaging (MRI). Given the sample sizes required to observe small neuroimaging effects, and the need to adjust for multiple testing across brain voxels and regions, the most convincing work in this area is derived from a more limited number of large-scale consortia studies, such as the Enhancing NeuroImaging Genetics through Meta Analysis (ENIGMA) collaboration[314], which includes a PTSD Workgroup with relevant data from thousands of individuals.

This work has suggested PTSD-related differences in subcortical structural brain parameters, including smaller hippocampal volume[315] and reduced microstructural integrity of the tapetum area of the corpus callosum (which connects right and left hippocampus)[316].

Cortical brain structures have also been implicated in PTSD by consortium data (i.e., reduced volume of lateral orbitofrontal gyri bilaterally[317]).

Smaller studies and meta-analyses involving hundreds of individuals have suggested that PTSD is associated with thinner cortical tissue in the right fusiform gyrus[318], and reduced gray matter in prefrontal (anterior cingulate and ventromedial) and temporal cortical regions[319].

Meta-analytic studies of resting state functional connectivity parameters have revealed increased connectivity in the ventral anterior cingulate and parahippocamal/amygdala regions, and decreased connectivity in the posterior insula, cerebellar pyramis, and middle frontal gyrus. This is thought to reflect PTSD-associated decreased default mode network activity (associated with internally focused mentalization and self-reflection) and increased salience network connectivity (associated with attention to external stimuli)[320,321].

Like many other biological investigations of PTSD, most neuroimaging studies are unable to determine if the structural or functional alterations that are observed represent risk factors for PTSD or consequences of the disorder, or if they could be relevant to understanding the chronicity of symptoms and the likelihood of positive treatment response. Research has only just begun to address these questions. For example, there is some evidence from longitudinal studies that the smaller hippocampal volume identified in individuals with PTSD represents a stable vulnerability factor for the disorder[322].

This conceptualization is further supported by studies of individuals who undergo MRI shortly after trauma exposure. The following neural parameters are predictive of future PTSD (over 3-14 months) when measured shortly after trauma exposure, suggesting that they represent premorbid vulnerability factors: a) less functional connectivity between the left dorsolateral prefrontal cortex and the arousal network (primarily defined by limbic structures); b) greater connectivity between the right inferior temporal gyrus and the default mode network; c) reduced right hypothalamic volume; d) greater activation of the inferior frontal gyrus while performing an emotion modulation task; and e) hyperactivation of the insula and dorsal anterior cingulate cortex during threat-related tasks[323-326].

However, in some of these studies of adult trauma exposure, individuals had also experienced childhood trauma, raising the possibility that the predictive results may have been confounded by trauma-related psychiatric symptoms that pre-dated the adult trauma exposure[326]. Further, failure to replicate associations between post-trauma task-based brain activation and future symptoms raises doubt about the utility of neural parameters for predicting chronicity of symptoms[327].

Other studies have reported evidence for the reverse direction of association. A study of 254 veterans found that PTSD symptoms at baseline were associated with greater cortical degeneration over the course of two years. This effect was augmented among older veterans,

suggesting that older individuals may be more neurologically vulnerable to the deleterious effects of traumatic stress[328].

Implications

There are at least four future directions or next steps for biological research on PTSD. First, except for genetic studies focused on DNA sequence variation, the majority of biological investigations are not designed to test whether biological factors increase risk of PTSD or are a consequence of developing the disorder. Second, most studies use a case-control design and, as a result, provide limited information on how biological factors may predict course or trajectories of PTSD. Third, because of the large numbers of subjects needed for robust findings, consortium analyses tend to pool heterogeneous PTSD diagnoses and populations, which leaves questions about whether different PTSD presentations are related to biological variation. Finally, some populations, especially those from low- and middle-income countries, have been neglected in PTSD biological research. This has been noted in genetic studies of PTSD, but is also the case in other areas. The result is limited knowledge of how biological factors related to PTSD may be shaped by context.

PREVENTION

The requirement of exposure to a traumatic event with specific characteristics appears to lend itself to the development of effective preventive strategies for PTSD. Unfortunately, despite considerable efforts, we are a long way from being able to prevent people from developing the disorder by intervening shortly after traumatic events occur.

A recent review[329] identified six randomized controlled trials (RCTs) considering pre-incident prevention, within the context of exposure to combat trauma (five trials) or to fire and emergency-services trauma (one trial). Various interventions were investigated, including attention bias modification training[330] and stress inoculation training[331]. The only statistically significant finding was in favor of attention bias modification training over a no-intervention control for the prevention of the development of PTSD after combat trauma[330], although replication is clearly required.

The same review identified 75 RCTs of post-incident preventive interventions[329]. These were separated into those that were conducted over a single session and those delivered over multiple sessions.

Two interventions in the single-session group were found to be superior to no-intervention: single-session eye movement desensitization and reprocessing (EMDR) and the Group 512

Psychological Intervention Model, an intervention for military personnel based on debriefing but supplemented with cohesion training[332]. Despite significant concerns around the quality of these studies and the risk of bias, the positive signals from them should not be ignored, and both interventions appear to be good candidates for further evaluation.

Among multiple-session interventions, only brief dyadic therapy[333] and self-guided Internet-based cognitive-behavior therapy (CBT)[334] were superior to no-intervention/treatment as usual, again with significant concerns about study quality and risk of bias.

As to multiple-session interventions for people with emerging symptoms but without a diagnosis of PTSD (indicated prevention), stepped/collaborative care, brief CBT with a trauma focus (CBT-TF), EMDR, and Internet-based guided self-help were superior to no-intervention/treatment as usual, with the strongest evidence for stepped/collaborative care and brief CBT-TF[329].

The International Society for Traumatic Stress Studies (ISTSS) guidelines[335] used the above results to identify Group 512 Psychological Intervention Model and EMDR as single-session interventions, and brief dyadic therapy and self-guided Internet-based CBT as multiple-session interventions with emerging evidence for the prevention of PTSD. CBT-TF, cognitive therapy, and EMDR were recommended as multiple-session early treatment options, although the level of recommendation for them as preventive interventions was “standard”, as opposed to the “strong” recommendation given to them for the treatment of established PTSD. Stepped/collaborative care was identified as an “intervention with low effect”, while Internet-based guided self-help and structured writing interventions were rated as having emerging evidence.

The guidelines also considered RCTs of pharmacological interventions to prevent PTSD, and found hydrocortisone to be the only drug that was superior to a placebo control condition, which resulted in its rating as an intervention with emerging evidence.

For the prevention of PTSD in children and adolescents, the guidelines found emerging evidence for self-directed online psychoeducation for caregivers and children and for children alone, and emerging evidence *not* to recommend individual psychological debriefing for children and adolescents.

The latest US Department of Veterans Affairs and Department of Defense (VA/DoD) guidelines[336] state that “for the prevention of PTSD among individuals who have been exposed to trauma, there is insufficient evidence to recommend for or against psychotherapy or pharmacotherapy in the immediate post-trauma period”.

The disappointing results of research to date mean that our focus should be on developing more effective preventive interventions, and on subjecting those with emerging evidence to more rigorous evaluation. There are also some interesting novel developments with respect

to early intervention, including the emergence of interventions with a purported mechanism of consolidation/reconsolidation of traumatic memories[337].

The current evidence strongly suggests that, pending the emergence of more effective universal and selective preventive interventions, a focus on practical pragmatic support delivered in an empathic manner may be the best way forward, coupled with the raising of societal awareness of PTSD to facilitate the early identification of people who would benefit from evidence-based treatment[338].

TREATMENT

In the last two decades, there has been a significant increase in the number of RCTs completed and in the types of treatment evaluated for PTSD. The systematic reviews that led to the ISTSS guidelines identified 361 RCTs[339].

The main treatments developed and evaluated to date can be classified as either psychological or pharmacological, but there are an increasing number of interventions, such as transcranial magnetic stimulation and yoga, that cannot be readily classified as either. There is also considerable interest in the development of pharmacologically assisted psychotherapy.

Another developing paradigm concerns alternative methods of delivering established approaches to treatment. Examples are guided Internet-based programs of CBT-TF[340], digital therapies such as capnometry-guided respiratory intervention[341], and support tools such as PTSD Coach (https://www.ptsd.va.gov/appvid/mobile).

The wide range of treatment approaches advocated for PTSD is to be welcomed, but brings with it challenges, not least in terms of evaluating the evidence available for different treatments and accurately determining their true effectiveness. Moreover, very little research has been done on matching individual persons with PTSD to the most effective treatments for them. This is further complicated by powerful lobbies for different approaches, potential conflicts of interests, the challenge of grouping related treatments in a meaningful way, and generalizing results from one population to another. These challenges are, of course, not unique to PTSD, but are important to remember.

The current evidence base for the treatment of PTSD is much stronger than ever before, but it is vital to acknowledge that there remain major gaps in our knowledge. Although several treatments have been shown to be effective for people with PTSD, exactly how effective they are, who is likely to benefit from them, and who can deliver them are all up for debate. It is also clear that the treatments with the strongest evidence do not work for everyone, are

relatively costly to deliver in terms of time and other resources, and have been challenging to disseminate, so that we need to identify more effective treatments in the future.

Psychological treatments

Psychological treatments for PTSD are commonly described as either trauma-focused or non-trauma-focused approaches. The former are by far the most researched. Within this group, CBT-TFs have been studied more than any other form of treatment. These include CBT-TF for children and adolescents[342], prolonged exposure therapy[343], cognitive processing therapy[344], cognitive therapy for PTSD[345], and more recently written exposure therapy[346]. Although clearly drawing on a wider range of therapeutic approaches, a number of other interventions have also been grouped as CBT-TFs (e.g., brief eclectic psychotherapy[347], narrative exposure therapy[348,349], and skills training in affective and interpersonal regulation with narrative exposure[350]).

Although the relative emphases and exact methods vary, CBT-TFs tend to include two elements. First, there is graded or controlled exposure to feared memories, particularly the content of flashbacks, or to feared situations, with the aim of making them less distressing and aversive. There are several candidate mechanisms that could account for the value of exposure. Habituation, a form of non-associative learning, refers to the decrement in response that occurs when a stimulus is repeated. Extinction refers to the loss of a learned association between a frightening event and previously neutral cues, which occurs when the cues are repeatedly presented in non-frightening situations. The current view is that extinction procedures create new memories of alternative contexts in which the cues are associated with safety rather than danger, and memories of these experiences inhibit retrieval of the memory of the original frightening event[351].

The other element is the use of cognitive techniques to help people with PTSD challenge distorted patterns of thinking. These include believing oneself to be inadequate, weak, or as having no future; seeing others as untrustworthy; and blaming oneself for the traumatic event occurring, for one's actions during it, and for subsequent symptoms. Negative appraisals of the self, of other people, and of the future predict the course of the disorder, often over and above initial symptoms[141,352].

The second most researched group of trauma-focused interventions is EMDR[353]. This involves focusing on a traumatic memory alongside the associated negative cognitions, affects and body sensations whilst being subjected to bilateral stimulation (e.g., through eye movements or taps). Distancing and free association are also part of EMDR. The mechanism underpinning this treatment remains unknown, despite several hypotheses. Some experts

argue that EMDR is a CBT-TF, but most guideline committees have considered EMDR and CBT-TF separately.

A new group of trauma-focused interventions that has gathered momentum over recent years are those purported to work through the mechanism of mobilizing and reconsolidating traumatic memories, so that they are less threatening[337]. Reconsolidation theory proposes that retrieval returns memories to a labile state in which they can be altered and then reconsolidated in a new form. These interventions use several different procedures, but all involve rapidly rewinding an imaginary film of the traumatic event with great precision. They are so brief that, despite exposure, habituation seems unlikely to be the underpinning mechanism.

Reconsolidation therapies have many similarities with another trauma-focused intervention with good evidence for effectiveness in PTSD, including cases related to childhood abuse. This is imagery rescripting[354-356]. This therapy also involves deliberately manipulating traumatic imagery in one's mind, in this case introducing new imaginary elements that increase feelings of mastery, control and self-acceptance. It has been suggested that the mechanism involves creating alternative, less threatening competitor memories that are then more likely to be retrieved when the person encounters trauma reminders in the future[357].

Non-trauma-focused approaches include a range of techniques, such as stress inoculation training (which aims to teach coping skills, so that the person can find new ways to deal with PTSD symptoms and to manage other stressful events in his/her life), relaxation techniques, supportive counseling, and interpersonal therapy[358].

Other emerging interventions are present-centered therapy and compassion-focused therapy. The former addresses negative identity changes (for example, helping with interpersonal disconnection through developing a positive therapeutic relationship and exploring interpersonal difficulties, or overcoming helplessness by problem-solving)[359]. The latter draws on the fact that people with PTSD can often express compassion to others but not to themselves, and addresses the experience of a shameful, inadequate or blameworthy self by techniques such as vividly imagining being the recipient of compassionate responses from actual or fantasized others[360].

Different forms of individual CBT-TF are recommended by all the main guidelines as a first-line treatment for PTSD. However, there are important differences, and some CBT-TFs are given more priority than others by different guidelines. For example, the ISTSS guidelines strongly recommend CBT-TF (undifferentiated), cognitive processing therapy, cognitive therapy, and prolonged exposure. Despite having similar evidence available, the latest VA/DoD guidelines only recommend cognitive processing therapy and prolonged exposure as first-line CBT-TFs; cognitive therapy is given a weaker recommendation[336]. Guidelines appear to consistently agree that group CBT-TFs have less supporting evidence than individual ones.

EMDR is also strongly recommended by most guidelines, although the latest UK National Institute for Health and Care Excellence (NICE) guidelines specifically state that it is not recommended for use in individuals with PTSD following combat exposure.

Guided Internet-based CBT-TF is given a lower-strength recommendation by ISTSS and NICE, although more recently published RCTs[361,362] have resulted in two specific forms of this intervention being recommended by NICE[363]. Narrative exposure therapy is given a lower-strength recommendation by most guidelines, but a strong one by NICE, while VA/DoD found insufficient evidence to recommend for or against it.

There is considerable heterogeneity between guidelines in terms of recommendations for non-trauma-focused psychological interventions. The VA/DoD guidelines include stress inoculation training, present-centered therapy, and interpersonal therapy among recommended interventions. The ISTSS guidelines include present-centered therapy among recommended interventions, while interpersonal therapy, relaxation training, and supportive counseling are listed among therapies with “insufficient evidence to recommend”.

Pharmacological treatments

There is agreement across guidelines that various pharmacological treatments can reduce the symptoms of PTSD, though most guidelines recommend them less strongly than psychological interventions. The reasons for this are worthy of some consideration. In meta-analyses, effect sizes for pharmacological treatments are much lower than those for psychological interventions and, consequently, a weaker recommendation appears to be justified. Notably, however, the standard comparator condition for pharmacological treatments is placebo, in contrast to either usual care or waitlist for psychological interventions. There are also major differences in terms of “effective blinding” of participants and clinicians between pharmacological and psychological treatment trials.

Some guideline committees – e.g., that for ISTSS guidelines – have tried to address the control-group issue with *a priori* agreements regarding the adjustment of evidence thresholds for different levels of recommendation according to the control condition used. This is a step in the right direction, but such agreements reflect the consensus of a committee and should be considered informed rather than necessarily correct.

Some treatment guidelines (e.g., NICE) group drugs together when making recommendations, whereas others do not. A clear example is given by recommendations for SSRIs: NICE guidelines just recommend SSRIs; ISTSS guidelines recommend the SSRIs fluoxetine, paroxetine and sertraline, but not others (based on the availability of RCTs in PTSD for those three specific drugs); and VA/DoD guidelines only recommend paroxetine and

sertraline. Venlafaxine is recommended by name by most guidelines. Quetiapine is rated as an intervention with emerging evidence by ISTSS guidelines.

Most guidelines do not consider augmentation, although systematic reviews and meta-analyses provide some evidence to support augmentation of either SSRIs or venlafaxine with the alpha1-adrenoceptor antagonist prazosin[364]. The VA/DoD guidelines, however, take a different stance and consider the evidence strong enough to recommend *against* prazosin for the treatment of PTSD.

Overall, it is clear that further research evidence is needed to guide the use of medications, especially SSRIs, in the treatment of PTSD. In particular, the features of the clinical picture of PTSD that can support their use, and their utility when combined with psychological interventions, should be the focus of specific research.

Emerging treatments

Increasing numbers of novel treatments for PTSD are being developed and tested. In the latest ISTSS treatment guidelines, 26 treatments were recommended as interventions with emerging evidence. Psychological treatment examples for adults include couple CBT-TF[365] and virtual reality therapy[366]. Group CBT-TF and group psychoeducation[367] were considered interventions with emerging evidence for children and adolescents.

All these interventions have their proponents, and all appear worthy of further research. Interestingly, a meta-analysis of CBT-TFs for veterans[368] found that the strongest effect sizes were for RCTs of reconsolidation of traumatic memories. Arguably, this treatment was wrongly classified as a CBT-TF, as it probably relies on a different mechanism.

Several emerging interventions use neither a psychological nor a pharmacological approach. To give two diverse examples, five RCTs of yoga and three RCTs of transcranial magnetic stimulation were considered by the ISTSS committee. This evidence, and subsequent systematic reviews and meta-analyses[369,370], suggest that both these interventions are likely to have a role in the treatment of PTSD in the future.

An example of an emerging intervention that combines a pharmacological and a psychological approach is 3,4-methylenedioxy-methamphetamine (MDMA)-assisted psychotherapy. MDMA is a psychostimulant and hallucinogen. Although not yet recommended by any guideline, the evidence for this approach appears to be strengthening. Its exact mechanism of action is not known, but it has been proposed that the properties of MDMA allow exposure to traumatic memories without overwhelming distress that can hamper processing[371].

Other non-invasive treatment approaches appear to show some promise for the future, for example controlled breathwork[372], although they clearly require more rigorous evaluation

before being recommended. It is important to acknowledge that alternative approaches to the treatment of PTSD may be more acceptable to some people than the current recommended first-line treatments. As argued in a seminal paper over a quarter of century ago, effective evidence-based practice is not dictated by RCTs and guidelines alone, but is "about integrating individual clinical expertise and the best external evidence"[373].

Treatment evidence for children and adolescents

Sadly, the level of evidence available to determine the most efficacious treatments for children and adolescents with PTSD is lagging far behind that for adults. It is therefore very difficult to make treatment recommendations confidently. That said, there is enough evidence available for most guidelines to make several treatment recommendations.

The main recommended psychological treatments for children and adolescents are CBT-TF delivered to caregiver and child, CBT-TF delivered to child alone, and EMDR, although the latter is less strongly recommended by NICE than by ISTSS. There is insufficient evidence to recommend any pharmacological treatments for children and adolescents with PTSD.

Adapting interventions in resource-limited settings and across cultural contexts

The translation of RCT evidence into practice represents a challenge particularly in low-resource settings and across cultural contexts. The relatively few RCTs for PTSD that have been conducted in resource-limited settings show promising results, for example in the case of group-based CBT-TF for bereaved children in Kenya and Tanzania[374], and group-based CBT for survivors of sexual violence in the Democratic Republic of Congo[375].

Other promising approaches include Islamic healing therapy, based on the principles of CBT-TF, adapted using a community-based participatory research process to be more accessible in the Islamic context[376]; treatments developed in Indigenous communities for PTSD and other mental health consequences of historical trauma[377]; and interventions aimed at helping persons address PTSD related to racial trauma[132].

More research is required to determine how best to implement the most efficacious treatments in a sustainable manner in low-resource settings. There is clearly a need for more accessible and cost-efficient forms of treatment that can be delivered/facilitated by therapists without highly specialist training. Guided Internet-based CBT-TF appears to be a good candidate for this, along with currently less developed non-invasive interventions such as imagery rescripting, reconsolidation therapies, and various non-trauma-focused approaches.

A helpful briefing paper recently published by the ISTSS[378] notes multiple barriers to implementing evidence-based interventions to support people affected by PTSD and other

conditions in low- and middle-income countries. These include stigma and the lack of mental health professionals. The paper makes recommendations for public health and policy, for researchers, and for practitioners/service providers. These include increasing mental health literacy and reducing stigma, training community health workers to deliver effective interventions, and developing culturally specific adaptations of evidence-based treatments.

Community-based interventions

It has sometimes been argued that the evidence supporting the effectiveness of trauma-informed psychological interventions at the community level is inconsistent, suggesting the need for alternative approaches[379]. Among the considerations are that measures of symptom severity alone provide an incomplete picture of the individuals' experience, making it necessary to evaluate other factors such as increased understanding of the mental health condition, skills building, coping, and well-being[380].

Since there is often a communal or societal component in the trauma experience, it is important to consider how this might be addressed. Community-based interventions would not only potentially benefit collectivistic societies, but could find more general application in situations of mass trauma exposures and among minoritized or under-served populations in high-income countries.

The Adaptation and Development after Persecution and Trauma (ADAPT) model[381] focuses on the core psychosocial pillars in a community that are likely to be disrupted and to need repair following mass trauma. These include the general sense of safety and security, the social bonds and networks that link community members, the availability of justice, the reinstatement of lost roles and identities, and a shared existential meaning.

Similarly, other recommendations emphasize the importance of interventions that address the broader social context of trauma, and the need for community-level support and healing, facilitating recovery by rebuilding and strengthening social support mechanisms[382].

Community capacity-building to foster resilience (conceptualized as dissemination of trauma-informed education and training, community outreach and engagement, and linkage of community members to resources) showed benefits with regards to emotional and instrumental support as well as in increasing the sense of community connectedness[383].

However, the evidence for the efficacy of community-based interventions in improving trauma-related symptoms is currently less than optimal, partly because less work has been done in this area compared to clinical-setting interventions, and the quality of research is also variable[384]. The small number of studies examining these interventions makes it difficult to evaluate their acceptability, feasibility and effectiveness[380].

Implications

Despite the progress made, there are many evidence gaps in the treatment of PTSD. Even the best-evidenced treatments require more research, and there is an urgent need for more effective treatments. Most RCTs to date have excluded people with more complex presentations of PTSD and, given their prevalence and the morbidity associated with such presentations, a research focus on them is required. It is to be hoped that the ICD-11 diagnosis of complex PTSD will help in this regard. There are clearly major opportunities to build on basic science to develop new interventions and to enhance the effects of existing treatments.

Evidence is currently lacking to determine whether recommended treatments work as well for people with certain characteristics as for others. Important relevant characteristics include age, gender, ethnicity, socioeconomic status, culture, nature and number of traumatic events exposed to, and complexity of PTSD symptoms. For some populations, significant adjustments are likely required to existing treatments to maximize their effectiveness. Such work is in progress. Examples include a RCT of EMDR for people with learning disability[385], and the development of approaches for older people with PTSD[386]. Asylum seekers and refugees clearly represent another group of people with a high prevalence of trauma-related problems and an urgent need for tailored approaches[387,388].

TRAUMA AND MENTAL HEALTH: FUTURE DIRECTIONS

Following the successful introduction of the PTSD diagnosis, it is now possible to discern a second phase in research on trauma and mental health that is a product of that success. One manifestation of this is the recognition that the construction of the PTSD diagnosis in terms of a response to a specific traumatic event does not reflect the reality of exposure to trauma[389]. A history of childhood and adult trauma, repeated episodes of trauma, or multiple types of traumatic event, are the rule rather than the exception. Subsequent stressors, not necessarily PTSD-qualifying traumatic events, contribute to the prediction of PTSD, particularly the delayed-onset type. In some individuals, particularly members of the military and emergency services, PTSD develops after lengthy periods of resilience to high levels of stressors and traumatic events. Yet, this knowledge is often not reflected in assessment instruments and research designs, or reported in scientific papers. Little is known about how these different histories impact on core symptoms such as re-experiencing, a current sense of threat, or disturbance in the sense of self.

Another manifestation of this new phase of research is the active questioning over the advantages and disadvantages of attempting to define trauma in objective terms. There is

increasing recognition that the experience of socially marginalized, neurodiverse and other relevant groups has not been sufficiently valued as yet. Increased focus on different populations, including people undergoing intensive care or those with psychosis, can be highly informative about the relative contribution to symptoms of the subjective and objective impact of stressful events, and about the value of standard trauma-focused interventions in these different circumstances.

Relatedly, it is becoming evident that there are several different PTSD phenotypes, including those with delayed onset, the dissociative subtype of DSM-5 PTSD, and ICD-11 complex PTSD. These developments suggest that, in the future, it will be necessary to talk about post-traumatic stress disorders in the plural. Some explanatory mechanisms are likely to be shared, but others may not. This has major implications for biological research, which is generally best served by focusing on a small number of clearly defined phenotypes.

An approach similar to the exploration of subjective experiences in schizophrenia[390], based on a greater involvement of experts by experience, could be useful in research on PTSD, focusing on intrusive memories and flashbacks, but also on shifts in the experience of the self in response to trauma reminders. Initial research in this area is promising, and provides both some theory and some methodological tools for isolating specific post-traumatic phenomena[246-248].

The reinstatement of threat to identity as one of the psychological foundations of PTSD has several advantages. As a broader concept, it is not tied to the specific negative cognitions that have been found to be pathogenic in Western samples, but acknowledges the role of other cognitions, social practices, and value systems that are important in different cultural contexts. It brings into play a wide variety of long-standing observations about the subjective experience of being traumatized, for example that individuals sometimes feel deeply alienated from others or as though they have been mentally destroyed. It also helps to explain the efficacy of interventions that are not primarily focused on the traumatic memory, but address more general physical, social and mental resources such as the quality of close relationships, self-acceptance, and problem-solving.

One question for the future is when interventions should focus primarily on disturbances to memory and when on disturbances to identity. In mass-trauma situations, there appears to be widespread acceptance that the initial focus should be on the depletion of identity-relevant resources such as housing, employment, social norms, and community structures[381,391,392]. Response is likely to require local or national governmental involvement.

In individual trauma, clinical services are usually ill-equipped to restore specific resource losses and are set up to deliver physical or psychological interventions. We know that memory-focused interventions have the potential to bring about positive changes to identity in the form of improved relationships, greater optimism, and more positive beliefs about the self. There

are promising developments in imagery-based interventions that may offer accelerated improvements. However, there is much to learn about whether and how identity-focused interventions, such as present-centered and compassion-focused therapies, reduce intrusive trauma memories and flashbacks. The optimal match between different interventions and various PTSD phenotypes is likely to be crucial.

One important issue on which evidence is lacking is how low- and middle-income countries can design trauma-related interventions that are tailored to be culturally and structurally valid, and how they can obtain the maximum return for their investment[387]. There is already a focus on brief transdiagnostic interventions delivered by para-professionals or peers, such as Problem Management Plus[393]. These interventions can be made more available using Internet and mobile technology resources, which have the potential to reduce barriers created by geographical isolation, stigma and cost[394]. Lacking to an even greater degree is evidence concerning the effectiveness of interventions for specific cultural idioms or concepts of distress[44].

To conclude, the explosion of knowledge about PTSD has revealed its central importance, but also its limitations in capturing the variety of psychopathological reactions that are made more likely by traumatic events. The next ten years are likely to see consolidation in the form of establishment of an accepted set of different phenotypes which will enable a more focused investigation of mechanisms and treatment response. Studies of different populations exposed to different types of stressors in different contexts will deepen our understanding of what is universal and what is specific about the response to trauma.

ACKNOWLEDGEMENTS

The authors are grateful to E. Wolf for her contribution to a previous version of this paper.

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