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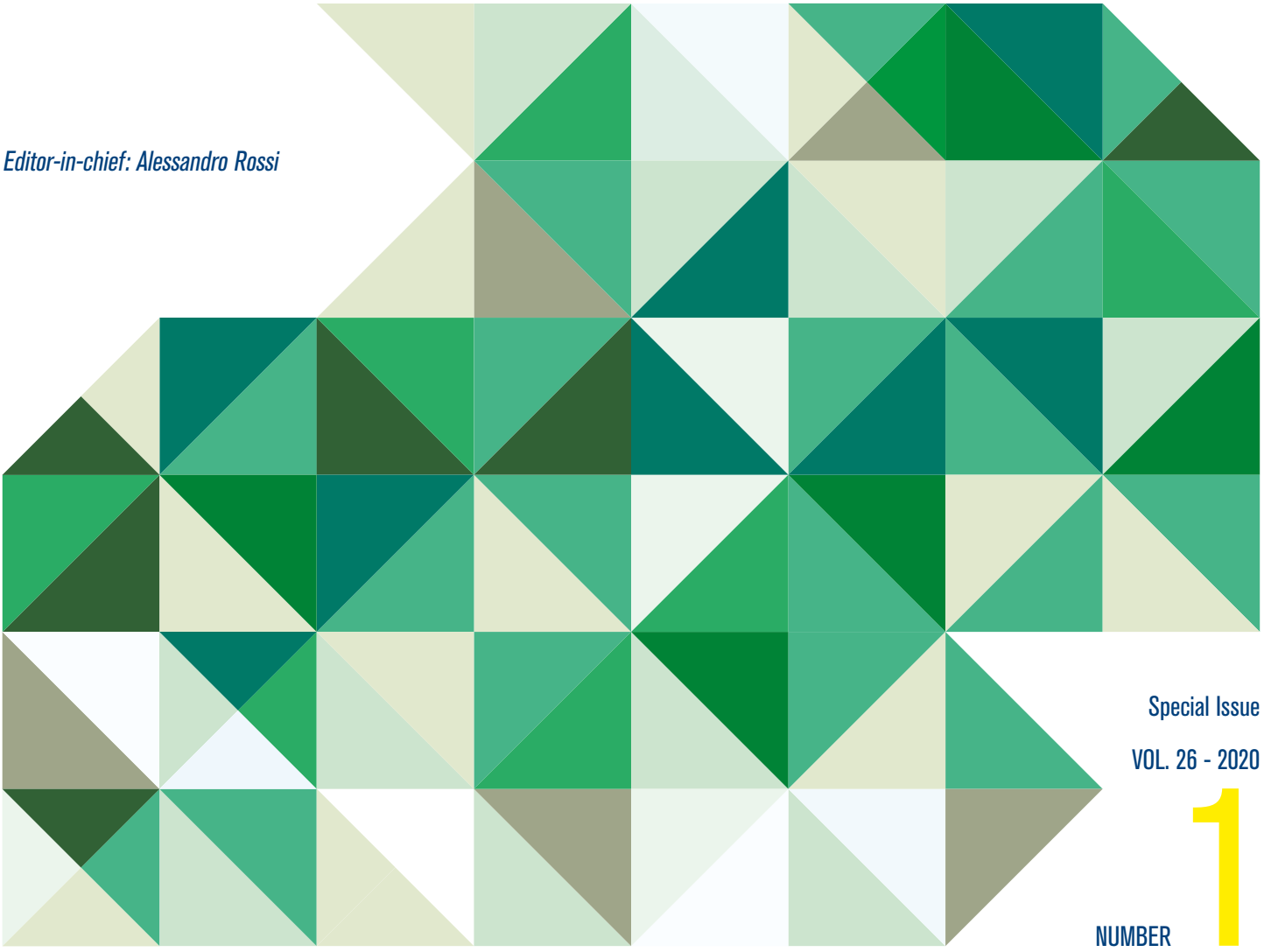

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Trauma: psychopathology, boundaries an treatment

Guest Editor: Liliana Dell'Osso, Alessandro Rossi

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Editorial

Trauma: psychopathology, boundaries and treatment

Liliana Dell'Osso[1], Claudia Carmassi[2], Alessandro Rossi[2]

[1] Department of Clinical and Experimental Medicine, University of Pisa, Italy; [2] Department of Biotechnological and Applied Sciences and ASL, University of L'Aquila, Italy

The traumatic nature of some mental disorders has been underlined for over a century; however, it is in the last 20 years that knowledge on epidemiological, clinical and neurobiological characteristics of psychopathological reactions to trauma exposure has gained an undeniable progress. First introduced in psychiatric nosography in the DSM-III (APA, 1980), in light of the evidence emerged in the veterans exposed to the Vietnam war, Post-Traumatic Stress Disorder (PTSD) and its related disorders, have been progressively investigated in victims of specific trauma, particularly sexual or physical violence, general population exposed to human made or natural disasters, up to wide epidemiological samples. Relevant neurobiological, genetic and neuroimaging findings have thus consistently emerged. As a matter of fact, a more accurate definition of these conditions has been achieved, leading to the acknowledgment of their distinctiveness from other mental disorders, particularly anxiety disorders, so that the DSM-5 first devoted a specific chapter to trauma and stress related disorders, highlighting their specific nature. Besides specific neurobiological alterations, these disorders still share the risk of a frequent chronic course, high comorbidity rates with other mental disorders, treatment resistance and high suicidal risk [1-6].

Increasing attention has been devoted to the role of childhood trauma, especially sexual and physical abuse and, most recently, emotional abuse and neglect. Although a spread of different kinds of childhood adversities, such as parental loss, separation, discord and bullying, are now known to contribute to later psychopathology, childhood trauma appears to have particular negative and long-lasting effects. Upon the DSM-5 redefinition of trauma, a special attention has also been devoted in most recent years to the impact of particular life experiences, such as those related to special working populations (e.g., emergency operators and first rescuers or caregivers), highlighting the role of preventive factors such as professional preparation and support. Conversely, subtle manifestations of traumatic experiences have been reported in fragile populations, like adolescents, women and minorities.

In this regards, important findings emerged from the investigations of not only full-blown manifestations of PTSD but also of its partial and sub-syndromal forms, that often represent a problem not only during the acute phase but also across extended periods of time after exposure. Trauma story, in fact, can help clinicians to better explore risk factors and psychopathologies surrounding traumatic events but there is a need to research-oriented instruments able to assess traumatic spectrum symptoms otherwise undetected. Consistently, a relevant role in neurobiological and clinical research has been driven by multidimensional approaches to these mental disorders, such as that suggested by the *Trauma and Loss Spectrum* model, developed by clinicians and researchers

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Correspondence
Alessandro Rossi
Department of Biotechnological and Applied Clinical Sciences (DISCAB), University of L'Aquila, via G. di Vincenzo 16/B, 67100 L'Aquila, Italy
E-mail: alessandro.rossi@cc.univaq.it

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of the *Spectrum-Project (www.spectrum-project.org)* [7]. During the past few decades, a large body of research has further increased our understanding of the relationships between early adversities and psychological difficulties later in life and intriguing findings suggested the potential role of altered neurodevelopment, particularly autism spectrum disorder (ASD) in its moderate forms with no cognitive or language impairment, as vulnerability factor for the impact of traumatic experiences, even multiple minor ones [8-10]. As a matter of fact, the ability to adjust has been shown to decline dramatically over time in ASD subjects in the aftermath of disaster exposure. Consistently, individuals with ASD have been suggested to represent a low-resilience group that could be specifically more prone to develop Trauma and Stress Related Disorders and, studies on the new concept of Adult Autism Subtreshold Spectrum (AdAS) [10] have hypothesized it as a possible matrix of vulnerability for the subsequent development of trauma related disorders, especially in their complex forms (e.g. complex PTSD).
Most recently, increasing evidence has further led to the awareness that traumatic experiences may play a key role as potential triggers for the onset or worsening of other mental disorders that post-traumatic stress ones, such as mood disorders and psychoses [11,12]. Clinical and neurobiological research, in fact, further supported the view that the effect of traumatic experiences is much broader than what is believed and this may encompass the entire lifespan [15]. If on one side, in fact, traumatic experiences in adulthood may contribute to a worsening of other mental disorders course and outcomes, childhood adversities have been associated with an increased risk of psychoses, mood and anxiety disorders, as well as other medical disorders in general. According to preclinical and clinical models, early adverse events can disrupt the homeostatic control of immune responses and lead to enduring inflammatory dysregulation at a peripheral and central level leading to microglia activation and neuroinflammation. These mechanisms have been hypothesized to relate to an increased risk of mental disorders, particularly mood and psychotic disorders.
Given the spread of potentially traumatic events, what is surprising is the ability of the individual to adapt, which protects him from turning towards trajectories of psychopathological development, encouraging researchon risk versus resilience factors. There has been growing interest in the concept of resilience [14,15] and the question as to whether psychotropic medications or psychosocial treatments might have resilience-enhancing effects. Resilience can have a role not only in interpersonal trauma but also in natural-disaster related trauma.
In conclusion, despite significant progress has been achieved in the clinical definition and neurobiological correlates of these disorders, there is still a lack of advancement within their psychopharmacologic treatment. However, attention is deserved if we consider that the clinical and social burden of inefficaciously treated PTSD is absolutely relevant. The impact of PTSD morbidity and mortality is further magnified by its substantial disruptions in family, workplace and societal contexts [16]. The relationship of the clinical response of psychotherapy vs pharmacotherapy in people with mental disorder and trauma comorbidity is complex and far from being elucidated [17]. In this issue we collected theoretical and clinical contribution of trauma boundaries to enhance the clinicians' awareness on clinical management of trauma spectrum disorders.

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Trauma, PTSD and post-traumatic stress spectrum: 15 years' experience on a multidimensional approach to trauma related psychopathology

Claudia Carmassi, Filippo Maria Barberi, Annalisa Cordone, Alessandra Maglio, Valerio Dell'Oste, Liliana Dell'Osso

Department of Clinical and Experimental Medicine, University of Pisa, Italy

SUMMARY

Objectives

The purpose of this article is to provide an overview of the studies conducted using the Trauma and Loss Spectrum-Self Report (TALS-SR) since its validation, also summarizing the structure of this psychometric instrument and the underlying dimensional approach.

Methods

In this article we revise the results obtained across several studies in which the TALS-SR has been used. The Trauma and Loss Spectrum (TALS), also known as post-traumatic stress spectrum, was developed in the framework of the Spectrum Project, an Italy-USA research collaboration project aimed at developing and validating tools designed to assess the spectrum of clinical manifestations related to DSM mental disorders. It represents a multidimensional approach to Post-Traumatic Stress Disorder and includes: potentially traumatic and/or loss events to which one can be exposed across his/her lifetime; a spectrum of acute peri-traumatic reactions; a broad range of post-traumatic stress and/or Complicated Grief (CG) spectrum symptoms. Both a clinical interview and self-report instrument were developed, namely the: Structured Clinical Interview for Trauma and Loss Spectrum (SCI-TALS), and Trauma and Loss Spectrum-Self Report (TALS-SR). Both instruments consist of 116 items, coded dichotomously (yes/no) and grouped in 9 domains. Two out of nine domains explore symptoms related to the pathologic grief reactions related to the loss of a loved one, also named as CG or Persistent Complex Bereavement Disorder (PCBD), this latter to date first included in the DSM-5, in the Section III of disorders that deserve further clinical attention.

Results

The instruments were validated and adopted in clinical samples, such as patients with PTSD, CG, affected by medical conditions (such as fibromyalgia), caregivers of children with chronic illnesses, Emergency Unit personell, as well as in general population samples (e.g. survivors to the April 2009 L'Aquila earthquake) and healthy controls. Studies comparing full and partial symptomatological PTSD, in accordance to either the DSM-IV or DSM-5 criteria, were also possible, due to the wide spectrum of trauma related sympotms encompassed by the TALS, including the DSM-5 ones. Furthermore, the relationships between post-traumatic stress spectrum and other psychopathological dimensions, such as mood, eating and adult subthreshold autism spectrum, were explored.

Conclusions

The use of the TALS-SR allows a valid exploration of the trauma and loss spectrum, in itself and in relation to other psychopathological dimensions. Moreover, it represents a valuable tool in clinical practice, for the diagnosis and management of PTSD.

Key words: PTSD, trauma, spectrum, loss, grief

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Correspondence
Filippo Maria Barberi
Department of Clinical and Experimental Medicine, University of Pisa, via Roma 55, Pisa, Italy.
E-mail: fil.barberi@gmail.com

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Introduction

Trauma related and post-traumatic stress syndromes have been subject of increasing attention in psychiatric research in most recent decades. Although introduced in modern psychiatric nosography with the publication of DSM-III, nosographic autonomy with respect to anxiety disorders was recognized only in the recently published DSM-5 where it was defined in a separate chapter (Trauma and Stress Related Disorders) along with: Reactive Attachment Disorder, Disinhibited Social Engagement Disorder, Acute Stress Disorder, Adjustment Disorder, Trauma-or-Stressor-Related Disorder Not Elsewhere Classified.

PTSD was, in effect, introduced in the DSM-III on the impulse of the evidence of substantial psychopathological conditions reported by Vietnam war veterans. Since then, clinical and neurobiological research has shown a growing interest in these topics: this has led to demonstrate increasing prevalence rates, at present at around 12% in the civilian populations of Western countries, therefore not directly exposed to war events [1,2]. Indeed, although PTSD was initially investigated mainly in military contexts, over the years other particular population subgroups have been taken into account – such as rape victims, survivors of terrorist attacks, first of all the one in N.Y. (USA) on 11th September 2001, or natural catastrophes - reporting a progressive increase in the prevalence of the disorder with a close relationship also to the changes of the diagnostic criteria through the various editions of the DSM. Major changes in PTSD diagnostic criteria were in fact acknowledjed in the latest version of the DSM that included: changes in the definition of the trauma; a broadening of the three symptomatological cluster criteria, defined in the DSM-IV-TR, into a four-criteria structure; and the introduction of three new symptoms.

The last decades have been characterized by the debate about the opportunity to adopt a broadening or narrowing approach both to the definition of the trauma and related post-traumatic stress symptoms. In the framework of the international joint research project named *Spectrum Project*, the Trauma and Loss Spectrum was developed [3,4], taking into account both the evidence of the importance of partial and/or sub-threshold PTSD "subthreshold" or "subsyndromal" [5,6] and the potentially debilitating impact of various traumatic and loss events, including those which, being less extreme, do not meet criterion A of the DSM. This is consistent with the aim of the spectrum approach, which places atypical and subthreshold forms along a *continuum*, from stable personality traits up to the full-blown disorder identified by DSM criteria. Therefore, the Trauma and Loss Spectrum[3,4,7] adopts a multidimensional approach which considers the dimension of potentially traumatic events, including the so-called "low magnitude" events (e.g., minor severity) and loss events, the features of acute or peritraumatic stress reaction and a wide range of post-traumatic symptoms, including the so-called maladaptive behaviors. This approach has been succesfully applied to a wide range of mental illnesses, such as Anxiety and Mood Disorders and, more recently, to Autism Spectrum Disorders. It is of interest how the simultaneous use of specifically developed psychometric tools (available at *www.spectrum-project.org*) makes it possible to analyse the relationships between these dimensions.

The Structured Clinical Interview for the Trauma and Loss Spectrum (SCI-TALS) and the Trauma and Loss Spectrum-Self Report (TALS-SR)

The Structured Clinical Interview for the Trauma and Loss Spectrum (SCI-TALS) and its related questionnaire (Trauma and Loss Spectrum-Self Report, TALS-SR) were developed to investigate the post-traumatic stress spectrum[4]. The SCI-TALS and TALS-SR are both made up of 116 items with a dichotomous answer (yes/no) investigating, on one hand, the exposure to a series of potentially traumatic and / or loss events to which a subject may have been exposed throughout his/her lifespan and, on the other hand, the spectrum of trauma and loss related symptoms, including maladaptive behaviors and personological features which may constitute manifestations and/or risk factors of a related stress syndrome. The items of SCI-TALS and TALS-SR are grouped into nine domains which are listed below:

1. loss events (items 1-10);
2. grief reactions (items 11-37);
3. potentially traumatic events (items 38-58);
4. reactions to losses or upsettings events (items 59-76);
5. re-experiencing (items 77-85);
6. avoidance & numbing (items 86-96);
7. maladaptive coping (items 97-104);
8. arousal (items 105-109);
9. personal characteristics/risk factors (items 110-116).

In the validation study excellent validity and reliability of the SCI-TALS were demonstrated [3]. The domain scores resulted significantly higher in patients with PTSD or CG than in healthy control subjects. High correlations emerged between the specific SCI-TALS domains and the corresponding scores on validated scales of similar constructs. Participants in the validation study reporting loss events and mourning symptoms had similar scores in all instruments except those with CGs, who had significantly higher scores in Domain II. A substantial consistency between SCI-TALS and TALS-SR was also demonstrated, confirming the reliability of this latter. The intra-class correlation coefficients of SCI-TALS, which

is administered by the clinician in the form of an interview, and TALS-SR, which patients fill in autonomously, ranged between 0.934 and 0.994, always exceeding the threshold of 0.90; in addition, TALS-SR has the advantage of a shorter time in administration (about 20-30 minutes) compared to the structured clinical interview. Similarly to the other spectrum instruments, both SCI-TALS and TALS-SR cannot be taken to substitute the Structured Clinical Interview (DSM-IV Axis-I disorders, SCID I/P), since they do not investigate the duration and severity of the symptomatology, which must be taken into account in order to diagnose PTSD in accordance to the DSM criteria. On the contrary, they are proposed as tools supporting the SCID in order to detect not only the full-blown disorder but also the sub-threshold symptoms and any atypical manifestations that, considered all-togheter, constitute the specifical clinical phenotype of each patient- which SCID fails to grasp due to its strictly categorical nature [3,4].

The concepts of trauma and traumatic loss

For what concerns the traumatic experiences and loss events, the TALS-SR and SCI-TALS, consistently with the aim of the aformentioned dimensional approach, investigate a broad spectrum of traumatic (Domain III) and loss events (Domain I). In doing so, these instruments encompass a wide and heterogenous spectrum of life-events, ranging from the death of a loved one to the end of a meaningful relationship, to the loss of reference figures in childhood or adolescence, to unwanted changes in economic or social status, or of physical integrity. In addition, the TALS-SR explores a new concept of trauma, including also the so named "low magnitude events" (Domain III) that have been cut-off, ignored or marginalised by the narrowing DSM 5 approach.

The Domain II explores the symptoms related to possible exposure to one or more of the loss events listed in Domain I. Typical, atypical or sub-threshold symptoms are reported in this domain, namely those which are relevant to the diagnosis of complicated or traumatic grief, recently introduced under the name of Persistent Complex Bereavement Disorder (PCBD) in the third section of the DSM-5, namely *disorders that deserve further clinical attention* [8,9]. The post-traumatic stress spectrum also includes a possible reaction by CG that may occur in the aftermath of a loss event. As a matter of fact, in the last decades several studies have been developed with the aim to validate the nosographic autonomy of pathological grief reactions. These conditions, once also called traumatic grief (Traumatic Grief, TG) or Prolonged Grief Disorder (PGD), have been shown to be associated with a significant and persistent impairment of social and working functioning, as well as with a high suicidal risk [10-14]. Hence, a number of clinical and neurobiological evidence emerged in the last decade, leading researchers to introduce in the DSM-5 for the first time the diagnosis of PCBD (Post-traumatic and dissociative disorders sub-group). The proposed diagnostic criteria include symptoms such as: the desire and the search for the loved one; the need to remember her and/or spend time with the objects that belonged to her or are associated to her; frequent, intense feelings of guilt and sadness related to the loss; recurring intrusive and/or unpleasant images; avoidance of stimuli that recall loss and the inability to adapt to it (difficulty accepting death, guilt or remorse, feeling that life no longer has a purpose and functional impediment). In accordance to the concept of spectrum, the TALS Domain II explores these symptoms together with seven additional items (experiencing pleasure or satisfaction in taking care of people"; "Feel the need to take care of others"; "Having difficulty asking for help"; "Create very close ties with people and things"; "Having the feeling of not being able to live without loved ones") investigating the attachment style of the bereaved subjects, which is hypotesized as a potential risk factor for PCBD development. The administration of the TALS-SR to a large sample from the general population of L'Aquila allowed us to analyze the relationship between PCBD and PTSD, the results enlighted the substantial impact of grieving on post-traumatic symptoms burden, as well as on PTSD development [15,8].

Domain III enlists the potentially traumatic events to which the subject may have been exposed throughout her life. It includes both the traumas acknowledged by either the DSM-5 and DSM-IV-TR (e.g., natural disasters, sexual abuse, serious accidents, repeated exposure to creepy details due to employment) and a series of so-called low-magnitude events which, though not being considered in the DSM to have such features as to be able to fulfill criterion A, have been related by some authors to the development of post-traumatic stress symptoms (e.g., failures in the school or work environment, legal issues, rupture of meaningful relationships, sexual harassment, abortions). In this regard, several studies have been emphasizing how, taking into account these potentially traumatic events, there is a significant increase in PTSD prevalence [16]. On the other hand, several studies have shown the presence of substantial subgroups of subjects (around 3.7%) who, after being exposed to extremely severe trauma (DSM-IV-TR), may manifest invalidating forms of PTSD, albeit subsyndromic, subclinical or partial ones (i.e. characterized by a number of symptoms lower than those required by the DSM-IV-TR to make the diagnosis). To date, the DSM-5 adopts a more restrictive definition of trauma thus recognizing PTSD when it is linked to direct or indirect exposure to specific set of traumatic

events, including death or threat of death, serious injury or sexual assault, while it does not include Criterion A2 of DSM-IV-TR (having experienced "feelings of intense fear, helplessness, horror").
Following this research path, TALS has been extensively used in order to detect post-traumatic spectrum symptoms in various settings, such as on caregivers of children with chronic illnesses, people working as emergency personell and people exposed to L'Aquila earthquake.
For what concerns the first one of the aformentioned research paths, epilepsy has gained clinical attention in as much as its phenotypic expression, i.e. seizures, have as peculiar features the unpredictability, the drama of the clinical picture, the impossibility to control the event. All this given, facing child epilepsy may represent a traumatic experience for parents, who often experience fellings of helplessness and inadequacy. Despite these considerations, DSM 5 narrowed the approach to the illness of one's child from "threatening disease in one's child" to "a medical catastrophe concerning one's child". Researches conducted on sample of parents of epileptic children showed a significant rate of full and partial PTSD, ranging from 10 to 15% and about 37% respectively [17]. The design of these studies, which have been conducted on couples of parents, allowed to deepen the inquiry into the issue of gender differences: consistently with literature, women showed higher rate of both partial and full-blown PTSD [17]. The overall consistency between the diagnosis of PTSD according to the DSM-IV and DSM-5 criteria was 92.9% in this group [18].
It is also interesting to inquire into the prevalence of post-traumatic spectrum symptoms and their impact on social and work functioning among people chronically exposed to traumatic experiences due to their work activity. This is the aim of a study conducted on a sample of 110 subjects employed at the emergency unit, whose results showed a PTSD prevalence of 15.7%, with higher prevalence of PTSD symptoms among female gender and a higher prevalence of maladaptative behavior among males [19].

Post-traumatic spectrum symptoms

Domain IV is the first among the spectrum domains specifically related to PTSD. It explores the characteristics of the acute response to trauma, that is a set of emotional, physical and cognitive responses to both loss and traumatic events, arising in moments immediately following exposure and often related to the subsequent onset of PTSD. Symptoms of criterion A2 of the DSM-IV-TR that characterized the traumatic event (having experienced feelings of fear, impotence and horror at the time of exposure to the trauma) were also included in this domain. These symptoms were object of extensive debate in the drafting of the DSM-5, since many authors have argued for their scarce diagnostic contribution through clinical and epidemiological studies [20,21]. In accordance to these works, they were eliminated from characterizing DSM-5 trauma criteria (the so called A2 criterion); hence, they were listed along with the symptomatological criteria, costituting a symptom (Persistent negative emotional state) of the new criterion D, which investigates the Negative Alterations in Cognitions and Mood [22].
Domains V, VI and VIII explore post-traumatic stress spectrum symptoms related to the three symptomatic criteria for PTSD diagnosis that were provided by the DSM-IV-TR, which are respectively: evocation of the traumatic event (eg nightmares, flashbacks, intrusive memories); persistent avoidance (e.g., of thoughts, discussions, places, activities or situations reminiscent of the traumatic event or loss) and numbing (e.g., considering unpurpose any activity that had been important in the past, feeling deprived of emotions and detached from other people, having difficulty to trust the others); increased arousal (e.g., concentration problems, feeling like you can't let your guard down, over-reactivity to unexpected stimuli, increased irritability and tendency to lose control for futile reasons, difficulty in falling and staying asleep). As already mentioned, it is noteworthy that one of the main changes introduced by the DSM-5 is the shift from the previous three symptomatological criteria (evocation, avoidance and numbing, increased arousal) to a four criteria structure: B) Intrusion symptoms; C) Persistent avoidance; D) Negative alterations in cognitions and mood; E) Alterations in arousal and activity. Moreover, the new symptoms added within the latter two criteria were already included in the TALS-SR, in accordance with the underlying dimensional approach. As a matter of fact, there is a correspondence between the new PTSD symptoms introduced in the DSM-5 and some TALS items, in particular between the new symptom D3 (to blame himself or others in a distorted way) and item 85 (It was never heard at fault for what happened?), and between D4 (persistent negative emotional state) and item 96 (... as if his life had changed forever? Did you ever think that things would never be the same again?). The new E2 symptom of the DSM-5 is instead reported within Domain VII of TALS. This correspondence allowed us to perform one of the first studies in literature comparing prevalence rates of the symptomatic diagnosis carried out in accordance to the DSM-IV-TR criteria and those obtained according to the the DSM-5 [22,23], also taking into account gender differences in the same sample [24]. A significant gender gap emerged, with women endorsing in higher percentage each DSM-5 symptom including the newly

introduced ones. The item exploring persistent negative emotional state (D4), resulted to be the more frequently endorsed in the female gender and, in general, the most endorsed item in the entire sample of survivors with PTSD. Conversely, men showed significantly higher rates as to the DSM-5 symptom exploring maladaptive or self-destructive behaviors (E2).

Domain VII investigates the so-called maladaptive behaviors (e.g., ceasing to take care of oneself, to take prescribed therapies, substance and alcohol use, undertake risky behavior, suicidal ideation, attempted suicide, self-harm) [25]. As already mentioned, some of these behaviors listed in TALS-SR are today included among the PTSD diagnostic symptoms accordingly with DSM-5. As a matter of fact, what was previously considered a complication of PTSD is to date recognized as a nuclear aspect of PTSD. The importance of such behaviors has been emerging from several studies conducted mainly on military personnel of Iraq and Afghanistan with PTSD, that showed a high prevalence of reckless driving [26], aggressions towards human beings or things, high rates of alcohol and substance abuse and violent attitudes [27-29] among these patients. These results are in line with other studies conducted on adolescents and young adults with PTSD survived to terrorist attacks or fires [30]. As in the case of Domains V, VI and VIII, there is a correspondence between the new symptom E2 (Maladaptive or self-destructive behavior) and the following items: 100 (Have you ever taken alcohol or drugs to alleviate psychological suffering?); 101 (Did you ever engage in risk-taking behaviors, such as driving fast, promiscuous sex?); 103 (Did you ever think about ending your life?); 104 (Did you ever intentionally scratch, cut, burned or hurt yourself?); and 105 (Did you ever attempt suicide?).

As mentioned above, a wide-scale and effective application of the TALS-SR took place in the context of studies conducted on the population affected by the L'Aquila earthquake in April 2009. In the framework of several studies developed in collaboration with the University of L'Aquila, the TALS-SR was administered to population samples exposed directly and /or indirectly to this event, at different time from exposure (10 and 21 months apart) and to survivors located at various distances from the epicentre. These researches enlighted a significant percentage of partial and full-blown PTSD, respectively up to 29.9 and 37.5% in a sample of 512 students at 10 months observation [31]. These studies also pointed out not only a remarkable gender gap in PTSD prevalence, with a risk peak of PTSD development among young women [32] but also some gender specific clinical features [33-36].

Finally, Domain IX includes 6 items that investigate personality characteristics and/or risk factors that may be related to the development of post-traumatic stress symptoms. They include feeling sensitive to stress and loss; being provocative; having the pleasure of being at the center of attention; feeling attracted by danger; undertaking risky activities. On other hand, in another study based on the use of TALS-SR, religiousness and spirituality emerged as protective factors with respect to the psychological difficulties deriving from the natural disaster [37].

Correlations between the trauma and loss spectrum and the mood and adult autism subthreshold spectrum

As mentioned above, different studies were carried out with the aim of exploring the relationships between different psychopathological dimensions, in particular between post-traumatic stress spectrum and mood disorders and autism spectrum disorders.

Researches that have been investigating the correlation between the TALS-SR and the MOODS-SR enlighted a strong interplay between these two dimensions, consistently with scientific literature [38]. Among the main achievements of these studies are worthmentioning the findings of a strong link between some of the mood components, such as depressive cognition and manic energy, and an increased risk of PTSD [39]. High PTSD prevalence rates among bipolar patients were also reported, with a substantial anamnestic gap for what concerns traumatic exposure with respect to healthy controls. Furthermore, lifetime manic spectrum symptoms resulted to be strongly related to the TALS-SR "potentially traumatic events" and "maladaptative coping" domains and constitued a significant risk factor for PTSD development, with hyperarousal and higher anxiety sensitivity potentially mediating this association [32]. In addition, a research on the impact of mood spectrum comorbidity on suicidality, explored by the MOODS-SR [40], in patients with PTSD, highlighted a significant correlation between mood spectrum and increased suicidality in PTSD. The existence of a significant correlation between mood alterations and PTSD symptoms has also been confirmed by studies conducted on caregivers: these studies pointed out that on one hand PTSD confers susceptibility to develop Major Depressive Disorder [41] while, on the other, a higher lifetime mood symptom burden reduces the PTSD gender gap, since it constitutes a predisposing factor to PTSD [17].

In recent years, growing interest has been focusing on adult autism disorder, with an increasing push towards a dimensional perspective [42]. In this framework, the development and validation of a self-report questionnaire, Adult Autism Subthreshold Spectrum (AdAS Spectrum), aimed to identify subtreshold autism spctrum symptoms

along a dimensional *continuum* [43], further widened the view in the field of post-traumatic research. The results of these studies have shown that high autistic traits (AT) on the one hand are linked to increased exposure to trauma, while at the same time confer a susceptibility to the development not only of trauma and stressor related disorders, but also of mood disorders [44]. Further studies have deepened the research into the motivations underlying such relationships, enlighting a major mediating role of rumination [45]: a study on 178 students indicated that a high AdAS score was associated to higher TALS-SR, MOODS-SR and Ruminative Response (RSS) scores and that the relationship between AT and mood spectrum resulted to be partially mediated by ruminations and trauma-stressor related symptomatology [45]. In addition, a subsequent study on the same sample showed how the relationship between AT and trauma and stress related symptoms prevailed on gender differences among high risk subjecs, with females scoring significantly higher than males only among AdAS low scorers [46]. The results of a study analizing the relationship between post-traumatic stress spectrum and subthreshold autism spectrum symptoms in a sample of parents of pediatric patients suffering from epilepsy went in the same direction, since it highlighted noteworthy correlations between AdAS and TALS score only in the subgroup of fathers [44]. In this perspective, trauma can act as a pathology booster in subject with undetected autism spectrum disorder, who are caracterized by a marked tendency to rumination, as has been highlighted in a recent case report illustring the clinical picture of a 35-years old woman with multiple psychiatric diagnosis and suicial ideation who reported an hystory of childhood trauma [47].

The role of new emerging trauma related symptoms

The relation between cicardian/seasonal rhytms and vegetative function (both being key features in bipolar diathesis) and sucidality has been explored in patients with PTSD. This issue, in fact, is still largely unexplored. The findings emerged from one of the studies suggested that lifetime disregulations in rhythmicity and vegetative functions may represent correlates of suicidality in patients with DSM-5 PTSD, even eliminating confounding factors such as co-occurrent mood disorders [48]. Increasing research is however warranted as a promising research path suicide and non-suicidal self-injuring focuses on the mediating role of dissociative symptoms [49], whose clinical relevance has been recognized by DSM-5, through the introduction of the dissociative subtype [50].

The combined use of TALS-SR and MOODS-SR has also allowed us to examine the impact of Post-traumatic spectrum symptoms on altered eating behaviours, suggesting a wide range of abnormal eating habits among PTSD sufferers, as well as the existence of a strong link between PTSD and somatic symptoms burden [51,52]. On the other hand, exploring TALS-SR scores in patients suffering from fibromyalgia [15], a statistically significant correlation between lifetime exposure to potentially traumatic events, in particular loss events, post-traumatic stress symptoms and severity of fibromyalgia, was detected.

Conclusions

In recent years, PTSD and stress related syndromes have been object of a interest [53]. Thanks to an increasing number of neurobiological, epidemiological and clinical studies, significant innovations have been introduced in the DSM-5, not only recognizing the autonomy of these forms within the wider field of anxiety disorders, but also aknowledging the clinical relevance of pathological reactions to grief. In this framework, the dimensional approach, exploited by a wide-scale use of the TALS-SR, has played an important role in this progress, allowing for an insightful exploration of post-traumatic stress syndromes and providing a robust contribution to the studies upon the new DSM-5 criteria. On the other hand, while the assessment and clinical relevance of partial and sub-threshold forms are still debated and the DSM-5 endorses a more restrictive notion of trauma, the use of TALS provides an important contribution to research not only into the clinical features of PTSD, but also into its etiopathogenetic factors and into the development of new and more effective intervention strategies.

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Original article

Autistic traits and rumination as vulnerability factors towards post-traumatic stress symptoms: shaping psychopathological trajectories

Liliana Dell'Osso, Dario Muti, Primo Lorenzi, Alessandra Della Vecchia, Claudia Carmassi, Barbara Carpita

Department of Clinical and Experimental Medicine, University of Pisa, Italy

SUMMARY

Recent studies on Autism spectrum disorder, while focusing on adult subjects, stressed the presence of full-threshold and subthreshold autistic symptoms in clinical populations, also providing valuable insights on how neurodevelopmental alterations may increase the risk towards the development of other psychiatric conditions. The present review takes into account the most recurring topics in this literature, such as the research on autistic traits and ruminative thinking, collecting evidences on the effects of these elements in clinical presentations. In particular, while autistic traits and ruminative thinking seem to act as vulnerability factors towards the development of post-traumatic symptoms after life events, they could be considered the starting point of different kinds of psychopathological trajectories depending from the specific neurobiological asset and its interactions with environment. In order to rethink the literature within a coherent theoretical framework, the Adult Autism Subthreshold Model is then discussed.

Key words: autism spectrum disorder, post-traumatic stress disorder, borderline personality disorder

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Correspondence
Dario Muti
Department of Clinical and Experimental Medicine, University of Pisa
Tel.: +39 391 1106376
E-mail: dario.muti1986@gmail.com

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Autism spectrum: a constantly evolving picture

Autism Spectrum Disorder (ASD) is defined as a condition characterized by alterations in brain connectivity with cascading effects on several neuropsychological functions. This early-onset disorder features communication deficits, alterations in social cognition, repetitive, stereotyped behaviours. Intellectual impairment might also be present [1,2]. The pathogenesis of ASD remains largely unknown; however, given its high heritability [3], a strong genetic influence is expected, and several genetic mutations associated with ASD have been identified, many of which are involved in the synaptogenesis and synaptic functioning. These observations trace back to the first outlines of this syndrome by Kanner and Asperger, who both independently reported how first and second degree relatives of the observed children shared some psychopatological features with their offspring [2,4,5].

A growing body of studies also stresses how environmental conditions, in particular those linked with intrauterine life and/or increased level of oxidative stress, may play a pivotal role towards neurodevelopmental alterations [6,7]. From a neurobiological point of view, some literature stressed that ASD should be considered as a condition predisposing to a subsequent development of alterations within brain connectivity, particularly concerning social brain areas implicated in specific aspects of mentalization, social cognition, and emotional processes [8,9].

Since the first observations by Kanner and Asperger, increasing literature has also stressed the presence of a broad spectrum of milder symptoms (which would feature social difficulties, cognitive and behavioural traits) among parents and siblings of ASD subjects, leading to shape the concept of a "broad autism phenotype" (BAP) [10-12]. Moreover, the introduction of specific psychometric instruments such as the Autism Spectrum Quotient (AQ) [13] and Adult Autism Subthreshold Spectrum (AdAS Spectrum) [11,14] allow to properly investigating the presence of autistic traits (AT) in both clinical and general population. Results from these studies highlighted how AT seem to be continuously distributed in the general population, being more frequent amongst some high-risk groups [11,13,15-22]. AT are reported to be particularly represented also in clinical samples of patients with other psychiatric disorders [20,21,23-31]. In this framework, DSM-5 switched from the previous distinction between high functioning autism (namely, Asperger's Disorder) and autistic disorder, featuring the broader category of "Autism Spectrum Disorder" [1]. Also neuroimaging studies have shown a continuity between ASD and BAP [10], while genetic studies reported how different phenotypes (non-clinical samples, AT, BAP, full-blown ASD) share a genetic risk continuously distributed across the population, implying that clinical thresholds, classically intended, could be considered arbitrary, since the disorder exists as a quantitative extreme of a continuum [32]. In a broader perspective, it is noteworthy that, while a wide literature reported, as described above, the presence of AT in patients with other psychiatric disorders [20,21,23-31], genetic studies seem to confirm this data, highlighting common underpinnings between ASD and mood disorders [33], which would involve in particular pathways regulating circadian rhythms [33,34]. Furthermore, recent biochemical studies reported also an involvement of pro-inflammatory cytokines, neurotrophins, and dysregulations of the immune system in ASD as well as in post-traumatic stress disorder (PTSD) and mood disorders [35-39]. On the other hand, neuroimaging and neurocognitive studies reported shared traits between AT and Feeding and eating disorders (FED). These elements, which are currently object of increasing investigation in the scientific literature, may suggest that the autism spectrum continuum should eventually be extended to other disorders, that have been traditionally considered as part of distinguished categories [40].

The transnosographic role of AT and ruminative thinking

The ASD comorbidity has been quite consistently described as an overlap with Attention deficit hyperactivity disorder (ADHD), anxiety and mood disorders [41]. Further studies, however, have proved a wider range of interactions.

Expanding on Gillberg et al. (1996) [42] seminal notion of overlapping features between Anorexia nervosa (AN) inflexibility and behavioural rigidity and the characteristic insistence on sameness which lies amongst the core symptoms of ASD, several studies explored the overlap between ASD clinical features and FED, particularly AN [43]. AN patients exhibit behavioural rigidity with a focus on food and weight (that may fit into unusual restricted/repetitive interests and behaviours), deficits in emotional intelligence and in theory of mind tasks, social anhedonia, and attention to detail, all typical features of ASD [27,43]. Moreover, ASD individuals show a high prevalence of food problems: the habit to be selective about food as well as the aversion to certain textures, colors, smells and temperatures are often associated with underweight [11]. A recent study reported a higher rate of AT amongst FED patients when compared with healthy controls, especially in subjects with restrictive patterns, suggesting that a restrictive food behaviour may be considered as part of an ASD female phenotype: interestingly, this hypothesis may lead to a different interpretation of the striking gender differences in both ASD (diagnosed mainly amongst males) and AN (diagnosed mainly amongst females) [28]. Recently, increasing literature is stressing the presence of sex-specific presentations of the autism spectrum, which may result in an underestimation of these conditions among females [20,27,29,43]. In particular, females with ASD/AT often show an apparently higher adjustment to social interactions, often through the employment of camouflaging and of other copying strategies which features the imitation of others' behaviours [2,27,28]. As a consequence of the higher awareness of their own social difficulties, females seem to show a higher social anxiety [11,28,44,45] It is noteworthy that social anxiety is another disorder with a significantly higher prevalence amongst females, and which seem to share with ASD an impairment of the social brain [15,46-49]. Moreover, the pattern of restricted interests and repetitive behaviours is often centered on subjects quite different from those typically reported amongst males, such as spending time with animals, reading fictions or focusing on food and diet [11,20,44]. As reported above, this latter data is supported by the body of studies that is stressing how AN may be better considered as a female phenotype of ASD [2,20,29,43].

However, this is not the only interesting overlap between autism spectrum and other psychiatric conditions, from a transnosographic point of view. In particular, an increasing number of evidences has been reported on the relationship between trauma and stress-related symptoms and AT/ASD. While trauma and autism had been linked since classical psychodynamic theories [50], early

evidence-based research on the topic yielded conflicting results. Among the first studies, focusing on a child population, some reported either no [41] or low [51] correlation between neurodevelopmental disorders and trauma or stress related symptoms in ASD patients, while others highlighted a quite relevant prevalence of PTSD in ASD [52] or, conversely, found that suicidal thoughts and behaviours, associated with depression and PTSD, were quite high amongst young ASD patients [53].
The different methodological approach and the heterogeneous population considered probably accounts for these conflicting data. Moreover, it has been widely considered how full-blown ASD patients might be unable to properly report traumatic events and to have them positively screened with a psychometric instrument, since the condition itself prevents proper mentalization and expression of traumatic and/or stressful situations [54,55].
A significant association of rumination and trauma/stress-related symptoms with mood symptoms and suicidality was also highlighted [22]. This is quite a specific indication: it is widely known, from a behavioural and cognitive point of view, how negative beliefs in both anxiety-related disorders and mood disorders are maintained by a stream of negative, ruminative automatic thoughts. A cyclic model about maintenance mode for depression, dubbed "vicious flower" has been described in 2010 [56], while one involving ruminative thinking in the maintenance process of anxiety and panic related symptomatology is known since the early '90 [57].
Hence, rumination and trauma/stress-related symptoms may be the common mediators of AT, mood spectrum symptoms [12,21,22,25,26,58,59] and suicidal ideation interplay [12,21,22,24,60]. According to the cognitive model of PTSD, excessive rumination over traumatic or highly distressing experiences may lead to faulty processing and the development of post-traumatic stress symptoms [61]. In this sense the presence of a BAP, which includes among its features the presence of rumination, could have a crucial role in the development of PTSD following a traumatic event [54,61-66]. Conversely, PTSD is characterized by a decreased interest or participation in daily activities and a feeling of detachment from others, thus resembling autistic symptoms as suggested by high scores in questionnaires assessing AT [29].
Negative ruminative thinking is particularly interesting from a transnosographic point of view, as it appears to be strictly implied in many different psychiatric disorders, such as Obsessive-compulsive disorder, affective disorders, psychosis, Borderline personality disorder (BPD) and PTSD [67-69]. It has been described as one of the main symptoms of ASD [70], belonging to the domain of restrictive/repetitive activities. This repetitive thought pattern is associated with demoralization, anxiety and bad ideation [71], which negatively influences problem solving and worse feelings processing, eventually leading to social isolation [56]. Several authors believe that negative ruminative thinking can play a role in the development of depression [71,72] and suicidal ideation and behaviours [21,22,24]. Acting as intermediary, rumination seems to increase the risk of depressive episodes, their duration and their severity, in response to negative life events [73,74]. Subjects with ASD [24]/AT [25] showed high rates of adjustment disorders, which may also be related to increased suicidality [24,53]. Recent data showed also an association between AT and PTSD [21,58], with higher rates of PTSD in subjects with AT after traumatic events. Therefore, it is possible that ASD subjects represent a low resilience group more vulnerable to develop trauma/stress-related symptoms and disorders [21]. In this regard, individuals with high levels of AT may show altered coping strategies and reduced attitude to manage with stressful situations. It has also been suggested that the vulnerability of patients with AT towards the development of trauma/stress symptoms after being exposed to life events could play a further role in the development of mood disorders [22].
A strong relation between ASD/ATs and suicidal ideation/behaviours, both in clinical and non-clinical samples, was also observed [12,21,22]. A high prevalence of suicidality has been reported in patients with ASD of different age groups [22,24,25,53,75-78], and, conversely, a diagnosis of ASD was found in 7.3% of subjects with a suicide attempts history [24]. More recently, a significant association between AT and suicidality has also been found, both in general population and in psychiatric patients [21,25,29]. It has also been proposed that burdensomeness and thwarted belonging may mediate the relationship between ATs and suicidal behaviour in general population [79]. A recent study reported a similar presence of suicidality between ASD and subjects with AT, and both groups showed a higher score than healthy controls [21]. Even in depressed subjects the presence of comorbid ASD is related to an increase in suicidality levels [25,78]. In these patients ASD is also associated with methods of greater lethality for suicide attempts [25].

BPD: where all comes together

According to DSM-5 BPD is a condition with a significantly higher prevalence among females, which begins in early adulthood and shows as his core feature a pervasive pattern of instability of interpersonal relationships, self-image, and affects, along with marked impulsivity [1,27]. Typical symptoms may include also a marked fear of being abandoned, feelings of emptiness and inappropriate anger, self-harming or suicidal threats and behaviours, dissociative symptoms and/or paranoid ideation [1,80].

A consistent number of studies highlighted a possible role of negative ruminative thinking in BPD [80-83], which may be implied in maintaining and increasing BPD psychopathology, as previously evidenced also for depressive symptoms [31,72,73,84-86]. In particular, BPD patients show a higher tendency to maladaptive cognitive processes, including rumination [82]. Also amongst depressed patients, on which many studies about rumination were focused, some authors highlighted a specific relationship between BPD and rumination [80,87,88]. This data increased the interest in investigating the specific relationship between rumination and BPD psychopathology, while recent research highlighted that BPD patients seem to show a specific vulnerability to develop stress-related rumination, and in particular rumination after negative interpersonal events and interpersonal exclusion, with slower recovery from distress [89-91]. Other studies stressed also how aggressive behaviours in these patients seem to be linked to the presence of anger rumination [89,92]. These findings are of particular interest in light of previous literature that reported a significant role of ruminative thinking for the development of psychiatric disorders after being exposed to traumatic events [40,59]. It should be noted that many studies highlighted also the presence of traumatic experiences, frequently in childhood, in clinical histories of BPD patients, often hypothesizing for this condition a pathogenetic mechanism which would imply the interaction between genetic vulnerability and early life events [20,30,31,93-99]. In this framework, according to a dimensional approach, some authors raised the hypothesis that PTSD may occur not only after being exposed to highly traumatic events (like those listed in criterion A of DSM-5) but also as a consequence of prolonged and/or repeated milder stressful experiences (and in particular interpersonal victimization, such as being exposed to bullying episodes, sexual harassment, or other aggressive behaviours, including by caregivers) [100-103]. The exposure to this kind of events may lead to the development of a specific phenotype of PTSD, called "Complex PTSD" (cPTSD) [100-103]. It is noteworthy that this condition, which often takes a chronic course, is considered to be characterized by a higher presence of dissociative symptoms and negative alterations of emotions and cognitions, including emotional dysregulation, negative self-image, maladaptive and self-injuring behaviours [104-106]. Moreover, it has been pointed out that chronic cPTSD may result, in time, in a deep instability of emotions, self-perception and interpersonal relationships, with marked impulsivity and often associated with substance abuse and self-injuring [54,104]. Such a clinical picture is consistently similar to that of BPD, and some authors also stressed that these subjects may actually receive more frequently a diagnosis with BPD instead that get their trauma-related condition recognized, especially if they not report a history of major traumas [104,105,107]. These considerations led to increase the interest in exploring the relationship between BPD and trauma and stress-related conditions: recently, a study by Dell'Osso et al. [80] evaluated the association of BPD, rumination, PTSD and mood spectrum (another dimension which has been frequently associated with BPD in the literature) in a sample of BPD patients with or without mood disorders and in healthy controls. The study reported a significantly higher presence of rumination (as measured by the Ruminative Response Scale, RRS) and PTSD-criteria fulfillment in BPD patients than in controls. Although BPD patients with mood disorders showed a higher rate of rumination and PTSD than patients with only BPD, according to the regression analysis results, the effect of rumination and PTSD symptoms seemed to prevail on the effect of mood symptoms in predicting BPD, confirming the association between BPD, PTSD and rumination and possibly implying a significant role of PTSD and rumination in BPD psychopathology. In this framework, increasing literature is suggesting the presence of overlapping features between ASD and BPD [2,29,108]. Some authors pointed out that distinguishing ASD without intellectual disabilities from personality disorders in adults could be challenging due to similarities in the pervasive pattern of behaviours that strikingly affect social functioning [109], and in particular BPD and ASD seem to share a common core in the impaired understanding of and reacting to emotions and interpersonal challenges [110]. BPD subjects often show significant empathy and theory of mind alterations, as well as difficulties in recognizing and interpreting emotions [111-113], which may be at the basis, together with the emotional dysregulation, of the pattern of instability in social relationships [2,21,29,54]. On the other hand, subjects of the autism spectrum often report a higher vulnerability to traumatic experiences, even if of milder intensity [54], which may result in a higher frequency of trauma and stress-related disorders, in particular adjustment disorders and cPTSD [60]. Treatments targeting social brain mechanisms, such as psychotherapies targeting mentalization or theory of mind, as well as intranasal administration of oxytocin, have been conducted in both BPD and ASD patients [114-117]. Studies that investigated comorbidity rates between ASD and BPD, reported a 15% prevalence of ASD amongst subjects with BPD, stressing also a higher suicidality and lower global functioning in the comorbid group [118]. On the other hand, a 9 to 10.6% prevalence of BPD has been reported among subjects with ASD [23,103]. Concerning AT, a study reported that about a half of 38 patients with BPD showed the presence of significant AT as measured by the AQ [119]. Dudas et al. [110] found that BPD patients reported higher levels of AT than controls, while comorbid

patients showed the highest levels of AT as measured by the AQ. More recently, Dell'Osso et al. [29] reported, in a sample of 50 BPD patients and 69 controls, significantly higher levels of AT (as measured by both the AQ and the AdAS Spectrum) in the BPD group. Moreover, in the same sample AT showed a significant impact on suicidality and exposure to physical or sexual abuse during lifetime. A similar result was reported by another study conducted in a non-clinical population of college students, where authors highlighted a higher risk of suicidal ideation amongst subjects who show both AT and BPD traits [120].

In a broader framework, it is noteworthy that, while BPD is a diagnosis with a strikingly higher prevalence amongst females, ASD is, conversely, diagnosed mostly amongst males; and this might lead to considerations similar to those raised about AN [1,20,27,43,121].

These data, together with the evidence of overlapping features and frequent comorbidity between the two disorders, led to hypothesize that BPD may be considered a female presentation of the autism spectrum, which may occur in particular when the subject is exposed to traumatic or stressful events during lifetime [2]. While FED may represent another possible trajectory for female autism spectrum in addition to BPD, on the other hand, it should be noted how BPD and FED showed significant comorbidity rates [122], further supporting the autism spectrum model for these conditions.

How ASD related traits shapes illness trajectories

As discussed above, recent studies stress the continuous distribution of AT in the general and clinical populations: within this framework, crossing the full-threshold symptomatology seems to be a matter of quantity rather than quality. These findings might be interpreted in light of a new coherent, dimensional and quantitative psychopathological model, such as the Adult Autism Subthreshold Spectrum Model (AdAS Spectrum Model) [2], rather than within a rigid categorical approach. The AdAS Spectrum Model is a comprehensive psychopathological theory which places on the same continuum full-blown symptoms, mild and atypical manifestations, behavioural traits, and personality features associated with the ASD diagnostic category. These traits may act as risk factors for other mental disorders, being continuously distributed from normality to pathology and including also non-clinical aspects of neuroatypicality, such as originality, creativity, divergent thinking [2,123]. This model considers firstly, as widely reported, the continuous distribution of AT. From this point of view, the ASD clinical phenotypes appear as an extreme manifestation of a gradual quantity. Moreover, the AdAS Spectrum Model features, amongst the possible psychopathological trajectories in the same continuum of the autism spectrum, also other kinds of clinical expressions, such as Schizophrenia, mood disorders, FED or BPD [124,125], proposing a coherent explanation of the higher rates of AT amongst clinical samples. In a broader perspective, according to this model, AT may be considered as the psychopathological correlate of the presence of a neurodevelopmental alteration that lead to different trajectories depending form the timing and the entity of the alteration and from its interaction with environment and life events [125]. Their presence may result not only in the development of psychopathological trajectories, but also allow hyperadaptive manifestations of atypical behaviours related to geniality [54,126,127]. At the same time, however, they act as a source of greater vulnerability and as risk factor for mental disorders and suicidality [2,22,25,125].

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Original article

Clinical correlates of trauma spectrum and bipolar disorder

Aurora Santucci, Simone Bolognesi, Arianna Goracci, Serena Piccione, Costanza Taddeucci, Pier Francesco Laurenzi, Andrea Fagiolini

Dipartimento di Salute Mentale e Organi di Senso, Azienda Ospedaliera Universitaria Senese

SUMMARY

Objectives

To evaluate the relationships between trauma and clinical correlates, quality of life and global functioning in a sample of individuals with bipolar disorder (BD).

Methods

65 subjects with BD type I or II, aged between 18 and 75 years, were assessed with the Clinical Global Impression - Severity (CGI-S), Trauma and Loss Spectrum Self Report (TALS-SR), Quality of life index (QL-index), and Global Assessment of Functioning (GAF) scales. Data analysis were performed using SPSS version 20.0. Basic statistics were used to describe the demographic, clinical and traumatic spectrum characteristics of the participants. Pearson's correlation analysis was performed to analyse the correlations between psychometric scores and clinical data. The independent t-test was used to compare the two groups (BD I and BD II).

Results

Statistically significant correlations were observed between BD severity, as measured by CGI-S, and TALS-SR mean scores in Domains pertaining to III ($p < 0.01$), IV ($p < 0.05$), VII ($p < 0.01$), VIII ($p < 0.05$) and IX ($p < 0.05$). No significant correlations were found between the score in the TAL-SR 'history of trauma' domain and number of hospitalisations, history of suicide attempts, quality of life and global functioning indexes. However, a statistically significant correlation emerged between Domain VII score and history of suicide attempts ($p < 0.01$). The majority of subjects (92.3%) believed that traumatic experiences had an impact on their BD symptoms.

Conclusions

Our data confirms a relationship between trauma spectrum and certain BD characteristics. The absence of a relationship between trauma history and number of hospitalisations, suicide attempts, quality of life and global functioning may be due to lack of statistical power. The significant relationship between suicide attempts and Domain VII -TALS-SR score is worth being better explored in longitudinal and prospective studies.

Key words: trauma spectrum, bipolar disorder, functioning

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Correspondence
Andrea Fagiolini
Dipartimento di Salute Mentale e Organi di Senso, Azienda Ospedaliera Universitaria Senese, Viale Bracci 12, 53100 Siena, Italy
E-mail: andreafagiolini@gmail.com

Conflict of interest
A. Fagiolini declares conflict of interest

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Introduction

Bipolar disorder is a chronic and recurrent mood disease, whose prevalence in general population rises above 1%, representing the fourth disability global cause in adolescents and young adults [1].

It is well known that bipolar disorder has a strong genetic etiology, however there are evidence that it could be influenced also by environmental events, such as childhood trauma [2,3]. Childhood trauma include physical, emotional and sexual abuse, physical and emotional neglect [4,5].

Several studies showed that young people with genetic vulnerability are more susceptible to developing bipolar disorder when exposed to trauma [6], as confirmed by some recent reviews that showed that adversities

during childhood are associated to bipolar disorder, representing a risk factor for its development [7,8].
Some studies [9] hypothesized that vulnerability to the development of bipolar disorder could manifest itself not only through genetic risk factors, but also through exposure to traumatic environmental factors related to the pathology of one or more family members. In this sense, familiarity for bipolar disorder could be mediated in part by traumatic events.
Between 30 and 50% of individuals with bipolar disorder suffered from childhood trauma [10], resulting often in a comorbid diagnosis of Post Traumatic Stress Disorder [11].
These traumatic experiences often lead to a worse clinical outcome: individuals with bipolar disorder who suffered from trauma are more likely to develop rapid cycling, suicide attempts, substance use or abuse, cognitive impairment, early and lifetime functional impairment, poor adherence to treatment [6,12-14].
Trauma in these patients can be expressed in different forms depending on the gender: it has been observed, in fact, how in females it is most manifested in negative thoughts and suicidal behaviors, while in males in aggression and heterodirect anger [15]; moreover, it seems that females with bipolar disorder with a history of traumatic events show more clinical characteristics of rapid cycling, an early onset of disease, an increased suicidal risk and a greater frequency of depressive episodes [1].
Traumatic events influence the severity of the disease not only during childhood, but also during adolescence and adulthood; it has been observed that the presence of stressful events in adult life correlates with a more severe symptomatology and with a greater recurrence of depressive symptoms [16].
Although several studies have highlighted the relationship between bipolar disorder and traumatic events, the frequency of the different types of traumatic experience in bipolar disorder is less studied. However, emotional trauma appears to be the most associated with DB [17,18].
Some authors specifically investigated the frequency of sexual abuse in bipolar patients, finding a significantly higher prevalence compared to the general population [10].
Traumatic events also seem to play a role in determining cognitive alterations: in fact, it has been observed that, in bipolar patients with a history of trauma, there is a compromise of all cognitive domains, including memory, attention, executive functions, IQ.
Underlying these deficits, several neurobiological mechanisms may be involved, inherent in neuroplasticity, inflammation, HPA axis and regulation of the circadian system. it appears that trauma may induce a dysregulated state of glucocorticoid release, which could alter normal neurogenesis and physiological brain development. In fact, imaging studies have shown, in bipolar patients with a history of childhood trauma, alterations of the prefrontal cortex, amygdala, corpus callosum, hippocampus, hypothalamus and pituitary. Another possible mechanism could concern BDNF-mediated neuroplasticity, whose serum levels are reduced in this population [19]. In addition, in these patients high levels of cytokines and inflammatory mediators are often observed; this could play a role in biological changes induced by trauma [20].
Literature points out that there is an important correlation between traumatic events and the onset and development of bipolar disorder and its characteristics, still the impact that these events have on the functioning of patients is less studied. Indeed, despite clinical evidence of global functional impairment in patients with bipolar disorder who experienced childhood trauma, only few studies [21] have been investigated the correlation between these two features.
Therefore, our study aims to analyze the prevalence of traumatic events in DB patients, with particular attention to the impact that trauma has on clinical manifestations, prognosis and overall functioning in these patients.

Aim of the study

Our aim is to outline the impact of the spectrum of trauma and loss on bipolar disorder, analyzing the frequency and showing the effects on the clinical features of the desease, over the quality of life and on the global functioning of the patient.

Materials and methods

Partecipants

The study sample included 65 adult out- and inpatients, recruited over a 3-month period, with a diagnosis of Bipolar Disorder (BD), seeking treatment at the Department of Psychiatry of the University of Siena. Inclusion criteria for patients were: diagnosis of BD type I or II according to DSM-5 and age between 18 and 75 years. Exclusion criteria were: diagnosis of post-traumatic stress disorder, severe systemic or neurological illnesses, inability to give consent or to perform Self-Report for Trauma and Loss Spectrum (TALS-SR).

Measure

Instruments and assessments

We collected patients' sociodemographic and clinical data through a structured interview. Patient's clinical condition was assessed via Clinical Global Impression - severity of illness (CGI-S), a scale that assesses the severity of the disease at the time of the interview, with a score ranging from 0 (normal) to 7 (extremely ill) [22].

An overall assessment of patients' quality of life was obtained through the Quality of Life Index - QL-Index, which is a simple and short tool of hetero-evaluation that has been created for the evaluation of patients suffering from oncological diseases, but it is often used in other pathological conditions. It consists of 5 item that explore activity, daily life, health, support and mood of patients and provides an overall judgment by the clinician about the accuracy of his assessment. The rating scale consists of 3 points (0-2) and the higher scores correspond to the positive responses. The index derives from the sum of the individual scores, so higher index scores express a better quality of life [23].

The overall functioning of patients was assessed via the Global Functional Assessment (GAF), a scale that considers the psychosocial and working functioning of the subject by placing it in a hypothetical continuum ranging from mental health (100) to very serious mental illness with risk of death (1), regardless of the nature of the psychiatric disorder: it has been included in the DSM- III-R and in DSM-IV as Axis V of the multiaxial classification [24].

TALS-SR

TALS-SR is a questionnaire consisting of 116 items that explores lifetime potentially traumatic or loss events and the set of symptoms, behaviors and personality characteristics that can predispose or detect a stress response syndrome.

The TALS-SR is divided into 9 domains: Domain I (loss events) describes loss events of different severity; Domain II (grief reaction) explores symptoms related to persistent grief in response to loss; Domain III (potentially traumatic events) includes potentially traumatic events that can occur lifetime; Domain IV (reactions to losses or upsetting events) investigates acute reactions to loss or traumatic events; Domains V, VI, VIII describe the symptoms related to re-experiencing, avoidance/numbing and hyperarousal respectively; Domain VII (maladaptive coping) searches for maladaptive behaviors; Domain IX (personal characteristics/risk factors) explores the personality characteristics that can represent a risk factor for the development of a symptomatology in relation to trauma and/or loss.

Items' response consist of yes or no and the domain score is obtained by adding the positive answers [25].

Statistical analysis

Data analysis were performed using SPSS (Statistical Package for the Social Sciences for Windows, IBM) version 20.0. Basic statistics were used to describe the demographic, clinical and traumatic spectrum characteristics of the participants.

Pearson's correlation analysis was performed to analyze the correlations between TALS-SR, CGI-S, QoL-I, GAF and clinical data (hospitalizations and suicide attempts). The independent *t-test* was used to compare the two groups (BD I and BD II) with respect to continuous quantitative variables, i.e. the average scores obtained in the TALS-SR domains.

Results

Demographic and clinical characteristics

Thirty-two of the 65 patients were women and the mean age was 50.2.

The sample was divided into 36 patients with bipolar disorder I and 29 patients with bipolar disorder II, among these 22 patients had psychiatric comorbidity: 12 (18.6%) with borderline personality disorder, 4 (6.2%) with narcissistic personality disorder, 3 (4.6%) with obsessive compulsive disorder, 1 (1.5%) patient with binge eating disorder, 1 (1.5%) with dependent personality disorder and 1 (1.5%) with attention deficit hyperactivity disorder.

Table I describes the CGI-S scores of the total sample (n = 65).

Analyzing the sample in terms of lifelong hospitalizations and suicide attempts, it emerges that 64.6% were hospitalized at least once in their lives and 21.5% made at least ≥ 1 suicide attempt. In particular 4.6% of the sample had ≥ 10 hospitalizations, 13.8% made one suicide attempt, 6.2% made two attempts, 1.5% made three attempts.

In our sample the average BMI was 27.46 (*sd* ± 5.81).

The average scores obtained regarding quality of life and overall functioning were 7.63 (*sd* ± 2.25) (QoL-I) and 70.60 (*sd* ± 16.01) (GAF) respectively.

Table II shows the mean TALS-SR domain scores obtained in our sample, in 30 patients with PTSD [25] and 30 healthy controls [25].

Furthermore, we assessed in the opinion of subjects, what impact the traumatic or loss event have had on the bipolar disorder: 36.9% rated a serious impact, 46.2% average, 9.2% mild impact and 7.7% no impact.

Correlations

We have linked the domains that mainly indicate the loss and trauma events with the patient's clinical condition, in particular by correlating TALS-SR Domain I (loss events) and Domain III (potentially traumatic events) respectively with the CGI-S: in the first case we didn't find any correlation, in the second one we obtained a statistically significant correlation ($p < 0.01$), indicating that the increase in potentially traumatic lived events corresponds to a worse disease severity.

By relating the CGI-S to the other TALS-SR domains, we obtained a statistically significant correlation in the case of Domain IV (reactions to losses or upsetting events)

TABLE I. *CGI-S scores of the total sample (n = 65).*

CGI-S	1	2	3	4	5	6	7
Sample n = 65	3 (4.6%)	21 (32.3%)	22 (33.8%)	10 (15.4%)	8 (12.3%)	1 (1.5%)	0

CGI-S: Clinical Global Impression - Severity. Frequency and percentage are reported.

p < 0.05, Domain VII (maladaptive coping) p < 0.01, Domain VIII (arousal) p < 0.05, Domain IX (personal characteristics/risk factors) p < 0.05.
By studying the correlation of domains I and III with hospitalizations (n°), suicide attempts (n°), QoL (score) and GAF (% score), there does not seem to be a statistically significant correlation in our study between the traumatic events and loss and the number of hospitalizations, suicide attempts, quality of life and general patient functioning.
However, an important statistically significant correlation emerges between Domain VII (maladaptive coping) and suicide attempts (p < 0.01), which explains the relationship between maladaptive behaviors following a traumatic experience and the greater risk of suicidal thoughts or acts.

Comparison between groups

We have compared, via independent t-test, the difference in the mean scores of Domain I and Domain III between patients with BD I disorder and II.
The results did not show a significant difference in the case of Domain I (loss events), while we found a significant difference (p < 0.05) between the two groups in Domain III (potentially traumatic events): average score was 5.64 (*sd* ± 4.18) in the BD I group, 3.66 (*sd* ± 2.62) in BD II group. This may point out that patients with BD I have more traumatic events in their lives than patients with BD II.
Furthermore, statistically significant differences between BD I and II emerged in Domain IV (p < 0.05), Domain V (p < 0.05), Domain IX (p < 0.07), indicating greater reactions to losses or upsetting events, re-experiencing and personal characteristics / risk factors in the BD I group.
These results are fully described in Table III.
Finally, we made a gender comparison by comparing the difference in the mean scores of the TALS-SR domains in males and females. In this comparison, no statistically significant differences emerged except for Domain VIII (arousal) in which the comparison of the averages between males (1.94 *sd* ± 1.66) and females (2.97 *sd* ± 1.67) was significant (p < 0.05).

Discussion

The results of our study show that, in the examined sample, there is a statistically significant positive relationship between the reported incidence of potentially traumatic events (domain III of TALS-SR) and severity of Bipolar Disorder (defined by CGI-S scores). Our results seem to be in accordance with available scientific literature data: a recent comprehensive review emphasized the high prevalence of traumatic events observed in the lifespan of BD patients, showing the importance that trauma might have in the development and natural course of disease [17].
To this end, a meta-analysis that collected data from 30 different studies found a positive association between the occurring of childhood traumatic events, and the severity of manic, depressive and psychotic symptoms experienced by the patients [26,27].
In order to assess the impact of trauma on the course of BD, a 2017 study by Aldinger and colleagues

TABLE II. *Mean TALS-SR domain scores obtained in our sample (n = 65), in patients with PTSD (n = 30) [25] and healthy controls (n = 30) [25].*

	Domain I	Domain II	Domain III	Domain IV	Domain V	Domain VI	Domain VII	Domain VIII	Domain IX
BD (n = 65)	4.85 (± 1.90)	12.98 (± 5.25)	4.75 (± 3.68)	8.18 (± 4.17)	4.05 (± 2.42)	4.71 (± 3.09)	2.02 (± 1.99)	2.45 (± 1.74)	2.66 (± 1.61)
PTSD (n = 30)	4.20 (± 2.19)	12.27 (± 6.84)	5.00 (± 2.79)	10.60 (± 3.19)	5.03 (± 1.47)	6.17 (± 2.86)	2.03 (± 1.47)	3.47 (± 1.28)	1.97 (± 1.38)
Controls (n = 30)	2.90 (± 1.51)	7.83 (± 4.62)	2.63 (± 2.19)	4.20 (± 3.34)	1.37 (± 1.45)	1.23 (± 1.77)	0.33 (± 0.84)	0.93 (± 1.17)	1.27 (± 1.28)

BD: Bipolar Disorder; PTSD: Post Traumatic Stress Disorder.

TABLE III. *Comparison of the mean scores of TALS-SR domains between Bipolar I disorder and Bipolar II disorder*

TALS-SR	BD	Mean ± SD	p
Domain I	I	5.14 (± 1.79)	0.168
	II	4,48 (± 1.99)	
Domain II	I	13,78 (± 5.05)	0.177
	II	12,00 (± 5.41)	
Domain III	I	**5,64 (± 4.18)**	**0.030**
	II	**3,66 (± 2.62)**	
Domain IV	I	**9,36 (± 4.13)**	**0.010**
	II	**6,72 (± 3.80)**	
Domain V	I	**4,58 (± 2.14)**	**0.045**
	II	**3,38 (± 2.61)**	
Domain VI	I	4,97 (± 2.86)	0.446
	II	4,38 (± 3.37)	
Domain VII	I	2,14 (± 2.11)	0.581
	II	1,86 (± 1.85)	
Domain VIII	I	2,64 (± 1.68)	0.324
	II	2,21 (± 1.82)	
Domain IX	I	**3,14 (± 1.71)**	**0.007**
	II	**2,07 (± 1.28)**	

TALS-SR: Trauma and Loss Spectrum Self Report, BD: Bipolar Disorder, SD: Standard Deviation.

analyzed the clinical features of bipolar patients who reported potentially traumatic life events in their medical history: they found early onset, greater tendency to rapid cycling, higher incidence of psychotic symptoms and higher risk of suicidal ideation and suicide attempts [28].

Several studies also agree that the presence of traumatic events in patients with BD correlates with greater comorbidity with substance use disorder. This correlation appears extremely important if we consider the negative impact that substance abuse can have on the course and prognosis of BD [17,28,29].

Furthermore, we analyzed the relationship between single patients CGI-S measures and TALS-SR remaining domains, finding a statistically significant positive correlation between disease severity and cumulative scores in Domain IV (reaction to losses or upsetting events), Domain VII (maladaptive coping), Domain VIII (arousal) and Domain IX (personal characteristics/risk factor). In particular, Domain VII (maladaptive coping) aims to identify the maladaptive behaviors that patients might develop following a traumatic experience, by investigating symptoms that are often associated with stressful events, impulsive conducts, self destructive behavior, somatic complaints, feelings of hopelessness and permanent damage.

As aforementioned, it seems that a positive correlation exists between the presence of past traumatic events in the life of bipolar patients, and a high risk of suicidal acts or thoughts: hence, suicidal behavior may represent the epiphenomenon of a maladaptive strategy, and Domain VII aims to investigate the presence of impulsive behavior or other maladaptive responses which may subtend suicidal thoughts and acts. In our study, we observed an important statistically significant correlation between domain VII (maladaptive coping) and suicide attempts ($p < 0.01$), confirming the relationship between maladaptive behaviors following a traumatic experience and the greater risk of suicidal thoughts or acts [17].

Scores obtained in Domain IX (personal characteristics/risk factors) also show a positive correlation with CGI-S score, and therefore with disease severity. Domain IX is aimed at identifying any personological changes induced by the traumatic event and, at the same time, investigates the presence of stable and pervasive personality traits that may predispose to the development/worsening of bipolar symptoms. To this end, Domain IX questions aim to investigate the presence of impulsiveness and marked reactivity to stressful events.

Comparing the results obtained by patients with BDI and BDII we found that the scores obtained in Domain III of TALS-SR (potentially traumatic events) are higher in the former group of patients (BDI). In line with our result, Dualibe and colleagues have found that there is a higher incidence of physical, emotional and sexual abuse in patients with BDI, rather than with BDII [17].

Analyzing the remaining TALS-SR domains, we also observed that the BDI group obtained higher scores in Domain IV (reaction to losses or upsetting events), Domain V (re-experiencing) and Domain IX (personal characteristic / risk factors), suggesting that patients with BDI may develop peculiar post-traumatic symptoms, and might show more frequently personological traits of vulnerability.

Comparing the scores obtained in the TALS-SR domains after clustering the sample by gender, no significant differences were found except in Domain VIII (arousal), where female patients obtained higher average scores. Some authors have hypothesized that among BD patients with a history of abuse, females are more susceptible to developing suicidal thoughts and behaviors, whereas males show an increase in irritability and aggression, thus larger studies may be useful to further explore sex differences in the response towards abusive experiences [30].

In addition, Etain and colleagues in a 2013 study hypothesized that the female gender could strengthen

the correlation between trauma and clinical characteristics of BD, mediating an additive effect. It seems that trauma in female subjects correlates more frequently with rapid cycling, age of early onset, suicidal behaviors, higher frequency of depressive episodes if compared to trauma in male patients [31].

Finally, we asked to patients their opinion on the impact of traumatic events on the course of their bipolar disorder: the majority of patients (92.3%) believe that traumatic experiences had some impact on psychiatric symptoms, whether of severe (36.9%), moderate (46.2%) or mild grade (9.2%).

Taking into account the subjective opinion of our sample, we furthermore emphasised the importance of accurately identifying trauma or potentially traumatic events in the life course of patients with BD.

Conclusions

Our data confirms previous findings pointing to a relationship between lifetime trauma exposure and BD characteristics. That we did not find a relationship between trauma and number of hospitalisations, suicide attempts, quality of life and global functioning is likely due to a lack of statistical power. The significant relationship between suicide attempts and Domain VII - TALS-SR score is worth being better explored in longitudinal and prospective studies. Of interest, over 90% of our study subjects felt that traumatic events negatively impacted the course of their disease. Larger, controlled, prospective studies are needed to explore more in depth issues such as the direction of causality and the possibility that an early treatment of BD may prevent trauma and trauma-consequences, and vice versa.

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Original article

The relationship between childhood trauma and aberrant salience: a preliminary study in patients with Schizophrenia

Pasquale De Fazio[1], Valentina Pugliese[1], Matteo Cattolico[1], Matteo Aloi[1], Cristina Segura-Garcia[2]

[1] Psychiatry Unit, Department of Health Sciences, University "Magna Graecia" of Catanzaro, Italy; [2] Psychiatry Unit, Department of Medical and Surgical Sciences, University "Magna Graecia" of Catanzaro, Italy

SUMMARY

Objectives

Aberrant salience represents one of the main pathogenetic mechanisms of psychotic symptoms. Exposure to childhood trauma constitutes a relevant environmental risk factor for subsequent development of Schizophrenia, but the possible influence of trauma on aberrant salience is poorly studied in literature. The primary objective of this study was to verify the association between childhood trauma and aberrant salience and secondly to evaluate the impact of clinical variables on aberrant salience.

Methods

Overall 53 outpatients (39 diagnosed with Schizophrenia and 14 with Schizoaffective Disorder) were recruited. The Childhood Trauma Questionnaire Short-Form (CTQ-SF), the Aberrant Salience Inventory (ASI) and the Positive and Negative Schizophrenic Symptoms (PANSS) were administered. Psychopathological differences according to ASI scores were evaluated and independent predictors of aberrant salience were assessed through linear regression analysis.

Results

Consistent with ASI scores, aberrant salience was present among 57% of patients. Aberrant salience was associated with higher severity of delusions, hallucinatory behavior, mannerisms and unusual thought content (PANSS) and emotional abuse/neglect (CTQ). According to linear regression analysis, emotional abuse during childhood and previous psychiatric hospitalizations are associated with higher aberrant salience.

Conclusions

The most striking results of this preliminary study was that patients with psychosis who had experienced an emotional abuse during childhood can be associated with a higher level of aberrant salience. Further studies are needed to understand the mechanisms thanks which childhood trauma influences the creation of salience, including the possible presence of both adaptive and aberrant alterations in the mechanism of salience processing.

Key words: Schizophrenia, aberrant salience, childhood trauma, emotional abuse, psychosis, trauma

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Correspondence
Pasquale De Fazio
Department of Health Sciences, University "Magna Graecia" of Catanzaro, viale Europa, 88100 Catanzaro, Italy
Tel.: +39 0961 712393
Fax: +39 0961 712393
E-mail: defazio@unicz.it

Conflict of interest
The Authors declare no conflict of interest

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Introduction

Over the past decade, several evidences have shown how exposure to childhood trauma represents an important environmental risk factor for subsequent development of Schizophrenia [1,2]. Childhood trauma is defined as a set of negative experiences faced by the individual before the age of 16 including emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect [3].

Several models have been proposed to explain the association between childhood traumatic events and psychotic symptoms, including

the presence of dysfunctional cognitive patterns, affective dysregulation, insecure attachment style and dissociative mechanisms [4].

Individuals with a personal history of childhood trauma have a threefold increased risk of developing Schizophrenia and tackling child abuse could result in a reduction of approximately 33% of cases of psychosis [5]. Exposure to childhood trauma has a significant impact on the clinical presentation of the disorder, relating with an early onset of illness, more frequent and prolonged hospitalizations, more serious global psychotic symptoms, suicidal ideation [6] and the need for more intensive treatment [7]. Literature supports a correlation between specific traumatic experiences in childhood and clinical manifestations in psychosis. Patients with Schizophrenia who experienced abuse and neglect in childhood show more clinical severity than those who have undergone other types of traumatic experiences [8]. Affected individuals with a history of physical abuse, sexual abuse and neglect also manifest prominent cognitive deficits, a reduced speed of information processing and alterations in working memory [9,10]. Repeated childhood traumas, in fact, cause structural and functional abnormalities on cerebral functioning. Stress can increase the release of dopamine in the mesolimbic areas, proportionally related to the increase of cortisol levels [11]. Several studies have demonstrated a negative impact of childhood trauma on higher cognitive functions, both in patients with psychosis and in high-risk probands [9]. Childhood adversities can induce long-term effects on neuronal growth and plasticity and on cognitive functions, through epigenetic modifications [12].

The cognitive processes underlying delusions and hallucinations include both attributing responsibility for negative events to other people, and interpreting internal thoughts or memories as events external to the subject [13]. Salience constitutes a physiological process of cognitive integration thanks to which objects and stimuli from the external environment and from internal representations reach attention, thus acquiring relevance and becoming able to influence thoughts and behaviors. The salient process has the purpose of directing attention to stimuli relevant to the individual (i.e. attractive, aversive, or supportive) and to the detriment of neutral or irrelevant stimuli [14]. The central processing of environmental stimuli also depends on the subject's life experiences, personal beliefs, as well as the socio-economic level in which the subject lives and has lived. The phenomenon of attributing meaning to stimuli is therefore not a static but rather dynamic mechanism, influenced by the needs of the individual in a precise moment of time [15].

Aberrant salience, or the assignment of salience or meaning to otherwise neutral or harmless stimuli, represents one of the main pathogenetic mechanisms of psychotic symptoms. Dopamine, which in physiological conditions mediates the salience of contextually relevant stimuli, during a psychotic state, determines the *de novo* creation of salience, which becomes remarkably aberrant [16]. The individual perceives these experiences as altered, not physiological, and tends to give them an organization or meaning, which ultimately leads to the pathological condition, primary to structure and concrete delusion. Hallucinations will likewise build around an aberrant meaning of internal representations of perceptions and related memories [17].

Moreover, the recent emerging field of computational psychiatry approach may offer useful models for salience integration [18,19]. In particular, according to Miyata [20], two kinds of computational models seem to be appropriate for the integration of salience: one is the neural network model that seems to be suitable for describing the relationship between different salience domains; the other type of model is the Bayesian inference model, in fact, several studies suggest that some domains of salience follow the same computational model of Bayesian surprise [21,22].

The pathogenetic hypothesis of aberrant salience allows to explain how neurobiology and subjective experiences intersect each other, promoting the onset of psychosis and the development of positive psychotic symptoms as a clinical entity [16]. At the same time, evidence supports the role of childhood traumatic experiences in the alteration of corticostriatal connections and the salience process [23]. A recent study has shown a significant relationship between exposure to childhood trauma and self-disturbances, or alterations in self-perception, the substrate on which abnormal experiences develop; the authors hypothesized that aberrant salience and alterations in self-perception constitute two fundamental elements of connection between history of childhood trauma and psychotic experience [24].

Based on the above, the main hypothesis was that a history of childhood trauma is associated with a greater level of aberrant salience. In the literature there are consistent data with the starting hypothesis of our work, however deriving from a single study conducted on the general population [24]. Accordingly, the primary objective of the study was to investigate the association between childhood trauma and aberrant salience in patients with Schizophrenia and Schizoaffective Disorder. The secondary objective was to evaluate the impact of clinical variables on aberrant salience and any correlation with a higher level of aberrant salience.

Matherials and methods

Participants and procedures

In this observational cross-sectional study, participants

were consecutively recruited at the Outpatients Unit of Psychiatry of the University Hospital "Mater Domini" of Catanzaro.
The inclusion criteria were: patients aged between 18 and 65 with a diagnosis of Schizophrenia or Schizoaffective Disorder according to DSM-5 [25] formulated through the Structured Clinical Interview for DSM-5 (SCID-5-CV) [26].
The exclusion criteria were: 1) diagnosis of dementia, intellectual disability or other medical conditions associated with psychiatric symptoms; 2) substance abuse; 3) conditions that did not allow the completion of the assessment, such as language problems, dyslexia or poor knowledge of Italian.
For this preliminary study,the sample consists of 53 patients: N = 39 patients with Schizophrenia and N = 14 patients with Schizoaffective Disorder.
The study was conducted in accordance with the latest version of the Helsinki Declaration and was approved by the local ethics committee. All participants provided written informed consent, in accordance with the ethics committee guidelines.

Assessment

Clinical and socio-demographics characteristics

The information collected includes: socio-demographics, psychiatric familiarity, age at onset of the disorder, duration of untreated psychosis (DUP), presence of psychiatric comorbidity, number of previous hospitalizations and antipsychotic therapy.
The daily dose of antipsychotic drugs took by each patient was expressed as the equivalent daily dose of chlorpromazine, based on the international consensus study by Gardner et al.[27].

Childhood Trauma

Childhood Trauma Questionnaire Short-Form (CTQ-SF) [3]: is a self-administered test of 28 items Likert type from 1 (never) to 5 (very often), that account for 5 subscales: emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect. The risk of childhood trauma is based on the cut-off scores of each of the subscales: emotional abuse (none = 5-8; mild = 9-12; moderate = 13-15; severe ≥ 16), physical abuse (none = 5-7; mild = 8-9; moderate = 10-12; severe ≥ 13), sexual abuse (none = 5; mild = 6-7; moderate = 8-12; severe ≥ 13), emotional neglect (none = 5-9; mild = 10-14; moderate = 15-17; severe ≥ 18), physical neglect (none = 5-7; mild = 8-9; moderate = 10-12; severe ≥ 13). CTQ reliability is good with high internal consistency scores. Sexual abuse, emotional neglect, emotional abuse, physical abuse, reported coefficients of 0.93-0.95, 0.88-0.92, 0.84-0.89 and 0.81-0.86, respectively. The test-retest coefficient was close to 0.80.

Aberrant Salience

Aberrant Salience Inventory (ASI) [28]: this self-administered questionnaire of 29 items with dichotomous response (yes/no), assesses the presence and level of aberrant salience and the vulnerability to psychosis. It assesses 5 factors in line with Kapur's conceptualization [16]: the increase in meaning, the quality/intensity of sensory perceptions, the alteration of understanding, the increase in emotionality and the acuity of the functions cognitive; it also assesses the presence of magical thinking, a psychotic-like experience that plays a key role and a close correlation with psychotic symptoms. ASI ≥ 14 indicates psychotic vulnerability to aberrant salience [28].

Clinical assessment

Positive and Negative Schizophrenic Symptoms (PANSS) [29]: is a clinician-administered tool of 30 items to evaluate the presence and severity of positive and negative symptoms and general psychopathology in Schizophrenia patients. In our study, the PANSS remission scale criteria were used according to the definition of remission developed by Andreasen et al. [30]. The 8 items considered include Delusions (P1), Conceptual disorganization (P2), Hallucinatory behavior (P3), Affective flattening (N1), Passive / apathetic social withdrawal (N4), Lack of spontaneity and fluidity in the interview (N6), Mannerisms postural (G5) and Contents of unusual thinking (G9); symptomatic remission is defined as a score of 3 ("mild") or less, on all items considered.

Statistical analysis

The data analysis was performed with the Statistical Package for the Social Science 22.0 (SPSS Inc., Chicago Illinois) and the data presented as averages, standard deviations, frequencies and percentages. The univariate analysis was applied to the comparison of means through the t-test for continuous variables and the chi-square test for categorical ones.
A stepwise linear regression model was used to identify independent predictors of aberrant salience. Variables that differed $p < 0.01$ at t-test entered into the multivariate linear regression model. The entry and exit criteria from the model were 0.2 and 0.4 respectively. The statistical significance level was set at $p < 0.05$.

Results

The socio-demographic and clinical characteristics are summarized in Table I. The average age of the sample is 39.3 ± 11.5; male, unmarried, unemployed and living with the family of origin prevail. Most patients, approximately 43%, report no familiarity with Schizophrenia spectrum disorders and related disorders. The age at onset of the

TABLE I. *Sample description.*

		N = 53	
		n	%
Mean age in years[a]		39.3	(11.5)
Gender	Male	34	(64.2)
	Female	19	(35.8)
Civil status	Married	10	(18.9)
	Divorced	2	(3.8)
	Single	41	(77.4)
Education (years)[a]		12.3	(3.1)
Employment	Employed	12	(22.6)
	Unemployed	24	(45.3)
	On pension	5	(9.4)
	Unpaid activity	4	(7.5)
	Invalid/retired	8	(15.1)
Living status	Alone	2	(3.8)
	Parents	34	(64.2)
	Partner	9	(17.0)
	Other	8	(15.0)
Diagnosis	Schizophrenia	39	(73.6)
	Schizoaffective Disorder	14	(26.4)
Familiarity for psychosis	Yes	10	(18.9)
	No	43	(81.1)
Age at onset (years)[a]		24.1	(6.8)
Duration of untreated psychosis (years)[a]		1.38	(2.1)
Previous psychiatric hospitalizations[a]		2.42	(3.3)
Daily equivalent dose of chlorpromazine (mg)[a]		440	(178)

[a]: *data are expressed as means and (SD).*

psychosis is on average 24.3 ± 6.8, while the duration of untreated psychosis (DUP) is 1.4 ± 2.1 years. The average dose of antipsychotics is 440 ± 178 mg/day in chlorpromazine equivalents.

The average values obtained with CTQ and ASI and the proportion of patients in remission to PANSS according to Andreasen [30] criteria are summarized in Table II.

The sample was divided according to the ASI scores andgroups were subsequently compared. Thirty patients (57%) scored over the threshold of ASI. Significant differences emergedas patients who scored ASI ≥ 14 had an earlier onset of illness ($p = 0.51$), more previous psychiatric hospitalizations ($p = 0.003$) and took higher average doses of antipsychotic drugs ($p = 0.02$). Furthermore, patients with a higher aberrant salience also exhibited higher means in items P1 ($p < 0.001$), P3 ($p = 0.046$), G5 ($p = 0.004$), G9 ($p = 0.017$) of PANSS and in the CTQ subscales emotional abuse ($p < 0.001$), emotional neglect ($p = 0.046$) and total score ($p = 0.003$) (Tab. III).

Finally, Table IV shows the results of the linear regression analysis. Those variables with significant differences ($p < 0.01$) at the previous t-test entered into the analysis as independent variables and ASI total score was considered the dependent variable. A background of emotional abuse and the number of previous psychiatric hospitalizations resulted to be predictors of higher aberrant salience ($R^2 = 0.240$; $F = 9.202$; $p < 0.001$).

Discussion

The present study aimed at evaluating the association between childhood trauma and aberrant salience

TABLE II. *Results of clinical assessment.*

		Mean	SD
PANSS-R[a]	Yes	13	(24.5)
	No	40	(75.5)
CTQ	Emotional abuse	8.7	(4.7)
	Physical abuse	7.0	(4.0)
	Sexual abuse	6.8	(4.1)
	Emotional neglect	11.8	(5.2)
	Physical neglect	8.1	(3.5)
	Total score	43.4	(15.5)
ASI	Increased significance	4.1	(2.0)
	Sharpening of senses	2.4	(1.5)
	Impending understanding	2.5	(1.6)
	Heightened emotionality	3.2	(2.0)
	Heightened cognition	2.8	(2.0)
	Total score	14.9	(7.7)

PANSS-R: Positive and Negative Schizophrenic Symptoms - Remission Criteria; CTQ: Childhood Trauma Questionnaire; ASI: Aberrant Salience Inventory; Symptomatic remission is defined as a score of 3 ("mild") or less on all of eight items (P1, P2, P3, N1,N4, N6, G5, G9). Emotional abuse (cut-off > 8); physical abuse (cut-off > 7); sexual abuse (cut-off > 5); emotional neglect (cut-off > 9); physical neglect (cut-off > 7). ASI (cut-off ≥ 14). [a]: data are expressed as frequencies and (%).

in patients with Schizophrenia and Schizoaffective Disorder. The secondary objective was to evaluate the impact of clinical variables on aberrant salience. Despite the small sample size and the observational cross-sectional approach of present investigation, these results seems to highlight thata history of emotional abuse during childhood and the number of lifetime psychiatric hospitalizations are associated with a higher level of aberrant salience.

Our research suggests an innovative aspect on identifying a specific correlation between distinct types of early traumatic experiences that could act as predictors directly related to the development and pervasiveness of the aberrant salience in patients with psychosis.

Various evidences support the relationship between exposure to psychosocial stress and alterations the development of salience. A study has shown that individuals exposed to childhood trauma report a reduction of reward response and increased psychotic experiences, suggesting the possible presence of both adaptive and aberrant alterations in the mechanism of processing the salience [31]. Considering the central role of dopamine in the processing of salience, the finding of an alteration of presynaptic function of dopamine in individuals who have experienced early traumatic

TABLE III. *Comparison of PANSS and CTQ scores according to ASI score.*

		ASI ≥ 14 N = 30		ASI < 14 N = 23			
		Mean	*SD*	*Mean*	*SD*	*t*	*p*
PANSS	Delusions (P1)	3.3	(1.2)	2.0	(1.1)	4.252	**< 0.001**
	Conceptual disorganization (P2)	3.3	(0.9)	2.7	(1.3)	1.920	0.060
	Hallucinatory behavior (P3)	2.4	(1.0)	1.8	(1.0)	2.041	**0.046**
	Blunted affect (N1)	3.5	(1.1)	3.0	(1.1)	1.624	0.111
	Social withdrawal passive/apathetic (N4)	3.6	(1.4)	3.0	(1.5)	1.578	0.121
	Lack of spontaneity of conversation (N6)	3.1	(1.3)	2.5	(1.4)	1.567	0.123
	Mannerisms and posturing(G5)	2.9	(1.2)	1.9	(1.1)	2.995	**0.004**
	Unusual thought content (G9)	3.5	(1.3)	2.6	(1.2)	2.457	**0.017**
CTQ	Emotional abuse	10.5	(4.8)	6.4	(3.4)	3.427	**< 0.001**
	Physical abuse	7.8	(4.2)	6.0	(3.4)	1.585	0.119
	Sexual abuse	7.8	(5.2)	5.6	(1.4)	1.968	0.055
	Emotional neglect	13.1	(5.6)	10.2	(4.3)	2.049	**0.046**
	Physical neglect	8.7	(4.1)	7.4	(2.4)	1.363	0.179
	Total CTQ	48.7	(17.0)	36.4	(10.0)	3.086	**0.003**

PANSS: Positive and Negative Schizophrenic Symptoms; CTQ: Childhood Trauma Questionnaire; ASI: Aberrant Salience Inventory. Significant results are in bold.

TABLE IV. *Linear Regression analysis.*

Dependent variable	Independent variables	*B*	*t*	*p*
ASI total score	(Costant)	-	4.539	**0.001**
	Previous psychiatric hospitalizations	0.308	2.191	**0.033**
	Emotional abuse	0.288	2.051	**0.046**

*ASI: Aberrant Salience Inventory. Significant results are in **bold**.*

experiences suggests that this may be a possible mechanism of mediation between childhood trauma and an increased risk of mental illness [32]. Further, the exposure to chronic psychosocial stressors is associated with functional alterations in brain regions responsible for processing salience and corticostriatal functional connectivity. These data suggest that exposure to psychosocial stress could lead to cortico-striatal dysfunction and consequently to development of aberrant salience [33].

In our study, it also emerged that a history of emotional abuse in childhood is predictive of a higher aberrant salience in individuals with psychosis. Evidence of a casual association between childhood trauma and aberrant salience is limited in the literature: a single study in the general population revealed a significant relationship between childhood abuse (emotional, physical and sexual) and the presence of psychotic-like experiences, demonstrating only an indirect mediation of aberrant salience in this association [24]. To date, to the best of our knowledge, there is no study in the literature that has investigated the relationship between childhood trauma and aberrant salience in a clinical population of patients with Schizophrenia.

Exposure to early trauma, in particular to interpersonal violence (emotional abuse, physical abuse or sexual abuse), can cause cognitive distortions in the processing of information in the individual (i.e. "people should not be trusted"; "people could be dangerous"). Studies have shown that child abuse is related to a decrease in Theory of Mind – ToM, or the ability to attribute mental states, beliefs, intentions, desires, emotions, knowledge – to oneself and to others, and the ability to understand that others have different mental states than their own [34]. The connection between ToM and exposure to childhood trauma has also emerged in patients with Schizophrenia and has been associated with alterations of the brain networks involved in the elaboration of mental states [35].

By extending the results of previous studies, where mediation of cognitive biases in processing information related to the content of beliefs was demonstrated (i.e. a pattern of negative beliefs or attention to the threat) [24], present data indicate that childhood traumas are also linked to the content of specific components of the aberrant salience, which lead to the assignment of an inadequate meaning to the stimuli. This result is consistent with a group of upcoming studies linking the experience of aberrant salience to the psychotic state and the risk of psychosis [36].

Moreover, it seems that interpersonal emotional violence in early age subjects has a stronger influence on aberrant salience than emotional or physical neglect. However, further studies are needed to replicate this association in clinical sample.

Lifetime psychiatric hospitalizations also were associated with aberrant salience; noteworthy, aberrant salience represents one of the main pathogenetic mechanisms underlying the production of florid positive psychotic symptoms (delusions, hallucinations and thought modifications) [16] and it is already present in the prodromal phase of psychosis, during which the individual experiences increased cognitive and sensory skills, associated with a sense of increased awareness of things. Common feelings at this stage include increased emotions difficult to manage, a sense of internal confusion, perception of important upcoming revelations [37].

A study pointed out that patients with schizophrenia with more florid production symptoms showed increased hemodynamic responses in the left insula, corresponding to a higher level of aberrant salience, compared to patients with less severe positive symptoms [38]. The presence of positive florid symptoms, especially the co-presence of hallucinations and delusions, compared to the presence of isolated symptoms, has been associated with a higher persistence of psychotic experiences with consequent worse clinical outcome and higher number of psychiatric hospitalizations. A specific hallucinatory-delusional state may represent an exacerbation of aberrant salience attribution, increasing the risk of an unfavorable clinical outcome [39].

Classical European psychopathology defines the following as the crucial elements in developing a more articulated delusional experience, starting from a pre-delusional phase, and its maintenance: the increase in meaning, the quality/intensity of sensory perceptions, the alteration of understanding, the increase in emotion

and the acuity of cognitive functions, or the dimensions of aberrant salience [37]. In our study, patients with a higher level of aberrant salience reported a higher score in the symptomatic dimensions of PANSS "Delusions", "Hallucinatory behavior", "Postural mannerisms" and "Unusual contents of thought", as well as a higher number of past psychiatric hospitalizations and a higher average dose of antipsychotic taken daily.

The abnormal transmission of dopamine is a crucial element among the theories that aim to explain how neurobiology correlates with the productive symptoms in psychosis; similarly, evidence supports a direct relationship between the presynaptic synthesis capacity of dopamine and the creation of aberrant salience in individuals at risk of psychosis [40]. Since antipsychotics tend to block D2 receptors, therapy could reduce positive symptoms by mitigating the creation of dopamine-mediated aberrant salience [16]. In fact, it has been shown that patients with Schizophrenia under treatment show reduced adaptive salience compared to healthy controls and therefore a higher level of aberrant salience[40]. This could support the result of our study, namely that a higher level of aberrant salience corresponded to a higher average dose of antipsychotic taken daily.

Conclusions

To conclude, the most striking result of our preliminary study is addressing the relationship between a psychosis-specific mechanism like aberrant salience and a transdiagnostic risk factor such as childhood trauma; specifically, our findings support the main hypothesis according which having experienced an emotional abuse in childhood can be associated with a higher level of aberrant salience in patients with psychosis.

Although our study did not examine neurobiological alterations (e.g. excessive dopamine release), our results could be interpreted as in line with predictions made by previous studies on the relationship between childhood adversity and behavioral expression of an excessive release of dopamine and therefore creation of aberrant salience [33].

In clinical practice, the results of this study increasingly strengthen the hypothesis that early traumatic experiences can be used as an indicator of disease progression, useful in identifying those patients with high risk of graver clinical manifestations and unfavorable course [33]. An accurate anamnestic investigation aimed at detecting childhood trauma during the psychiatric evaluation of a patient suffering from psychosis, can be fundamental for an adequate diagnostic-therapeutic path.

Numerous evidences underline how the prevention of childhood trauma should be one of the objectives within programs driving to promote mental health and that early detection could be important to implement the possible interventions targeted at improving the outcome on long term in disadvantaged children [41]. Our study suggests, on the other hand, that aberrant salience could be an important mediator between the experience of trauma and the development and maintenance of psychotic symptoms; the early detection of aberrant salience in disadvantaged children/adolescents could be also an important target in the prevention of the onset of psychosis [42]. Further studies are needed to increase understanding of the mechanisms thanks which childhood trauma influences the creation of salience, including the possible presence of both adaptive and aberrant alterations in the mechanism of salience processing.

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Original article

Increased BDNF levels after a trauma A pilot study on clinical and non-clinical samples, exposed or non-exposed to an earthquake

Paolo Stratta[1], Roberto L. Bonanni[1], Francesca Pacitti[2], Adriano Angelucci[2], Nicola Origlia[3], Luciano Domenici[3,4†], Claudia Carmassi[5], Liliana Dell'Osso[5], Alessandro Rossi[4]

[1] Department of Mental Health, ASL 1, L'Aquila, Italy; [2] Cellular Pathology Laboratory, Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, Italy; [3] Neuroscience Institute, CNR, Pisa, Italy; [4] Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, Italy; [5] Department of Clinical and Experimental Medicine, University of Pisa, Italy

SUMMARY

Background

Brain-Derived Neurotrophic Factor (BDNF) modulates synaptic modifications that can constitute part of brain adaptive processes in the aftermath of trauma exposure. Thus, BDNF increase could be determined either in psychiatric patients or healthy subjects who, despite exposed to stressful events, did not develop stress-related symptoms.

Methods

BDNF plasma levels were evaluated in a clinical and a non-clinical populations exposed to the 2009 L'Aquila earthquake and in a comparable population not exposed to such event or other trauma.

Results

Statistically significant differences emerged according to diagnosis (clinical samples vs. controls), while a trend toward significance was found according to exposure (exposed vs. not-exposed subjects). The exposed clinical sample showed statistically significant higher BDNF levels than the not-exposed one.

Conclusions

Lack of statistical difference between exposed and not exposed subjects suggests that no BDNF modification intervened after the stressful event. Exposed samples however showed the highest BDNF levels with a trend toward significance. A ceiling effect that impede the possibility of exceeding a possible maximum level in the control sample can be hypothesized. Clinical sample shows instead room for stress related BDNF increase. If so, such a BDNF increase could have a neuroprotective adaptive role after stress.

Key words: Brain-Derived Neurotrophic Factor (BDNF), stress event, ceiling effect, stress adaptation, earthquake

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Correspondence
Paolo Stratta
Department of Mental Health, ASL 1, via Capo Croce 1, 67100 L'Aquila, Italy
E-mail: psystr@tin.it

Conflict of interest
The Authors declare no conflict of interest

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Introduction

Brain-Derived Neurotrophic Factor (BDNF) is one of the most important neurotrophin involved in cerebral synaptic plasticity and cognitive functions regulation. It is highly sensitive to environmental factors and its increase enhances neurogenesis, neurite sprouting, electrophysiological activity with beneficial effects on cognitive functions such as learning and memory [1-3]. Alterations in the BDNF expression and functioning has been widely linked with stress both in animal and clinical studies suggesting a possible resilience correlate [4-13].

Synaptic modifications can constitute an adaptive process to stress events and BDNF is a relevant modulator of such modifications [14]. In the aftermath of stressful events exposure, a relevant information processing is needed in order to identify opportunities and possibilities to overcome the encountered difficulties. Serum BDNF levels have been reported to be involved in decision-making processes [15].

If the process is successful, the rapid BDNF capacity of performing cerebral modifications could avoid unwanted stress consequences and pathologies [16,17]. On the other hand, if no such neurotrophin and synaptic plasticity modifications append, pathological stress consequences could result [18].

In this study, we aimed to study BDNF changes in subjects who did not show psychiatric symptoms or worsening of symptoms despite having experienced a relevant stress event such as an earthquake.

We hypothesized that if no stress-related symptom or relapse/worsening of ongoing psychopathology appeared in subjects who suffered relevant stress, BDNF variation could be due to stress exposure. Thus, we enrolled a sample of subjects exposed to the same stress event, i.e. a clinical and non-clinical populations exposed to a natural catastrophe (i.e. the 2009 L'Aquila earthquake), and compared it to a similar population not exposed to such trauma. Because natural disasters are random events that expose unselected populations to the same trauma, they offer the opportunity to explore the effects 'triggered' by a unique trauma, disentangling confounding issues of pre-existing risk for exposure to traumatic events.

Methods

Study participants

In the framework of a study on clinical and neurobiological factors related to post-traumatic stress spectrum symptomatology in the aftermath of an earthquake exposure [12], we considered a sample of healthy control subjects and depressed/anxious patients exposed to such trauma compared to a sample of healthy control subjects and depressed/anxious patients not exposed to this event or to other relevant trauma.

The total sample included: 1) fifteen healthy control subjects with no current or lifetime DSM-IV-TR disorder or use of psychotropic medication exposed to the L'Aquila 2009 earthquake (10 women and 5 men; mean age ± SD: 46.3 ± 10.6 years); 2) a consecutive sample of 11 outpatients (5 women and 6 men; mean age ± SD - 42.2 ± 10.2 years), 8 with major depression (MDD) and 3 with panic disorder (PD). These subjects were diagnosed before the earthquake and did not show worsening or relapse of the symptoms after the event. The healthy subjects were recruited from among those accompanying the outpatients. The recruitment was performed about two years after the traumatic event (July-December 2011) at the National Mental Health Care Service facilities in L'Aquila; 3) a consecutive sample of 10 outpatients (5 women and 5 men; mean age ± SD 52.3 ± 12.3 years) with a diagnosis of MDD or PD were recruited at the Clinic of Psychiatry of the Department of Clinical and Experimental Medicine of the University of Pisa (Italy); 4) thirty-seven healthy control subjects were enrolled from Pisa (23 women and 14 men; mean age ± SD 33.1 ± 7.4 years) by the same recruitment method used in L'Aquila. These two latter samples were not exposed to the L'Aquila 2009 earthquake or to other relevant trauma in their lifetime.

At the time of BDNF evaluation all patients were treated with low doses of benzodiazepines and / or antidepressants, as the Ethical Committee did not allow any drug free period. No patients were treated with antipsychotics or mood stabilizers.

The Ethics Committees of the Azienda Sanitaria Locale of L'Aquila and of the Azienda Ospedaliero - Universitaria of Pisa approved all recruitment and assessment procedures. All subjects included provided written informed consent, after receiving a complete description of the study and having the opportunity to ask questions.

Procedures

All subjects were assessed by means of the: Structured Clinical Interview for DSM-IV Axis-I disorders Patient Version (SCID-I/P) [19] for psychiatric diagnoses; Clinical Global Impression (CGI), for the severity of illness.

Venous blood samples were taken in the morning (between 8:00 and 9:00 am), to avoid diurnal variations of BDNF levels [20]. Blood samples were processed using enzyme-linked immunosorbent assay (ELISA) protocol on plasma to determine BDNF values that are expressed as pg/ml.

Statistical analyses

The descriptive statistics on the BDNF levels showed high skewness (1.33) and kurtosis (2.75). In order to control the gaussian distribution, BDNF values were log transformed reaching satisfactorily distribution indexes (skewness - 0.31 and kurtosis - 0.24). One-way analysis of variance (ANOVA) and two-way analysis of covariance (ANCOVA) were utilized. Main effects were further analyzed with post hoc planned t-test analysis. Chi square and Pearson's r correlation were also used. All analyses yielding a p-value less than.05 were considered significant.

Results

Among the four sub-samples, statistically significant age differences emerged (1-way ANOVA F = 14.9, d.f.

TABLE I. *Comparison of BDNF plasmatic levels (pg/ml, mean ± SD) and age between depressed/anxiety (dep/anx) patients and healthy subjects, exposed or not exposed to the earthquake.*

Subjects	Plasma BDNF	Age
Dep/anx exposed (n = 11)	3650.6 ± 1648.2	42.2 ± 10.2
Dep/anx not exposed (n = 10)	2495.0 ± 1335.9	52.3 ± 12.3
Controls exposed (n = 15)	6004.8 ± 4100.2	46.3 ± 10.6
Controls not exposed (n = 37)	5526.2 ± 2659.4	33.1 ± 7.4

Two-way ANCOVA for plasmatic BDNF, after natural logarithm transformation, with exposition and diagnosis as factors and age as covariate. Exposure factor $F = 2.7$; $p < 0.10$. Diagnosis factor $F = 14.3$; $p < 0.0005$. Exposure by diagnosis interaction $F = 1.6$; $p = 0.20$.

3, $p < 0.0005$), but not in gender distribution ($X^2 = 5.7$, d.f. 3, NS) or in the correlation with BDNF. No significant difference in CGI severity of illness scores between exposed and not exposed clinical samples (L'Aquila *vs* Pisa) was found.

BDNF plasma levels in the four sub-samples are reported in Table I. Two-way ANCOVA was used considering diagnosis, i.e. clinical sample *vs* controls. and exposure, i.e. earthquake exposed *vs* not exposed subjects, as factors; age was considered as covariate. Statistically significant difference was observed according to diagnosis ($F = 14.3$; $p < 0.0005$), but not to exposure ($F = 2.7$; $p < 0.10$), or exposure by diagnosis interaction ($F = 1.6$; NS). Post-hoc planned t-tests showed statistically significant difference between exposed and not-exposed clinical samples ($t = 2.1$, d.f. 19, $p < 0.05$).

Discussion

The lack of global statistically significant difference between earthquake exposed and not-exposed subjects would corroborate the null hypothesis that no BDNF modification intervened after the stressful event.

Some considerations however have to be made: although the difference did not reach statistical significance, exposed subjects showed the absolute highest BDNF levels, and a trend toward significance emerged with respect to not-exposed subjects ($p = 0.09$). Further, a statistically significant difference emerged in BDNF levels between the two clinical samples with exposed patients showing significantly higher levels.

The possibility of a ceiling effect cannot be excluded, in particular among healthy control subjects where it could not be possible to exceed a certain level. However, if a ceiling effect could explain findings in healthy control subjects, this could not be the case of clinical samples where a significant difference between exposed and not-exposed patients was found with almost twice as much of the neurotrophin levels in the former. Although BDNF decrease in subjects with affective disorders as well as panic disorder is a well reported finding [21–27], the possibility for a stress related increase seems to be possible. As BDNF peripheral levels may parallel changes occurring in the brain, the trend of plasma BDNF increase in L'Aquila clinical and healthy control samples, with respect to not-exposed subjects, could be interpreted as a residual 'signal', two years after the trauma, related to a neuroprotective reaction to the stress.

Our results are in line with several studies from both animal and human models eventually.

Increase in BDNF expression has been observed after stress in rats hypothesized as part of a coping compensatory response to stressful stimuli [28,29].

In humans, subjects with trauma but not showing Post Traumatic Stress Disorder (PTSD) symptoms evidenced higher BDNF serum levels compared to patients affected by PTSD [30]. Elevated serum BDNF levels were found in imprisoned women, likely suffering from prison-related stress without PTSD [31]. Peripheral levels elevation has been observed in worker exposed to occupational stress [32]. BDNF increased levels have been interpreted as further evidence of BDNF involvement in stress response, as contribution to neuron protection under stress reducing behavioral sequelae of PTSD [33].

Some important limitations should be taken into account while interpreting these results. First of all, the sample size that, despite not large, should be sufficient for a pilot study of heuristic value. Second, healthy control subjects samples required the exclusion of any kind of symptom. Third is the selection of comparison groups in a quasi-experimental design where the samples are not equated prior to manipulation of the independent variable (i.e. earthquake exposure). Fourth, the time from exposure: BDNF levels were assessed two years after the earthquake occurred and thus we cannot exclude that a putative early BDNF increase, well superior to that we observed, may have occurred in the aftermath of the event followed by a trend toward the normalization over time. Fifth, the lack of assessment of post-traumatic stress symptomatology at the time of the earthquake. Although a PTSD diagnosis has been excluded at the SCID interview, the possibility of some trauma symp-

toms could have been emerged in the aftermath of the event that could be related to BDNF modifications, cannot be excluded.

Globally, our results shed more light on the mechanisms regulating BDNF levels in response to stress, delineating a landscape somewhat more complex than what could be expected from the somewhat inconsistent literature on PTSD alone [5,12,13,34,35].

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Original article

Somatization and traumatic events in asylum seekers and refugees resettled in Italy

Lorenzo Tarsitani[1], Liliana Todini[1], Valentina Roselli[1], Riccardo Serra[1], Valentina Magliocchetti[1], Dunia D'Amore[1], Bianca Della Rocca[1], Massimo Pasquini[1], Paola Massetti[2], Massimo Biondi[1]

[1] Department of Human Neurosciences, Sapienza University of Rome, Italy; [2] Department of Public Health and Infectious Diseases, Sapienza University of Rome, Italy

SUMMARY

Objectives

Individuals who experienced a forced migration, such as asylum seekers and refugees, are at elevated risk of trauma-related psychological and somatic distress as compared to non-migrated counterparts. The relationship between traumatic events and somatization is poorly explored in this population. We aimed to assess the impact of traumatic events on somatization and the possible link with stress-related vulnerability in a sample of asylum seekers and refugees.

Methods

Asylum seekers and refugees referring to the Day Service of Migration Medicine of the Umberto I Hospital for routine screening of infectious diseases were consecutively recruited. The following instruments were administered: ad hoc questionnaire for the collection of socio-demographic and migratory variables, Somatic Symptom Scale 8 (SSS-8), Life Events Check List (LEC-5), Stress-related Vulnerability Scale (SVS).

Results

Eighty-five subjects were included (males = 80, 94%; mean age = 28.3; SD = 7.4). The mean score of SSS-8 was 5.3 (SD = 5.9), with 68% of participants reporting at least one clinically significant somatic symptom. The mean LEC-5 total score was very high (9.8; SD 3.2). Bivariate correlations among SSS-8 total score, LEC-5 total score and SVS Lack of Social Support subscale score were, respectively: r= 0.347 (p = 0.002), r = 0.539 (p < 0.001). Multivariate analyses confirmed the correlation between SSS-8 total score, LEC-5 total score (β = 0.491; p = 0.01) and SVS Lack of Social Support subscale (β = 1.236; p < 0.001) to be significant over and above sociodemographic and migration-related confounders.

Conclusions

Medically unexplained somatic symptoms were associated with the number of lifetime traumatic events and with post-migratory perceived lack of social support in asylum seekers and refugees.

Key words: forced migration, traumatic events, somatization, stress, perceived social support

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Correspondence
Lorenzo Tarsitani
Department of Human Neuroscience, Sapienza University of Rome, viale dell'Università 30, 00185 Rome, Italy
E-mail: lorenzo.tarsitani@uniroma1.it

Conflict of interest
The Authors declare no conflict of interest

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Introduction

In the last two decades, an increasing number of people are forcedly displaced worldwide. In 2019, Europe hosted the largest number of international migrants. Forced migration has grown noticeably faster than voluntary migration [1].

Forced migration is an important risk factor for the development of trauma-related psychological distress and a wide range of mental disorders [2,3].

Somatization is the presentation of physical symptoms or complaints which are not based on a medical condition and are considered as a response to psychosocial stress [4]. Medically unexplained somatic symptoms are the rule rather than the exception in primary and secondary care

and they are associated with considerable disability and costs [5], independently of psychiatric and medical comorbidity [6]. Somatization among immigrants often leads to under-diagnosis and misdiagnosis of mental disorders in medical settings, increasing the barriers to the already underutilized mental health services [7]. Unrecognized and untreated mental disorders can lead to increased symptom severity and consequent emergency referrals with harmful coercive interventions and worse outcomes [8].

Several studies suggest that immigrants from low- and middle-income countries tend to express emotional distress with somatic symptoms [9]. Ethnicity, geographic origins and cultural models can shape the tendency to experience somatic distress [10]. Language and cultural differences between health care providers and migrant patients affect clinical assessment and management [11], worsening the impact of somatization.

High levels of medically unexplained somatic symptoms were found in immigrants in primary care [12,13]. Somatization scores were found higher in immigrants referred to general medicine services as compared to native patients [14].

Only a limited number of studies have been performed so far, which showed high rates of somatic complaints in refugees, ranging from 27 to 84% [11]. Lifetime exposure to traumatic events is very high in asylum seekers and refugees.

Non-immigrated patients with somatization disorders report more traumatic events with respect to non somatizers [15]. Hence, high levels of somatization following forced might be explained by trauma. Strong associations among somatization symptoms, Posttraumatic Stress Disorder [16] and complex Posttraumatic Stress Disorder [17] were shown in asylum seekers and refugees. Victims of torture and inter-human violence have a high risk of both somatization and post-traumatic symptoms [18]. However, mediating and moderating variables of the relationship between trauma and somatization are scarcely investigated.

A study on both voluntary and forced immigrants in primary care showed that patients with somatization reported more stress due to post-migratory living difficulties [19]. Post-migratory perceived stress and lack of social support might play a role in the relationship between pre-migratory traumatic events and somatization in the host country.

To date, the relationship between traumatic events and somatic symptoms, and the possible role of post-migratory stress in refugees in the general population remains unclear. There is also a lack of research on the impact of traumatic events in African refugees despite an over-representation in Europe [20].

The aim of this cross-sectional study was to assess the impact of traumatic events on somatic symptoms and the possible association with post-migratory stress-related vulnerability in a non-clinical sample of asylum seekers and refugees.

Methods

Participants

Asylum seekers or refugees referring for the first time to the Day Service of Migration Medicine of the Umberto I University Hospital in Rome for routine screening of infectious diseases were recruited from November 2017 to February 2019. Inclusion criteria were written informed consent and age 18 or older. Individuals with clinical signs of mental disorder during the assessment were referred to the Migration Psychiatry Service of our Hospital. Cultural mediators were involved when needed. This study is part of a larger epidemiological investigation which was approved by the Local Ethical Committee.

Measures

An *ad hoc* questionnaire was administered for the collection of socio-demographic and migratory variables. The Somatic Symptom Scale 8 (SSS-8) [21] was developed as an abbreviated 8-item version of the Patient Health Questionnaire 15, to assess the presence and severity of common somatic symptoms. Somatic symptoms assessed include stomach or bowel problems, back pain, headache, chest pain, asthenia and others. Each item is scored 0 to 4, with higher scores indicating greater presence and subjective impact of somatic symptoms.

The Life Events Checklist (LEC-5) [22] assesses the lifetime presence of an individual's exposure to 16 serious traumatic life events (e.g. fire or explosion, transportation accident, physical assault, sexual assault, life-threatening illness or injury). It has been widely used in cross-cultural settings and it is strongly associated with psychopathology.

The Stress-related Vulnerability Scale (SVS) [23] is a 9-item self-administered rating scale, scored on a 4-point Likert scale. It yields scores on three subscales, named 'Tension', 'Demoralization', and 'Reduced Social Support', respectively. Higher scores indicate greater subjective stress-related vulnerability. The SVS was used in both clinical [24] and non-clinical [25] samples.

Statistical analysis

Bivariate analyses were conducted for continuous variables in order to demonstrate the correlations between LEC-5 and SSS-8, SVS Lack of Social Support Subscale, sociodemographic and migration related variables. In order to test these correlations, we first analyzed the multivariate correlations between SSS-8 total score as a dependent variable and LEC-5 total score,

TABLE I. *Bivariate associations.*

	1	2	3	4	5	6	7	8	9	10	11	12
Age	1											
Sex	-0.11	1										
N children	0.40**	0.08	1									
N siblings	-0.01	0.18	-0.13	1								
Route	0.16	0.07	0.15	-0.10	1							
Prison	-0.09	-0.22*	0-.27*	0.06	-0.21	1						
Friends in Italy	-0.14	0.04	-0.06	-0.01	0.09	-0.24*	1					
Connationals in Italy	0.339**	-0.22*	0.10	-0.13	0.08	0.11	-42**	1				
SSS total	0.26*	-0.07	-0.13	-0.07	-0.06	0.10	-0.025	0.24*	1			
SVS total	0.24*	0.09	-0.14	-0.07	-0.02	0.01	0-.09	0.20	0.78**	1		
SVS supp	0.15	-0.02	-0.11	-0.12	-0.05	0.14	-0.17	0.23	0.54**	0.82**	1	
LEC total	-0.07	-0.15	-23*	-0.09	-0.13	0.31**	0.12	0.04	0.35**	-25*	-18	1

*SSS = Somatic Symptom Scale 8; SVS = Stress-related Vulnerability Scale; S Lack of Social Support S supp = SVS Lack of Social Support Subscale; LEC = Life Events Checklist; * = p < 0.05; ** = p < 0.013.*

SVS total score, SVS Lack of Social Support subscale and possible confounders as independent variables in a stepwise multivariate regression model. Secondly, a multivariate regression model was built including SSS-8 total score as a dependent variable and LEC-5 total score, SVS Lack of Social Support subscale and possible confounders as independent variables. The alpha value was set to.05; all tests were two tailed. Data were analyzed with the Statistical Package for Social Sciences (SPSS), version 17.0.

Results

Eighty-five subjects were included in the study. Two subjects denied the consent to participate. The mean age was 28.3 (SD = 7.4) (range 18-49 years); 80 (94.1%) were males. Participants had a mean education level of 8.5 years of study (SD = 4.1). The mean length of stay in Italy was 19 months (SD = 18 months). Participants were asylum seekers or refugees coming from Sub-Saharan African countries (80%), North African countries (7%) and Asia (13%). The most represented countries of origin were Nigeria (21%) and Eritrea (16%). Sixty-five immigrants (77%) arrived in Italy trough the Central Mediterranean route and 37 (44%) of them were detained for migration-related reasons.

All samples reported at least one lifetime traumatic event, with 13% reporting 5 or less traumatic events, 55% between 6 and 9 and 32% more than 9. The most common traumatic events were "combat or exposure to war-zone" (80%), followed by "witnessing sudden violent death" (79%), "physical assault" (78%) and "assault with a weapon" (77%). The mean LEC-5 total score was 9.8 (SD 3.2).

The mean score of SSS-8 was 5.3 (SD = 5.9), with 68% of participants reporting at least one clinically significant somatic symptom.

SVS mean score was 8.88 (SD = 5.44; min = 1.0; max = 22.0) with the highest score in the SVS Lack of Social Support subscale (mean=4.73; SD= 2.14; min = 1.0; max = 9.0) followed by SVS Demoralization subscale (mean =2.25; SD = 2.16; min = 0; max = 9.0).

As shown in Table I, the bivariate model showed significant correlations between SSS-8 and LEC-5 ($\beta = 0.539$; $p < 0.001$), SVS total scores ($\beta = 0.778$; $p < 0.001$), SVS Lack of Social Support subscale ($\beta = 0.539$; $p < 0.001$) and age ($\beta = 0.264$; $p = 0.015$).

The stepwise multivariate linear regression model showed SVS Lack of Social Support subscale to represent the second most predictive variable in the model after the SVS total score ($\beta = 1.092$; SE = 0.352; $p = 0.003$; tables available upon request). Further multivariate analyses were carried out including only this subscale. The final multivariate model predicting SSS total score (Tab. II) shows a significant predicting role for age ($\beta = 0.244$; SE = 0.083; $p = 0.005$), LEC total score ($\beta = 0.491$; SE = 0.184; $p = 0.010$) and SVS Lack of Social Support subscale ($\beta = 1.236$; SE = 0.270; $p < 0.001$).

Discussion

This cross-sectional observational study on young immigrated asylum seekers and refugees in Italy shows a significant association among pre-migratory traumatic

TABLE II. *Multivariate model predicting SSS total score*

	B	SE	p
Nationality	-0.162	0.077	**0.039**
Age	0.244	0.083	**0.005**
Gender	0.568	2.282	0.804
Marital Status	-0.451	0.775	0.563
N children	-1.174	0.641	0.072
N siblings	-0.025	0.171	0.885
Prison	-1.490	1.244	0.235
Friends in Italy	0.535	1.352	0.694
Route	-0.243	0.556	0.664
Connationals in Italy	0.198	0.560	0.724
SVS supp	1.236	0.270	**0.000**
LEC total	0.491	0.184	**0.010**

SVS supp = SVS Lack of Social Support Subscale; LEC = Life Events Checklist. Significant p values are highlighted in ***bold****.*

events, post-migratory reduced social support and somatic symptoms. To our knowledge, this is the first study to assess the role of both traumatic events before migration and post-migratory perceived vulnerability on somatic symptoms in forced immigrants in Europe.

A very high exposure to serious traumatic events (a mean of 9.8) was reported by our sample, which mainly consisted of young men immigrated from Sub-Saharan Africa trough the Central Mediterranean route. Another study that assessed the number of serious traumatic experiences in Africans migrated to Europe found a comparable mean of 9 events with a higher SD [20]. The several on-going conflicts in various African countries might explain these figures. Moreover, the Central Mediterranean route of migration is *per se* a complex and severe traumatic event with high risk of human rights violations and death [26]. The same study by Steel and collegues [20] found a greater number of traumatic events in men, which is in line with the prevalence of men in our sample.

The high levels of reported somatic complaints in our non-clinical and non-help seeking sample confirm the high rates of somatization found in refugees worldwide [11,16,18]. Age was found as an independent predictor of somatic symptoms, which may originate from somatic diseases instead of unexplained symptoms in older subjects [27]. However, no serious clinical condition was found on clinical assessment in our sample.

The role of traumatic events as predictors of somatic symptom levels is in line with all the studies showing the relationship between trauma and psychopathology [11,15], being somatization a response to psychological stress by definition [4].

According to the new insight on the relevance of post-migratory living difficulties in mental health of refugees [19,20], the role of SVS Lack of Social Support subscale as an independent predictor of levels of somatic symptoms presence and impact suggests that post-migratory living difficulties might mediate the impact of trauma on somatization. A bulk of data demonstrated that perceived social support reduces the noxious effects of stress on health in the general population [28]. Post-migratory living difficulties, such as social isolation and loneliness, are associated with the onset of post-traumatic stress disorder in refugees [19]. Social-related support in the host country might buffer the effect of pre-migratory traumatic events on somatization.

A note of caution about the generalizability of our findings is warranted. First, the representativeness of our sample, which consisted of young, mainly male refugees was likely limited. Also, as we studied subjects mainly immigrated from Africa, our findings might not generalize to other cultures and this issue needs to be addressed in future investigations. Also, SVS measures general perceived stress-related vulnerability, including reduced social support. A more specific assessment of post-migratory living difficulties is needed in future investigations on their role in somatization in refugees exposed to traumatic events.

In conclusion, we found that medically unexplained somatic symptoms were predicted by the number of lifetime traumatic events and by post-migratory perceived lack of social support in asylum seekers and refugees. Somatization is associated with considerable disability and it often leads to under-diagnosis of mental disorders and inadequate treatment. Somatic symptoms should be detected and treated early in traumatized forced migrants.

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Original article

Adverse experiences in childhood: association with metacognition, personality disorders and distress

Ilaria Riccardi[1,2], Elena Bilotta[1,2], Luigi Leone[3], Giuseppe Nicolò[1,2], Michele Procacci[1,2], Antonio Semerari[1,2], Antonino Carcione[1,2]

[1] Third Centre of Cognitive Psychotherapy, Rome, Italy; [2] Italian School of Cognitive Psychotherapy (SICC), Rome, Italy; [3] Department of Social and Developmental Psychology, Sapienza University of Rome, Italy

SUMMARY

Objectives

Several studies provided evidences that Personality Disorders (PDs) are characterized by an impairment in the abilities to reflect on one's and others' mental state. These abilities have been often named as metacognition or mentalization. There are also evidences that adverse experiences in childhood (ACE) (abuse, neglect, maltreatment) affected metacognition and are associated to PDs and symptom distress. The present study aims to explore metacognition, distress and severity of personality pathology in relation to the presence or absence of adverse experiences in childhood (ACE) in a sample of 373 outpatients diagnosed having a PDs. The hypothesis was that metacognition is most impaired in patients that experienced adversities in childhood, as there is higher symptoms distress and major personality impairment. The metacognitive Differentiation and Integration sub-functions are hypothesized to be more compromised in ACE group than in the no-ACE one.

Methods

All the patients have been scored using SCID-II, Metacognition Assessment Interview, SCL-90-R. ACE has been detected through a clinical interview. In order to test the associations among metacognition, symptoms distress (GSI-SCL-90-R) and personality severity (number of SCID-II criteria) with ACE, we run a series of ANOVAs using the dichotomous ACE variable (0 = no ACE; 1 = at least 1 ACE) as the grouping variable.

Results

Results confirmed that metacognition is more impaired, symptoms distress is higher and personality is more compromised in ACE group. The metacognitive Differentiation and Integration sub-functions are the most compromised.

Conclusions

The study is a contribute to explore the association between trauma, metacognition and personality disorders and provide suggestions to further studies to focus on pathways leading to the comprehension of impact of ACE on psychopathology.

Key words: adverse childhood experiences, trauma, metacognition, personality disorders

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Correspondence
Antonino Carcione
Third Centre of Cognitive Psychotherapy, via Ravenna 9, 00161 Rome, Italy
E-mail: carcione@terzocentro.it

Conflict of interest
The Authors declare no conflict of interest

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Introduction

Several authors agree that personality disorders (PDs) are characterized by an impairment in the ability to understand and reflect about one's one and/or others' mental states [1-7], often defined as *mentalization* [4,8,9] or *metacognition* [10-13]. These constructs are referred in numerous studies as similar concepts, so there is a broad consensus indicating that they refer to almost the same psychological function [5,14,15]. In this paper, we use the term *metacognition* operationalised as the set of abilities necessary for 1) identifying mental states and ascribing them to oneself and others

on the basis of facial expressions, somatic states, behaviour and actions; 2) reflecting on and reasoning about mental states; 3) using information about mental states to make decisions, solve problems or psychological and interpersonal conflicts and cope with subjective suffering [16]. However, along the paper we can use quite indifferently metacognition, mentalization or reflective function referring to any reflection and reasoning of individuals on their own and others' mental states. Semerari et al. [5] (2014) supported evidence that metacognition is specifically impaired in PDs if compared to a clinical sample of no-PD patients and that dysfunction is significantly correlated to the severity of personality pathology (measured as the number of criteria met at the *Structured Clinical Interview for DSM-IV* - SCID II). Carcione et al. [7] consider metacognition as a core aspects of personality disorders and found that poor metacognition is related to the severity of personality pathology, and that increase of metacognition predicts the improvement in personality dysfunction, symptom distress, interpersonal and psychosocial functioning. In particular Semerari et al. [6,10] and Carcione et al. [7] found that the ability to differentiate between fantasy and reality (i.e. Differentiation) and the ability to form coherent narrative and to integrate mental states (i.e. Integration) were the most compromised in PDs.

Several studies have also confirmed that Adverse Childhood Experiences (ACE) are highly predictive for the development of a Personality Disorder (PD) in adulthood [17-19].

The development of these abilities has been correlated to caregiving or environmental disruptions, as severe abuse, neglect or maltreatment occurred in childhood [20]. In fact, children with a history of maltreatment exhibit significantly poorer reflective abilities compared to non-maltreated.

Other authors have underlined that ACE leads to a disorganization of attachment, causing difficulties in the recognition of emotions and, above all, in the ability to form coherent representations of oneself and others [21,22]. There is evidence that deficits in mentalization in children are associated with low levels of parental mentalization, abuse and neglect [23-26]. Mentalization has also been found to mediate the relationship between abuse and externalizing difficulties in adolescents [27].

Summing up, ACE show an impact on the development of individuals' ability to identify and reflect on their own and other people's mental states [28] and this lack of awareness would prevent the development of good skills to master suffering and interpersonal conflicts [13]. Vice versa, the development of good reflective abilities despite exposure to adverse life events seems to be associated to most resilience [15], and to a better recovery [29]. However, despite these studies showing association between ACE and impairment of reflective abilities, the results are not seeming definitive. In fact, for example, some studies examining community samples of women with histories of childhood maltreatment do not show clear dysfunctions [30,31].

Furthermore, there is evidence that specific adverse event can be associated with reflective abilities, psychopathology or emotional regulation. Honkalampi et al. [32] found that among patients with Major Depression, only early experiences of emotional and physical abuse and neglect are associated with difficulties in describing feelings in adulthood. Zlotnick et al. [33] provided evidence that in an outpatient sample a greater severity of emotional neglect and physical neglect, rather than abuse, was significantly related to higher levels of alexithymia.

However, adverse experiences are not supposed to impact only on reflective abilities. Large evidence supports the idea that ACE impact on general and mental health throughout the lifespan [34,35]. Concurrently with metacognition and mentalization, also ACE have been associated with PDs, but the results are not fully explaining. An interesting and extensive paper by Hengartner et al. [36] points out that traumatic experiences in childhood are not enough to cause a PD, but can be also relevant – and in some cases even more – socio-economic variables, poverty, school climate, divorce etc. The authors also suggest that childhood adversity impacts PDs in a dose-response relationship. Furthermore, Kessler et al. [37] provide evidence that childhood adversities have strong associations with all classes of psychiatric disorders, and not specifically with PDs. We can agree with Samuels [38] that there is still a need for others studies about PD risk factors in the general population.

Considering all these observations, we can argue that the associations among trauma, reflective abilities and PDs are not clear. The aim of this study was to explore metacognition, distress and severity of personality pathology in relation to the presence or absence of ACE. We hypothesized that :1) metacognition, 2) personality pathology and 3) symptom distress were most impaired in group that experienced adverse events in childhood. Specifically, we assumed that differentiation and integration functions were the most associated to ACE as result of difficulties to manage different representations of oneself and others' and to elaborate a coherent narrative of traumatic events.

Materials and methods

Participants

The sample consisted of 373 individuals who searched for treatment in an Italian outpatient clinic between 2015 and 2019. The mean age of the sample was 32.19

TABLE I. *Characteristics of the sample.*

N	Gender	Age M(SD)
373	166 M (44.5%) 207 F (55.5%)	32.19 (11.13)

Percentage of diagnosis for personality disorders										
AV	DEP	OBS	PA	DE	PAR	ST	HIS	NAR	BDL	AS
4.8	4.8	24.4	14.2	3.5	7.5	0.3	0.3	11.3	26.0	2.9

M = Male; F = Female; AV = Avoidant PD; DEP = Dependent PD; OBS = Obsessive PD; PA = Passive-Aggressive PD; DE = Depressive PD; PAR = Paranoid PD; ST = Schizotypal PD; HIS = Histrionic PD; NAR = Narcissistic PD; BDL = Borderline PD; AS = Antisocial PD.

(SD = 11.13), ranging from 18-65 years. 166 participants (44.5%) were male and 207 (55.5 %) were female. All participants met DSM-IV-TR [39] diagnostic criteria for PD (SCID-II) [40]. Inclusion criteria consisted of patients with at least one PD (including those with histories of suicidal attempts or self-harm). Exclusion criteria comprised substance dependence, psychotic disorders, bipolar I disorder, delirium, dementia, or mental retardation. Individuals who were enrolled in the study provided written informed consent. Table I shows demographic and diagnostic characteristics of the study sample and percentage of PD diagnoses.

Instruments and measures

Adverse Childhood Experiences (ACE)

To detect Adverse Childhood Event (ACE) we used a method similar to the one suggested by Chiesa & Fonagy[18] in a relevant study. Through an extensive standardized anamnestic interview, which detects information similar to the Cassel Baseline Questionnaire [41], conducted by a psychologist and a senior psychiatrist, the presence/absence of experiences of sexual abuse, neglect and violence/physical abuse was detected in the pre-treatment phase. We used Chiesa & Fonagy's [18] criteria to classify ACE: *neglect* has been defined as the lack of parental support (between 0 and 16 years) indicated by a separation from a primary caregiver (usually the mother or father) over 1 year; *sexual abuse* has been defined as pre-adolescent sexual contact (usually under 14 years) with an adult or forced and violent sexual violence, even after puberty; *physical violence/maltreatment* has been defined as physical or psychological abuse by the caregiver. Psychological abuse includes rejection, hostility and contempt by caregivers or even cruel and sadistic behaviours [42,43]. As Chiesa and Fonagy [18] point out in their paper, all these definitions agree with those suggested by Bifulco, Brown, & Harris [44] in the Childhood Experiences of Care and Abuse Interview coding system (CECA).

A binary variable (presence = 1; absence = 0) was created when detecting anamnestically these events. In this work, a total score was created, without distinguishing the type of experience. Therefore, we created an index scoring from 0 to 3, where 0 corresponded to the absence of adverse experiences; > 1 at least one type of event, while 3 corresponded the presence of three adverse experiences.

The Structured Clinical Interview for DSM-IV [40] was used to obtain diagnostic Axis-II profiles on the basis of the criteria of the DSM-IV [39] (AmericanPsychiatric Association, 1994), which yields 11 different categories of PD diagnoses. In this study, satisfactory inter-rater reliability was found in the application of the SCID-II. 20 SCID-II were rated twice; internal consistency of traits of PDs ranged from 0.71 and 0.89 for the majority of the PD diagnoses; only four PDs (obsessive-compulsive, dependent, schizotypal, and passive-aggressive) had alphas above.60. Inter-rater reliability was adequate for both trait scores (a two-way mixed absolute agreement model for ICCs ranged between 0.87 and 0.99, mean = 0.94) and categorical diagnoses (average k = 0.89).

The Symptom Checklist-90-R. The SCL-90-R [45] is a 90 item self-report inventory designed to reflect the psychological symptom patterns of psychiatric and medical patients. It is a measure of current (state) psychological symptom status. The SCL-90-R measures nine primary symptom dimensions and generates an estimate of global psychopathology, the Global Severity Index (GSI), which has been adopted in the current study as a measure of symptoms distress. The scale showed good reliability (α = 0.97).

The Metacognition Assessment Interview (MAI). The MAI [46,47] is a semi-structured clinical interview designed to elicit and evaluate metacognitive abilities of the participant, in a brief narrative of a psychologically significant experience or event. During the interview, the participant is requested to describe the most troubling interpersonal experience of the previous six months, a time frame selected in order to facilitate recall and to permit test-retest, avoiding recall biases, in the evaluation of changes during psychotherapy.

The reported experience must be autobiographical, personal, and it must involve another person, so that ability to understand the mental state of others can be evaluated. Once the description of the episode is completed, the interviewer asks a list of questions, divided into four modules, to elicit and evaluate the 16 basic facets constituting metacognitive sub-functions (four facets for each sub-function). The interviewer assigns to each of the 16 basic facets a score ranging from 1 to 5, using a Likert scale. For each sub-function the score ranging from 4 to 20, for the MAI global from 16 to 80. The metacognitive functions assessed by the MAI are: Monitoring (MON), Integration (INT), Differentiation (DIF), Decentration (DEC) and Global score. Monitoring (MON) is the ability to identify and label the components of our mental states in terms of emotions, thoughts, motivations and desires. People who can monitor effectively find it easy to give appropriate answers to questions such as 'What do you think?' and 'How do you feel?'. Impairment of this function compromises both the individual's ability to describe his/her internal states and the ability to explain reasons and motivations underlying his/her behaviour. Integration (INT) refers to the more general capacity of individuals to reflect upon different mental states, identifying internal contradictions, conflicts and patterns. This metacognitive function allows us to organise mental contents adaptively in terms of significance and subjective priority and thus to maintain behavioural coherence. An integration disorder makes mental processes and behaviours contradictory and unstable. Differentiation (DIF) indicates the ability to recognise the representational nature of mental states, distinguishing clearly between internal psychological content and external reality. In presence of differentiation's impairments, imagination takes on the properties of the real world. In this perspective, if the patient is unable to recognise the subjectivity of his/her mental representations, he/she is also unable to maintain critical distance from his/her own representations. Decentration (DEC) refers to the ability to assume other people's perspectives and to make plausible hypotheses about their mental states. Specifically, it means being able to reflect about others' intentions, thoughts and desires, independently of one's own personal point of view.

In the present study, the MAI was administered and scored by three senior interviewers blinded to the clinical diagnosis of the participants. Preliminary inter-rater reliability evaluation was carried out on 20 interviews. To estimate the correlation for every single function rated bydifferent judges, the Intraclass Correlation Coefficient (ICC) was used. A two-way mixed absolute agreement model was applied to carry outthe ICC for each dimension of the MAI. The ICC for the MAI's functionsranged from.55 to.72 for MON; from.50 to.67 for INT; from 0.49 to 78 for DIF; and from 0.45 to 0.61 for DEC; all analyses were significant ($p < 0.001$) and provided good inter-rater reliability. Internal consistency of the MAI dimensions was estimated with Cronbach's alpha, which ranged from 0.85 to 0.89.

Procedure

All measures were administered at baseline. Personality disorder evaluation and diagnosis were made by a clinical team (composed of psychologists and psychiatrists) in accordance with DSM-IV criteria. The study was extensively explained to each participant, who signed a written consent form before entering the study, and the local Ethical Committee approved the evaluation protocol. Following informed consent, all participants completed all the self-report measures and the interviews.

Statistical analyses

In order to test the associations among metacognition, symptoms distress (GSI) and personality severity (number of SCID-II criteria) with ACE, we run a series of ANOVAs using the dichotomous ACE variable (0 = no ACE; 1 = at least 1 ACE - see below for details) as the grouping variable.

Results

The distribution of the variable ACE revealed that 68.9% of the sample reported no adverse childhood event; 22.5% of the sample reported 1 adverse event; 8.3% reported 2 adverse experiences, while. 0,3% (only one case) of the sample had 3 adverse childhood experiences. In order to test the differences between patients with no ACE and with at least 1 ACE we dichotomized this count variable coding 0 as absence of ACE (n = 257) and 1 indicating at least one ACE (n = 116).

Results are summarized in Table II.

Significant differences between the two groups were found but for monitoring and decentration dimensions. The No ACE group showed higher levels of differentiation, integration and the total score of MAI and lower levels of symptom distress and PD severity than the ACE group. Significant effect sizes went from moderately small ($d = 0.22$) to medium-sized ($d = 0.48$).

Discussion

The current study explored metacognition, distress and severity of personality pathology in relation to the presence or absence of ACE. We hypothesized, according to previous research [18,48], that: 1) metacognition, 2) personality pathology and 3) symptom distress was most impaired in group that experienced adverse events

TABLE II. *ACE related differences on the measured variables.*

Measures	No ACE M(SD)	ACE M(SD)	F (1,371)	Cohen's d
Monitoring	11.17 (2.14)	10.74 (2.07)	3.34	0.20
Differentiation	10.09 (1.80)	9.27 (1.88)	16.12***	0.44
Integration	10.26 (1.93)	9.78 (2.36)	4.20*	0.22
Decentration	9.96 (2.24)	9.47 (2.57)	3.49	0.20
MAI total	41.49 (6.91)	39.27 (7.78)	7.64**	0.30
Symptom distress	1.39 (0.65)	1.58 (0.75)	6.54**	0.27
PD severity	17.11 (6.29)	20.28 (6.89)	19.12***	0.48

****: $p < 0.001$; **: $p < 0.01$; *: $p < 0.05$.*

in childhood. We also assumed that integration and differentiation sub-functions were the most associated to ACE. Therefore, we split a sample of PD patients in two groups, with or without ACE.

As expected, metacognition is more impaired in the ACE group, where integration and differentiation were the most compromised functions. Furthermore, the mean differences between the two groups are significant for metacognition global score (MAI global score) and for integration and differentiation as hypothesized.

These results are in line with different studies, even if most papers refer to borderline personality disorder (BPD). Liotti and Prunetti [22] have suggested that traumatic experiences in childhood produce impairments in reflective abilities, and in particular to form coherent representations of oneself and others (integrative function) caused by the disruption of attachment patterns in BPD. Also Semerari et al. [6,49], Brune et al. [50], Fonagy et al. [21] found that impairments in integrative function characterize BPD. The results are also consistent with other studies showing that the attachment representations of individuals with PD are unresolved in relation to trauma and loss [51] and that in sample of individuals with BPD, 89% were coded as unresolved from 75% [52], to 89% [53]. And consistently with Semerari et al. [6,49], and Fonagy et al. [21], the correlation with differentiation also appears to be significant. Carcione et al. [7] provided evidence that differentiation and integration were the most impaired functions at the baseline in a sample of 193 outpatients treated with Metacognitive Interpersonal Therapy [54].

In the study by Brune et al. [50] the decentration, measured throughout performance in a novel cartoon-based task, was found strongly associated to impaired mentalization, while in our paper does not emerge a difference between the two groups in this sub-function, but in differentiation. This could be explained because the different kind of instrument used to assess reflective abilities. Keeping in mind that Differentiation and Decentration imply the ability to consider the subjective and representational nature of the thought in self-refection area and in comprehension of others mind respectively, it's possible that, compared to MAI, the novel cartoon task could be less sensitive to distinguish the two sub-functions.

Another hypothesis of this study was that symptom distress, measured by the GSI-SCL 90-R index, was higher in ACE group, as also general personality pathology, measured through the number of SCID-II criteria satisfied, were more compromised. Our results are in line with previous findings that have confirmed that childhood experiences of loss and/or abuse were significantly associated with later onset of PD and higher level of psychiatric distress [55-58].

In spite of the statistical significance of our data, we consider appropriate to note that some recent studies, although providing evidence on the association between traumatic events, reflective abilities and PDs, suggest that the relationship may not be direct and ACE by itself would not be sufficient to compromise reflective abilities and generate PDs. For instance, Cirasola et al. [57] found that the association between childhood experiences of trauma and current PD diagnosis would be, at least partly, mediated by the degree to which participants resolved early traumatic experiences. The author also found that unresolved state of mind could be one mechanism through which childhood trauma may increase the risk for PD, mediating the relation between trauma and PD diagnosis.

This study presents some limitations and some strength. The ACE index we used is clearly rough. It serves the end of looking for associations with other variables, but is not suitable for purposes that need higher measurement reliability and validity. Furthermore, it is possible that different types of traumatic events (physical violence, neglect, psychological abuse)

could have a different impact on metacognitive abilities, as suggested by Berthelot et al. [48], showing evidences that is emotional maltreatment, and not physical forms of maltreatment, that in particular influences borderline pathology through its effects on mentalization measured as Reflective Function. Psychological abuse seems to affect mentalisation more than other forms of maltreatment because it directly attacks the child's mind [42].

Heterogeneity of the sample represents at the same time a strength and a weakness of the study. It is a strength because it provides a sample of PDs quite wide and is one of the few studies that consider an adult clinical sample (see also [18,50]), while most are centered on childhood [59,60] and adolescence [61]. Majority studies are focused on BPD and this can represent a bias in PDs research [62] considering that about 50% of the patients diagnosed as having a PD are diagnosed having at least another PD co-occurring, with that other diagnosis (Axis I according to the DSM-IV) [63,64]. To have information more closed to the real clinical practice, in this paper we decided to use a sample composed by all the personality disorders. But at the same time this can be a limitation because ACE may be more related to the development of a specific kind of PD than others, for example BPD on which most of the studies have been done. The study also lacks of a third control group composed by individuals without a diagnosis of PD.

Another limitation may be the use of cross-sectional design; while the results provide some evidence of the interaction between childhood abuse, metacognition and personality pathology in the adult population, no conclusions can be drawn regarding causality or temporal relationships.

Another strength of the study is the use of an interview and not of self-report to evaluate metacognition, as underlined by Quek et al. [61] who highlighted this limit in his study. It seems paradoxical to ask a person who is supposed to present difficulty in reflecting on himself, if he has difficulty in reflecting on himself, so self-report measures to evaluate reflective abilities are vulnerable to recall and reporting biases.

Conclusions

This paper provides a further contribute to the hypothesis that adverse childhood experiences represent a significant variable that impact on the good development of metacognition (as measure of reflective ability) lifetime in individuals diagnosed as PDs. This is particularly true for the integration and differentiation metacognitive sub-functions, that generally appear to be the most impaired in PDs samples. Further studies are desirable to explore the several independent pathways that could be link early adversity to PD diagnosis, given the need for studies of PD risk factors in the general population. This could be useful for the comprehension of the core features of PDs, to improve treatment.

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Review

Early stress and dissociation: psychopathological pathways

Mario Amore[1,2], Gianluca Serafini[1,2]

[1] Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili, Clinica Psichiatrica, Università di Genova, Genova; [2] IRCCS Ospedale Policlinico San Martino, Genova

SUMMARY

Objectives

In the last two centuries, researchers tried to investigate the complex effects of early life stress on developing brain as well as the mechanisms underlying dissociation that may be frequently linked to traumatic experiences. Clinically, dissociation may be found in many psychiatric disorders and may be defined as the disruption of important human functions such as memory, identity, consciousness, thinking, emotions, body representation, motor control as well as behavior. The aim of the present review was to selectively review data about the link between traumatic experiences, dissociation and psychopathological patways.

Methods

A detailed search regarding the association between traumatic experiences, dissociation, and psychopathological patways has been carried out.

Results

Based on the most relevant included studies (n = 16), a chronic hypothalamic pityuitary adrenal (HPA) axis dysregulation (that may include both hyperactivity and hypoactivity) has been found in subjects with childhood traumatic experiences. The dysregulated stress system in subjects who have suffered from early traumatic conditions is able to promote important neuroendocrine and immune impairments together with inducing inflammatory-related conditions. Exposure to early-life traumatic experiences may be also linked to relevant psychopathological and neurocognitive consequences with multiple psychopathological conditions that may be developed in individuals with a positive history of traumatic experiences. Importantly, early adversities are closely related to enhanced chronicity, suicidal behavior, and poorer treatment response.

Conclusions

Although dissociation may be diagnosed both in acute and chronic conditions, many clinicians are, unfortunately, not able to correctly detect these conditions. The main implications related to the link between trauma, dissociation, and most relevant psychopathological conditions are discussed.

Key words: early stress exposure, traumatic experiences, dissociation, psychopathological patways, emotional-behavioral disturbances

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Correspondence
Mario Amore
Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), Section of Psychiatry, University of Genoa,
IRCCS Ospedale Policlinico San Martino,
Largo Rosanna Benzi 10, 16132 Genoa, Italy
Tel. +39 0103537668 (office)
Fax +39 0103537669
E-mail: mario.amore@unige.it

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The impact of early stressful experiences on developing human brain

Approximately in 400 BC, Plato was the first to recognize the fragility of the developing human brain stressing the impact of early experiences and the importance of trauma on the development of human brain functions. In the last two centuries, researchers tried to investigate the complex effects related to early life stress on developing brain as well as the mechanisms underlying dissociation and dissociative disorders (which are frequently linked to early stressful experiences), especially by a neurobiological

point of view. Seminal studies clearly demonstrated in 1970 the negative behavioral effects and the complex consequences related to early maternal separation in baby rhesus monkeys [1]. These studies are based on the assumption that trauma and adverse early experiences such as abuse or maltreatment may induce the presence of "scars" leading to significantly impaired wellbeing and psychosocial disability [2,3]. Currently, research tried to analyze the nature of these "scars" in the effort to identify the exact nature of the biological vulnerability underlying early stress and recognize the illness trajectories together with the multiple psychopathological pathways associated to early stress.

Exposure to early-life traumatic experiences may be linked to relevant psychopathological and neurocognitive consequences. Importantly, child abuse and maltreatment may be considered as leading causes of disability and are significantly associated with the emergence and maintenance of psychiatric conditions according to the Centers for Disease Control (CDC) [4]. Furthermore, there are studies in the current literature supporting the notion that early adversities are closely related to enhanced chronicity [5], suicidal behavior [6], and poorer treatment response [7]. Adverse childhood experiences are also linked to learning and behavioral problems, impairments in school performance [8], enhanced school absence [9], and significantly reduced verbal Intelligence quotient (IQ) [10] exerting important effects on the individual functioning. Overall, traumatic experiences have been documented in 15% to 60% of children and adolescents [11] with early adversities representing a public health priority worldwide.

From chronic developmental stress to dissociation

Dissociation may be considered one of the possible adaptive responses to early-life stress perceived as a traumatic experience or chronic developmental stress exerting important consequences for the individual functioning. Some researchers [12] suggested that trauma and dissociation need to be addressed at the crossroad of neurobiology and psychopathology. Interestingly, dissociation may be found in many psychiatric disorders and may affect both the phenomenology as well as treatment response in psychiatric conditions [13]. The recent history of psychiatry is closely linked with the history of dissociation and dissociative disorders (related to the existence of trauma).

Dissociation is associated with as the disruption of important human functions such as memory, identity, consciousness, thinking, emotions, body representation, motor control as well as behavior [14]. Dissociative conditions represent acute and transient reactions to stressful life events or interpersonal problems and may manifest in the form of stupor (usually considered a mild transient state of dissociation) but even as acute psychotic conditions. The emergence of dissociative conditions may be with the following symptoms: palpitations, fainting, shaking, depersonalization, and non-epileptic seizure. Overall, it has been hypothesized that dissociative conditions are aimed to self-protection in response to specific or aspecific threats [15].

According to recent diagnostic manuals, amnesia with fugue, depersonalization, derealization, identity confusion/alteration are the five primary dissociative disorders but dissociative identity disorder is the most pervasive form covering all the entire spectrum of dissociative symptoms [12,14]. In DSM-5, dissociative fugue has been considered as a specific subtype of dissociative amnesia as it is not confirmed as a separate condition (similarly to previous editions). Interestingly, the DSM-5 diagnostic criteria for post-traumatic stress disorder (PTSD) now include the existence of a dissociative subtype (PTSD-DS) [14]. By a clinicial point of view, dissociative disorders are not recognized as a unitary phenomenon in the community and some individuals may claim only some symptoms which appear prevalent in their current symptomatology.

Although dissociation may be diagnosed both in acute and chronic conditions, many clinicians are, unfortunately, not able to correctly detect dissociative conditions. Existing studies exploring the link between early life trauma and dissociative identity disorder documented significant rates of childhood adversities in the histories of individuals with dissociative identity disorder relative to other diagnostic groups [16] Spiegel et al. [16] also suggested that childhood sexual abuse is very common, childhood physical abuse often present and both sexual and physical abuse/maltreatment (performed by multiple perpetrators) present in a percentage variable between 77% to 100% in patients with dissociative identity disorder. Overall, 5-12 years are needed for patients with dissociative disorders in order to reach the correct diagnosis while during this period at least 3-4 incorrect diagnoses were usually carried out by clinicians with important negative consequences in terms of clinical management and treatment.

Psychobiological and neurobiological theories in the field of trauma and dissociation

Abnormally prolonged stress reactions may exceed the individual adaptive ability to fight stressful situations and enhance the likelihood of psychopathological responses. According to Trauma Model, dissociation is considered as a psychobiological state/trait having a protective role against traumatic or pervasive early experiences [17]. It has been suggested that dissociation modulates the impact of trauma by psychobiologically

attenuating the negative implications of trauma directly through the activation of different states of consciousness. Dissociation has been described in humans as the equivalent of the animal "freeze" in the context of a life-threatening danger when the "fight or flight response" has generally failed [18]. Based on Porges' theory [19], given the failure of fight-flight sympathetic stress responses, the dominance of the primitive vagal parasympathetic system is directly linked with the freeze response. Many evidence (e.g., genetic, developmental, neurobiological, and psychophysiological) supported the existence of a model in which the exposure to chronic repeated traumatic experiences is associated with the emergence of a freezing behavior [16].

Hypothalamic pituitary adrenal (HPA) axis hyperactivity as well as higher circulating cortisol levels, enhanced cortisol awakening response, increased adrenocorticotropic (ACTH) hormone and enhanced cortisol responses to psychosocial stress or endocrine challenges have been all documented in adult patients with childhood traumatic experiences representing one of the most specific form of early life stress [20-23]. In particular, it is well-known that the pathophysiology of stress-related disorders is closely related to a chronic dysregulation of the HPA [24] with the hyperactivation of the stress system that is related to the hypersecretion of ACTH and arginine-vasopressin (AVP) by the hypothalamus and ACTH hypersecretion by the pituitary [25]. These events determine abnormally higher cortisol levels due to the "insensitive" negative glucocorticoid feedback of the HPA axis loop. However, there are also reports regarding the existence of HPA axis hypo-activity (e.g., lower circulating cortisol levels, blunted cortisol stress responses) in similar populations and study designs [26-28]. This abnormally reduced activity might represent a compensatory adaptation related to a negative feedback hypersensitivity of glucocorticoids, downregulated secretion of corticotropin releasing hormone (CRH)/AVP to the pituitary [23] or a long-lasting glucocorticoid catabolism drop associated with higher active cortisol persistence in liver and kidney [29] (Fig. 1).

The dysregulated stress system in subjects who have suffered from early traumatic conditions is able to promote important neuroendocrine and immune impairments, and induce inflammatory-related or immunosuppressed conditions [30]. In particular, childhood traumatic experiences may activate an abnormal inflammatory response through the secretion of pro-inflammatory cytokines, and the stimulation of systemic acute-phase proteins such as C-reactive protein [31]. A positive history of childhood traumatic experiences has been reported as an independent risk factor for peripheral immune dysregulation and long-term, low-grade inflammatory excess in adulthood [32]. Stress-related alterations in pro-inflammatory pathway have been supposed as one of the most relevant biological links through which the environment may influence the general health [33]. It has been reported that neuroendocrine responses to stress may enhance the transcription of pro-inflammatory genes encoding for the production of interleukin-1 beta, interleukin-6, interleukin-8, cyclooxygenase 2 and tumor necrosis factor alpha [34]. However, several non-

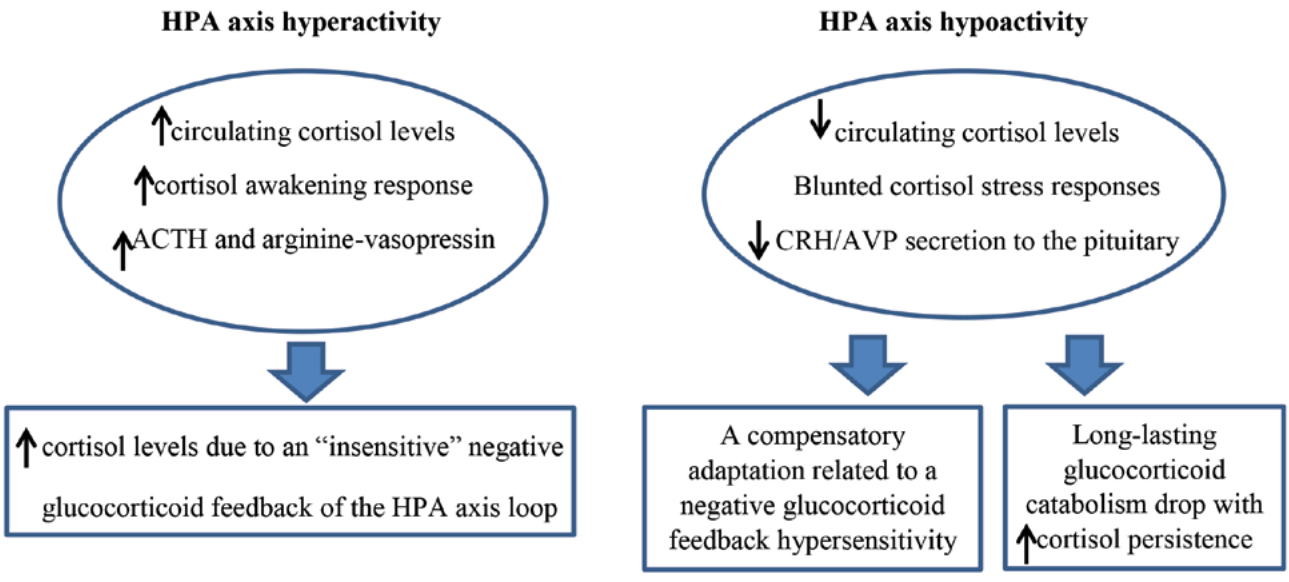

FIGURE 1. *Chronic HPA axis dysregulation in subjects with childhood traumatic experiences.*

stress pathways that might contribute to differential gene expression are associated with increased drinking and smoking as well as higher rates of obesity enhancing the risk of mortality [35].

In addition, existing evidence suggested that the abnormally impaired human microbiome could be another pathway linking childhood traumatic experiences with altered neuroimmune reactions and might abnormally impair neurodevelopment with long-lasting effects on general health and behaviors [36]. According to a very recent study from Taft et al. (2019), more than 30% of patients with inflammatory bowel disease reported significant PTSD symptoms and 25% manifested a clinical PTSD diagnosis since disease onset, with the majority of patients stating that their PTSD was mainly related to their inflammatory bowel disease experiences. Based on the recent growing understanding about the brain-gut-microbiome axis [37,38], the negative impact of stress on disease course may help clinicians to recognize psychological distress as a component of inflammatory bowel disease patient care and treatment [39].

Evidence also reported a correlation between childhood adversities, endothelial dysfunction, and increased superoxide production [40] with reduced endothelial nitrous oxide system and dysfunctional endothelial Angiotensin II-mediated signaling as well as sensitization to Angiotensin II-induced vasoconstriction [41]. Evidence demonstrated that a history of traumatic experiences may be associated with an increased risk of endothelial injury and dysfunctions (reported as on the initiating event in atherosclerosis [42] and consequently cardiovascular diseases) [43-45]. Thurston et al. [46] stressed the importance of considering trauma exposure as an important psychosocial factor in midlife women's cardiovascular health based on the findings of their study on 272 nonsmoking peri- and post-menopausal women in which over 60% of the sample reported at least one traumatic exposure, 18% had three or more exposures and a greater number of traumatic exposures was linked to poorer endothelial function.

The stress system is even interconnected with alterations in metabolism with evidence reporting that chronic stress is associated, during critical periods of growth and development, with a significant disruption of circadian and metabolic system having permanent adverse effects on body size and composition as well as associated physical inactivity, emotional eating disorders, and disrupted sleep pathway. Sleep disturbances have been reported very frequently after traumatic experiences with insomnia and trauma-related nightmares as the most common symptoms closely linked to stress-traumatic events [47]. In addition, severe sleep disorders with sympathetic activation and disruptive nocturnal behaviors (that may be defined as extreme nocturnal manifestations of traumatic experiences encompassing nightmares, disruptive nocturnal behaviors, and comorbid insomnia) are frequently reported in the context of traumatic experiences [48].

Relevantly, the response to early developmental cues may be facilitated by persistent changes in the transcriptome playing a very relevant role in long-term biological trajectories of stress-related diseases [49,50]. This is mainly related to the assumption that early development represents a particularly sensitive period for epigenetic modification of the genome [51] with one of the most investigated epigenetic marks being DNA methylation, proposed as an important epigenetic mechanism through which childhood maltreatment may exert long lasting effects on gene expression and human behavior [52]. Importantly, the timing of childhood maltreatment/abuse has been suggested as crucial in determining the severity of epigenetic alterations [51]. To this specific regard, some researchers [53] suggested that exposure to trauma occurring earlier in the course of development could lead to enhanced damage, supposing the existence of a critical temporal vindow in which childhood abuse/maltreatment seems able to more significantly affect and modify the human epigenome. It is presumable that DNA methylation together with alternative epigenetic marks and mechanisms may act at the interface of genes in association with life experiences, behavioral regulation, and mental health [52].

Trauma and dissociation: possible psychopathological pathways

Severe impairments in child development, disruption of attachment security and self-regulatory processes, poorer physical/mental health outcomes have been described after the exposure to childhood traumatic experiences in both childhood and adulthood [54]. From childhood to adulthood, it has been suggested that approximately 70% of individuals may experience at least one lifetime traumatic event [55]. The area of stress is clinically a condition of great complexity, with many studies that have been conducted on this topic and many controversies regarding different psychopathological pathways related to the exposure to early tramatic experiences. Table I summarizes the most relevant studies about the association between early stress, dissociation, and multiple psychopathological patways related to early traumatic experiences. Overall, 13 cross-sectional and 2 longitudinal follow-up studies investigated the relation between early stress, dissociation, and multiple psychopathological patways. Among cross-sectional studies, there are contributions [56-58] stressing the link between child sexual abuse, behavioural problems, attachment insecurity, and psychological difficulties while

TABLE I. *Most relevant studies about the association between early stress, dissociation, and multiple psychopathological pathways related to traumatic experiences.*

Author(s)	Sample	Study design	Psychometric and instrumental measurements	Main results	Limitations	Conclusions
van Duin et al.[56]	41 parents; 44 children (30 boys, 14 girls)	Cross-sectional study	1) Diagnostic Infant and Preschool Assessment; 2) Anxiety Disorders Interview Schedule for DSM-IV Child Version, parent Interview Schedule; 3) Children's Revised Impact of Event Scale, (PV); 4) Child Dissociative Checklist; 5) Child Sexual Behavior Inventory; 6) Child Behavior Checklists 1-5 and 6-18; 7) Attachment Insecurity Screening Inventories 2-5 and 6-12 years; 8) Impact of Event Scale – Revised; 9) Parent Emotional Reaction Questionnaire; 10) Experiences in Close Relationships	Overall, 3% of child victims reported PTSD, 30% sexual behavior problems, 24% internalizing problems, 27% attachment insecurity, and 18% any psychiatric disorder but 39% were asymptomatic. In parents, feelings of guilt, shame, and anger about the abuse of their child were found. 19% showed PTSD symptoms, 3% avoidant, and 8% anxious attachment problems in their intimate relationship. Finally, 25% of child victims and 45% of parents received psychological treatment	1) The children's ages restricted to a single informant source; 2) The study represents a biased subgroup of families; 3) The study participation itself may have mitigated possible negative outcomes; 4) The small sample size; 5) The lack of a control group	Child sexual abuse in very young children was linked to both sexual and non-sexual behavior problems and attachment insecurity, but rarely with PTSD or dissociation
Schalinski et al.[61]	49 females; 16 healthy controls	Cross-sectional study	1) Life Event Checklist; 2) Clinician Administered PTSD Scale; 3) Shutdown Dissociation Scale; 4) Resting state magnetoencephalography	Increased delta and reduced beta power were found linked to dissociative symptoms. Theta and alpha oscillatory power (in particular childhood sexual abuse) were modulated by adversity-related measures	1) Results are based on women with comorbid depressive symptoms; 2) No reliable source for the early infancy are available about childhood adversities	TRA in neural organization vary with exposure to adversities but even with the potential to evoke ongoing shutdown responses.
Karatzias et al.[59]	82 subjects with a history of interpersonal trauma and 78 non-clinical controls	Cross-sectional study	1) Young Schema Questionnaire-Short Form; 2) PTSD Checklist-Civilian Version; 3) The Symptom Checklist-90; 4) Dissociative Experiences Scale; 5) Rosenberg self-esteem scale	Survivors of interpersonal trauma showed higher maladaptive schemas than controls. Schemas in the domains of Disconnection and Impaired Autonomy were associated with all psychopathological characteristics	1) The sample consisted only of subjects with interpersonal trauma; 2) Different schema profiles may be active in different trauma groups; 3) limited information are available concerning the severity/duration of trauma	Findings stressed the importance of interventions targeting schemas in the domains of Disconnection and Impaired Autonomy

follows **TABLE I.** *Most relevant studies about the association between early stress, dissociation, and multiple psychopathological pathways related to traumatic experiences.*

Author(s)	Sample	Study design	Psychometric and instrumental measurements	Main results	Limitations	Conclusions
Thomson and Jaque[62]	209 dancers who were exposed to traumatic events	Cross-sectional study	1) Adverse Childhood Experiences; 2) Beck Depression Inventory II; 3) Coping Inventory for Stressful Situations; 4) Dissociative Experience Scale-II; 5) Internalized Shame Scale; 6) Inventory of Childhood Memories and Imaginings; 7) Posttraumatic Stress Diagnostic Scale; 8) State-Trait Anxiety Inventory; 9) Traumatic Events Questionnaire	A higher distribution of PTSD (20.2%) in dancers relative to normal population (7.8%) was found. Dancers showed a higher frequency of family members with PC, more difficulties to deal with trauma, and more suicidal thoughts. PTSD group of dancers showed more childhood adversities and adult trauma, higher levels of anxiety, depression, dissociation, and shame. Relative to no-PTSD group, PTSD group reported higher fantasy proneness and emotion-oriented coping strategies (linked to psychological instability)	1) The evaluation of traumatic events and dissociative symptoms were based on self-administered questionnaire; 2) The lack of a control group; 3) The study results are not generalizable to more homogeneous groups of dancers; 4) The study included only dancers who met PTSD Criteria A	Dancers should be helped to early address abuse/maltreatment. By understanding PTSD in dancers, medical and mental health treatment protocols may be carried out to manage the impact of disabling PTSD symptoms
Jepsen et al.[63]	55 early traumatized inpatients	Cross-sectional study	1) Somatoform Dissociation Questionnaire-20; 2) 28-item Dissociative Experiences Scale-II; 3) Impact of Event Scale; 4) Symptom CheckList 90 Revised; 5) Beck Depression Inventory-II; 6) Structured Clinical Interview for Dissociative Disorders-Revised	Overall, 32.7% reported psychoform and SDS; 40% SD symptoms; 27.3 non-dissociative symptoms. The highly dissociative group showed younger age, more frequency of living alone, higher levels of post-traumatic and general distress, more frequent reports of suicidality, self-mutilation, eating problems, and less favorable treatment response	1) The small sample size reducing power to detect a medium effect size to 0.40; 2) Retrospective self-report may be vulnerable to recall or bias. 3) The assessment of childhood abuse did not include a validated measure	The present findings suggest the importance of using dissociation measures to identify subgroups of patients with severe psychopathology who may be more treatment resistant

follows **TABLE I.** *Most relevant studies about the association between early stress, dissociation, and multiple psychopathological pathways related to traumatic experiences.*

Author(s)	Sample	Study design	Psychometric and instrumental measurements	Main results	Limitations	Conclusions
Price te al.[60]	1676 youth aged 4-18	Prospective longitudinal study	1) My exposure to violence; 2) Revised-child behavior checklist 6-18 years; 3) Emotionality, activity, sociability, and impulsivity temperament survey; 4) Family socioeconomic status	Interpersonal traumas including significant interpersonal proximity were associated with oppositional defiant and conduct problems. Nearly all the symptom domains were positively linked to direct trauma experiences and emotionality	1) Lack of information regarding subjective experiences of social betrayal; 2) Examination of TE carried out only in the year prior to assessments at the second and third waves 3) relevant information about past TE might have been missed; 4) Data was collected every two to three years; 5) Anxiety subscale derived from the Revised-child behavior checklist-R had poor-moderate reliability	Each symptom domain was predicted by at least one type of trauma experience. The present findings underlined the important role of traumatic experiences in the etiology of childhood psychopathological pathways
Gaon et al.[57]	505 outpatients	Cross-sectional study	1) Dissociative Experience Scale; 2) Trauma History Questionnaire; 3) Impact Of Event Scale; 4) Post-traumatic Diagnostic Scale	Overall, 97% reported nearly one lifetime traumatic event. At the time of occurrence, TE were experienced as meaningful and severe. Victims reported that the effects of sexual and childhood emotional abuse remained very intense lifetime and were perceived as powerful experiences. However, TE such as natural disasters and battle trauma were linked to long-term effects of low intensity	1) The evaluation of traumatic events and dissociative symptoms were based on self-administered questionnaire; 2) The use of a clinical interview in a randomized sample of participants was not carried out; 3) The Post-traumatic Diagnostic Scale was not available in Russian/Spanish; 4) Only 90.3% of participants completed all the questionnaires	The screening and procedures to diagnose PTSD should be more accurate. Among all traumatic experiences, sexual abuse exerted the most relevant effects on later life

follows **TABLE I.** *Most relevant studies about the association between early stress, dissociation, and multiple psychopathological pathways related to traumatic experiences.*

Author(s)	Sample	Study design	Psychometric and instrumental measurements	Main results	Limitations	Conclusions
Etter et al.[58]	173 adult psychiatric inpatients	Cross-sectional study	1) Symptom Checklist-90-Revised; 2) Dissociative Experiences Scale; 3) Structured Interview of Self-Destructive Behaviors; 4) Structured Interview for PTSD; 5) Structured Interview for Social Support as a Child; 6) Jacobson's structured interviews interpersonal violence and sexual experiences	Depression, dissociation, self-destructive behavior, PTSD, and global psychopathology were negatively associated with positive affect. Significantly less positive affect were found in subjects who experienced both physical and sexual abuse relative to those with only physical or no abuse experiences. Lower childhood social support and greater severity of sexual abuse predicted lower positive affect	1) The potential for error in subjects' recollection of childhood experiences and reports of low positive affect; 2) The reliability/validity of the positive affect items were not performed; 3) Findings are limited to psychiatric inpatients population	Subjects experiencing multiple types of early adversity, more severe sexual abuse experiences, and less social support are at higher risk of psychological difficulties
Kleim et al.[64]	222 assault survivors	Prospective longitudinal study	1) Trauma History Interview; 2) Depressive Attributions Questionnaire; 3) Beck Hopelessness Scale – short form; 4) Cognitive Processing Questionnaire; 5) Posttraumatic Cognitions Inventory; 6) Response to Intrusions Questionnaire; 7) State Dissociation Questionnaire	MDD and PTSD models predicted both MDD and PTSD symptom severity, but disorder-specific models predicted the respective outcome best (43% for MDD, 59% for PTSD). Maintaining cognitive variables (hopelessness and self-devaluative thoughts in MDD; cognitive responses to intrusive memories and persistent dissociation in PTSD) showed the clearest specific relations with outcome. Model-derived variables predicted MDD and PTSD at 6 months over and above the initial diagnoses	1) The number of variables in the structural equation models was limited due to restrictions in sample size; 2) The numbers of trauma survivors within the disorder categories were too small in order to investigate subgroups of "pure" disorders; 3) Results were limited as they have been derived only by a sample of assault survivors	The study stressed the importance of cognitive factors in the development of depression and PTSD after trauma

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Author(s)	Sample	Study design	Psychometric and instrumental measurements	Main results	Limitations	Conclusions
Matos et al.[65]	90 participants from the general population	Cross-sectional study	1) Shame Experiences Interview; 2) Impact of Event Scale – Revised; 3) Rumination Responses Questionnaire; 4) White Bear Suppression Inventory; 5) The Dissociative Experiences Scale – Revised; 6) Depression, Anxiety and Stress Scale	Emotion regulation processes (e.g., brooding, thought suppression and dissociation), were found to mediate the association between shame traumatic memory with others and MDD. Shame traumatic memory with attachment figures had a direct effect on MDD but only brooding partially mediated this relation	1) The transversal study design; 2) Findings may not be generalized to clinical populations; 3) The use of self-report instruments to evaluate traumatic events and dissociation	These results stressed the importance of addressing shame memories, especially those involving attachment figures, particularly when working with patients with depressive symptoms and/or that find compassion difficult or scary
Matos and Pinto-Gouveia[66]	11 subjects from the general population	Cross-sectional study	1) Experience of Shame Scale; 2) Depression, Anxiety and Stress Scales; 3) Impact of Event Scale-Revised	ESE revealed TM characteristics. Importantly, TME were linked to current feelings of internal and external shame in adulthood. Current shame and MDD were found associated. More depressive symptoms were showed by subjects with more TSM. An effect of shame traumatic memory on the relation between shame and MDD was finally reported	1) The transversal nature of the study design, the use of self-reports questionnaires, the possibility of selective memories in participants' retrospective reports and the use of a general community sample, are some methodological limitations that should be considered	Shame memories have TM characteristics, able to affect shame but also moderate the impact of shame on MDD. Interventions need to address shame memories
Simeon et al.[67]	46 participants with depersonalization disorder, 21 with PTSD and 35 healthy controls	Cross-sectional study	1) Dissociative Experiences Scale; 2) Cambridge Depersonalization Scale; 3) Toronto Alexithymia Scale; 4) Tellegen Absorption Scale; 5) Cognitive Failures Questionnaire; 6) Childhood Trauma Questionnaire	Higher absorption and cognitive failures scores were found in the DD and PTSD groups. Elevated alexithymia (DIF) were reported only in the DD group. Alexithymia-DIF was the only predictor of both DD and depersonalization scores. Finally, CTE and absorption predicted amnesia scores	1) The cross-sectional design that did not allow causal relations between constructs; 2) The self-report nature of measures (although they are well-validated instruments)	The link between depersonalization and alexithymia appeared to be specific rather than broadly related to early CTE or to trauma-spectrum psychopathology

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Author(s)	Sample	Study design	Psychometric and instrumental measurements	Main results	Limitations	Conclusions
Semiz et al.[69]	579 male patients diagnosed with APD	Cross-sectional study	1) Structured Trauma Interview; 2) Turkish version of the Dissociative Experiences Scale	CSA, physical abuse, neglect, and early separation from parents were more common among APD subjects than controls. APD group reported more dissociative symptoms and 50.4% reported pathological dissociation. Overwhelming childhood experiences of all four types were significant predictor of APD. CTE and comorbid features relevant to APD were linked to dissociation	1) It remains unclear whether these findings are specific to antisocial personality disorder; 2) It was not possible to control for the presence of comorbid Axis II and some Axis I diagnoses; 3) The use of retrospective reporting of childhood traumatic events further limits the generalization of the main findings	CTE are important components in the etiology of APD. Dissociative symptoms in patients with APD appear as a defense against significant childhood trauma and persist into adulthood
Riggs et al.[70]	80 inpatients	Cross-sectional study	1) Adult Attachment Interview; 2) Experiences in Close Relationships Scale; 3) Millon Clinical Multiaxial Inventory III; 4) Dissociative Experiences Scale; 5) Dissociative Disorders Interview Schedule – Self-Report Version	Personality dimensions were closely linked to self-reported romantic attachment style; fearful adults showed the most maladaptive personality profiles. Self-report dimensions of self and other contribute to different psychological dysfunctions. Adult Attachment Interview unresolved trauma was linked to dissociation and PTSD; unresolved trauma and loss contributed to schizotypal and borderline personality disorder scores as well	1) The comorbidity/prevalence of MDD should be taken into account when interpreting results; 2) The sample size did not allow to generalize findings; 3) Retrospective reports of childhood trauma and parent–child relationships may have introduced subjective biases; 4) Data collection did not permit the examination of temporal/causal relation between attachment/personality and psychopathology	Results partially supported theoretical predictions concerning distinct measures of adult attachment in the anlyzed sample

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Author(s)	Sample	Study design	Psychometric and instrumental measurements	Main results	Limitations	Conclusions
Mellman et al.[68]	83 inpatients	Prospective follow-up study	1) Clinician Administered PTSD Scale; 2) Initial Subjective Reactions Scale; 3) The Peri-traumatic Dissociation Scale; 4) COPE	At follow-up, 24% of the available 50 subjects met criteria for PTSD and an additional 22% met criteria for two of three symptom clusters. At follow-up, PTSD severity was independently predicted by early symptoms of elevated arousal and coping with disengagement	1) It is possible that the variation of these findings is related to the nature of the traumas; 2) It is possible that the impact of prior mood and anxiety disorders and prior trauma has been attenuated; 3) The sample was predominantly composed by Hispanic subjects	In the setting of severe injury, early manifestations of enhanced arousal and use of certain coping styles were associated with the risk of developing PTSD
Ogawa et al.[71]	168 young adults	Cross-sectional study	1) Pre-school Behavior Questionnaire; 2) Teacher Report Form; 3) The Youth self-Report; 4) Child Dissociative Checklist; 5) Dissociative Experiences Scale; 6) Life Events Inventory; 7) Adolescent Perceived Events Scale; 8) The Adolescent Life Stress scale; 9) The Adolescent Health Survey; 10) The Carey Infant Temperament Scale; 11) The Projected Self-Esteem scale; 12) Ainsworth Strange Situation; 13) Wechsler Adult Intelligence Scale	First, age of onset, chronicity and severity of trauma predicted dissociative symptoms. In addition, both the avoidant and disorganized patterns of attachment predicted dissociation. Childhood dissociation may be a more normative response to disruption and stress while dissociation in adolescence and young adulthood may be more indicative of psychopathology	1) The checklist measures of dissociation were not designed to detect dissociation; 2) The relatively small number of participants with clinical dissociation; 3) The preliminary nature of the present study findings; 4) Sexual abuse has been underreported as information to this regard was extremely limited	Dissociative behaviors is usually more frequent early in life and may gradually become more indicative of psychopathology with age

Note: Antisocial personality disorder (APD); childhood sexual abuse (CSA); childhood traumatic events (CTE); depersonalization disorder (DD); difficulty identifying feelings (DIF); early shame experiences (ESE); major depressive disorder (MDD); Parent Version (PV); post-traumatic stress disorder (PTSD); psychiatric conditions (PC); somatoform dissociative symptoms (SDS); Trauma-related alterations (TRA); traumatic memory (TM); traumatic events (TE); traumatic memory experiences (TME).

others [59] suggested the relevance of interpersonal traumatic experiences in determining higher maladaptive schemas (especially, in the domains of Disconnection and Impaired Autonomy) and subsequent higher psychopathological characteristics. The importance of interpersonal proximity as associated with specific neuropsychiatric conditions such as oppositional defiant and conduct problems was also stressed by longitudinal studies [60]. In addition, existing reports [61] suggested the variation with exposure to adversities of trauma-related alterations in neural organization. While some studies [62] focused on specific populations (e.g., dancers), other reports contributions [63] supported the importance of using dissociation measures to identify subgroups of patients with severe psychopathology or the relevance of specific factors such as cognitive profile [64], shame memories [65,66], alexithymia-difficulty identifying feelings [67], and early enhanced arousal or specific coping styles (based on a longitudinal follow-up study [68] in the development of psychopathological pathways related to traumatic experiences). Childhood experiences may be also considered as important com-

ponents of specific psychopathological conditions such as antisocial personality disorder [69], while unresolved trauma and loss may be frequently found in the history of individuals with schizotypal and borderline personality disorders [70]. Finally, there are studies reporting that dissociation gradually become more indicative of psychopathology with age [71].

Here, as follows we list different psychopathological conditions that are clinically associated with traumatic experiences.

First, *dissociative disorders* are, no doubt, the most important response to traumatic or overwhelming experiences during childhood and they have been carried out by individuals in order to attenuate psychological distress and promote coping and survival [16]. The dissociative psychopathology which is closely related to chronic developmental stress and traumatic experiences may be historically articulated in dissociative disorders which may have a fluctuating chronic course over years. Dissociative disorders have been first introduced by Janet and Freud when they initially described traumatic hysteria that included dissociative and amnesic phenomena [72]. Dissociation is the first human psychobiological process against trauma-related threats while maltreatment and complex traumatic experiences such as sexual or physical abuse, emotional maltreatment or unpredictable parenting are usually linked to the development of long-term dissociative reactions during childhood such as PTSD responses [73]. Importantly, alterations in self-regulatory processes, poorer impulse control, impairments in interpersonal relations, impulse and self-perception abnormalities may be all linked with trauma-related dissociation. The fundamental characteristic of dissociative disorders (dissociative amnesia, depersonalization, derealization, identity confusion, and identity alterations) is the disruption of one or more mental functions. Dissociative disorders are fundamental phenomena of dissociative psychopathology that may vary in terms of spectrum of severity [13].

In addition, evidence [74] reported that a traumatic reactive disorder related to trauma occurs with a prevalence above 20%. Although *PTSD* is usually considered a construct which is still under construction conceptually, it may be considered a trasversal diagnosis through the different contexts of the human activities [72]. PTSD has been separated in DSM-5 by the group of Anxiety Disorders and included in a new group named Trauma- and Stressor-Related Disorders [14].

One of the most relevant recognized pathways related to PTSD is the dissociative subtype of PTSD defined by symptoms of depersonalization and derealization together with other PTSD symptoms [75]. There are authors [76-78] suggesting that the dissociative subtype of PTSD ranges from 12% to 50% of PTSD cases. Subjects with the dissociative subtype of PTSD may develop ovewelming depersonalization and derealization and may endorse significantly childhood trauma and adult sexual trauma [79,80]. Kerig et al. [81] reported a higher prevalence rate (83%) of dissociative subtype for PTSD in young adolescents having troubles with the juvenile justice, and they also identified a three-factor dimension of post-traumatic dissociation including depersonalization/ derealization, amnesia, and loss of conscious control. In addition, these individuals may exert higher levels of avoidant and borderline personality disorder behaviors [79,80]. Beyond the classical definition of PTSD by DSM-5, ICD-11 describes two diagnostic entities with different symptom profiles defined as PTSD and complex PTSD. Interestingly, disturbances in Self-Organization, which affect emotional regulation, interpersonal relationships, and identity arising soon, repeatedly, and prolonged in time may be usually found in complex PTSD.

Chronic dissociative depression may be identified as a specific psychopathological construct that tends to have a earlier age of onset when compared to major depressive disorder representing a distinct psychopathological pathway related to traumatic experiences and dissociation [13,82-83]. Sar et al. [82] reported that relative to those with a major depression, individuals with dissociative depression were more likely to suffer from pervasive worthlessness and guilt, abnormally reduced concentration, suicidal behavior, loss of appetite, and weight alterations. Thus, chronic dissociative depression may be recognized as a more severe illness subtype relative to major depression without dissociative aspects.

Affect dysregulation may be considered another crucial psychopathological pathway related to the occurrence of traumatic experiences. Subjects suffering from affect dysregulation may be distinguished from those with bipolar disorder by the abrupt nature of affective changes occurring many times daily and having a very brief duration, with these patients that usually perceive the abnormal nature of their mood changes [13]. Patients with affect dysregulation are often misdiagnosed with a bipolar mood disorder or cyclothymic disorder according to the multiple fluctuations related to post-traumatic affect dysregulation. Importantly, there are also individuals with dissociative disorders that meet criteria for borderline personality disorder [84]. Evidence [13,85] suggested that among subjects with borderline personality disorder, over 70% suffer from a *dissociative disorder with borderline personality disorder* criteria usually reporting interpersonal aspects of dissociation. Symptoms of somatization and conversion may be also common among those with dissociative disorders with more than 25% of individuals with dissociation [86] and at least 50% of psychiatric inpatients [87] who reported having experienced

at least one conversion symptom lifetime. Patients with *dissociation and comorbid conversion symptoms* usually suffer from predominant somatic symptoms such as non-epileptic seizure, have more psychiatric comorbidity, childhood traumatic experiences, suicide attempts, and non-suicidal self-injury. However, dissociative disorders may even reach the severity of acute psychosis (*dissociative disorder with psychotic features*) [88] with the acute dissociative disorder that may clinically resemble a clinical condition of delirium, mania, or schizophrenic disorder given the existence of psychotic characteristics. Generally, palpitations, fainting, shaking, and depersonalization are very common during these episodes with patients that are very worried about the clinical manifestations of their dissociative episode. Another psychopathological pathway related to dissociative disorders is even *amnesia with fugue*. However, only a minority of fugue cases get a solitary diagnosis of dissociative fugue with the majority of cases involving dissociative fugue in the context of a chronic dissociative disorder [88]. Some authors [89,90] also proposed the existence of a *dissociative subtype of schizophrenia* with those having a positive history of childhood emotional abuse/maltreatment who tended to have more dissociative symptoms and more positive symptoms of schizophrenia and the subgroup with highest childhood sexual/physical abuse and physical neglect who tended to have more general psychiatric comorbidity, enhanced borderline personality characteristics, and more frequent somatic complaints [90]. Relevantly, dissociative disorders may also suffer from substance abuse (*the dissociative disorder subtype with substance abuse*) with dissociative conditions that may be observed in over 15% of individuals who suffer from substance abuse [90]. Most patients with dissociative symptoms initiate early to use substances, very frequently in early adolescence. A dissociative disorder may be predicted by suicide attempts, childhood emotional abuse, and female gender. Moreover, the comorbidity with migraine, attention deficit hyperactivity disorder, comorbid obsessive compulsive disorder may be also clinically observed [88] (Fig. 2).

Finally, according to a novel classification system initiated by National Institute of Mental Health with the aim to integrate diagnostic elements derived by neuroscience, cognitive sciences and other research areas con-

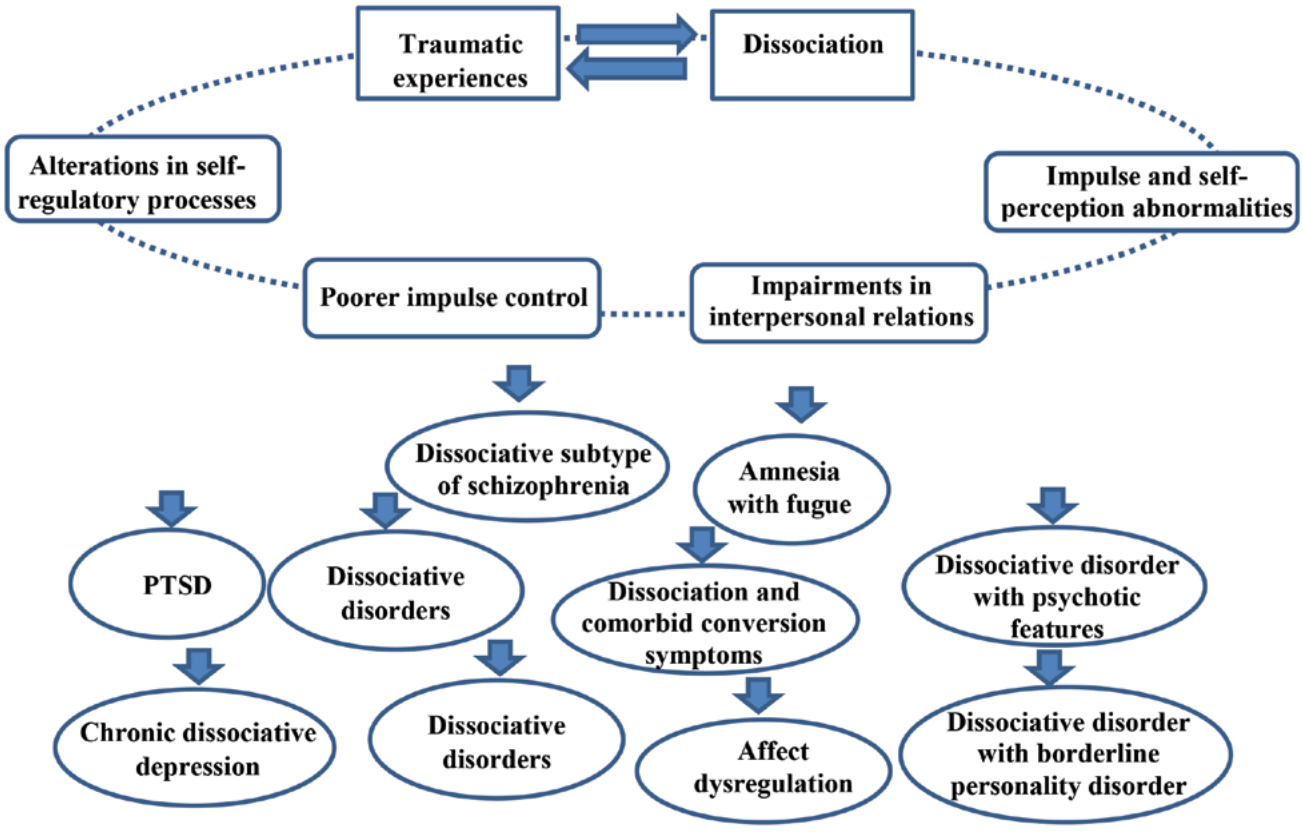

FIGURE 2. *Psychopathological pathways related to the exposure to tramatic experiences.*

tributing to new nosological information and promote a more personalized medicine for mental disorders, the Research Domain Criteria (RDoC) project proposed the following five domains for the area of trauma and dissociation: the systems with negative value, systems of positive valence, cognitive systems, social processes, and alert/regulatory systems [91,92]. According to RDoC criteria, new diagnostic groups might be identified based on emerging novel neurobiological correlates that will probably help clinicians to explore novel therapeutic and preventive strategies. To this specific regard, Weston[93] clearly proposed a new theoretical model of PTSD identifying the hyperarousal subtype based on the complementation of the symptoms with the neurobiological basis sustaining them according to RDoC criteria.

Conclusive remarks

As suggested by Cuijpers et al. [94], the careful identification of all the factors related to risk and resilience after exposure to childhood traumatic experiences is of critical importance for public health interventions. Future studies are required in order to understand the molecular pathways related to neural circuits disruption after early trauma exposure as well as the complex effects of psychopathological dysregulation related to traumatic experiences. These studies may shed light into the complex illness trajectories linking early stress in childhood to psychopathology in adulthood. Further evidence also need to investigate the impact of possible confounders as well as the combined effects at the epidemiological, biological, and epigenetic level on adult psychopathology including conditions associated with suicidal behavior and negative outcome in subjects with stress-related disorders [95-97]. Finally, screening strategies are needed in order to detect specific at-risk conditions, and given the early exposure to trauma help to better predict individual treatment response for patients population [98].

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Review

The biological correlates of childhood trauma in first episode psychosis

Sarah Tosato[1], Simona Tomassi[1]

[1] Section of Psychiatry, Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Italy

SUMMARY

Objective

To overview biological mechanisms connecting childhood trauma to the development of psychosis.

Methods

We reviewed the evidence regarding biological correlates associated with childhood trauma in individuals affected by first episode psychosis (FEP) in terms of: 1) Hypothalamic-pituitary-adrenal (HPA) axis & cytokines levels; 2) gene × environment interaction, epigenetic and gene expression modifications and 3) metabolic biomarkers.

Results

Childhood trauma and early psychosis even when explored separately were found associated with several biological correlates. Regarding the immune system activity, in terms of both HPA axis functioning and cytokines levels, FEP patients exposed to childhood trauma showed 1) a less reactive HPA axis, characterized by a blunted cortisol awakening response, and higher serum levels of Tumor necrosis Factor-α (TNF-α) and C-reactive protein (CRP) in comparison with patients without childhood trauma. Genetics and epigenetics were also proven significantly different in traumatized FEP in comparison with non-exposed individuals. Specifically, first 2) the Val/Val genotype at the Val158Met polymorphism in the COMT gene, the A allele at rs4713916 and rs9296158 single nucleotide polymorphisms (SNPs) and the TT homozygosis at rs1360780 SNP in the FKBP5 gene were demonstrated to be risk factors for psychosis in traumatized individuals. Second, childhood trauma in FEP was proven significantly associated with global DNA hypo-methylation and lower BDNF gene expression. Finally, regarding metabolic changes associated with childhood trauma in FEP 3) higher levels of glycated hemoglobin and higher c-peptide and insulin levels were proven in patients exposed to childhood trauma in comparison with those without childhood trauma.

Conclusions

This review has given evidence regarding associations between childhood trauma and its biological correlates in first episode psychosis. Nonetheless, future studies are warranted to investigate putative biological mediators and their temporal sequence in order to elucidate developmental trajectories.

Key words: childhood trauma, first episode psychosis, epigenetic, HPA, cytokines, metabolism

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Correspondence
Sarah Tosato
Section of Psychiatry, Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, piazzale L.A. Scuro 10, 37134 Verona, Italy

Conflict of interest
The Authors declare no conflict of interest

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Introduction

Childhood trauma is a complex phenomenon, significantly conditioned by bio-psycho-sociocultural elements. In Italy, almost one children out of 100 (9.5‰) is victim of maltreatments: among them, 6.9 and 4.2% refers physical and sexual abuse respectively, 13.7% reports psychological abuse, while 47.0% relates neglect, both physical and emotional[1]. The effects of childhood trauma can last a lifetime. Adults who were abused or neglected as children have a higher risk of perpetrating or being a victim of violence, becoming obese [2] or developing severe mental disorders, such

as schizophrenia [3,4]. In the general population, individuals recalling a history of childhood trauma show a threefold risk to undergo psychotic like experiences in their adulthood [5]. In turn, individuals affected by psychosis show an increased rate of childhood trauma up to the 47% of cases [4]. Specifically, 26, 39 and 34% of patients affected by psychosis refer sexual, physical and emotional abuse during childhood [6]. Female patients appear to be particularly vulnerable, showing the highest rates of sexual abuse (47.7%), and physical abuse (47.8%)[3]. Moreover, first episode psychosis (FEP) patients showed a two-fold higher prevalence (85.7 *vs* 38.7%) of childhood trauma when compared with healthy controls [7]. Severe sexual abuse was reported in 15.0-18.2% of FEP individuals, while severe physical abuse in 15.2-21.6% [8,9]. Indeed, childhood abuse has been associated with younger age of onset, earlier first admission, double hospitalization rate [4], more severe positive and dissociative symptoms [3], worse cognitive performance, lower quality of life and more deteriorated social-relational functioning [4].

Any reasonable theory that aims to explain how childhood traumatic experiences might favor later on the development of psychosis should account an integrated bio-psycho-social approach. Several paradigms have been developed focusing on diverse elements such as the stress response system, psychological elements, and environmental factors [10]. From a biological point of view, hypothalamic-pituitary-adrenal (HPA) axis functioning and cytokines levels, genetics, epigenetics, and proteomics (including biomarkers related to glucose metabolism) have been investigated to better understand the association between childhood trauma and psychosis.

The main aim of this narrative review is therefore to provide an overview of the potential biological mechanisms connecting the exposure to childhood trauma to the development of psychosis. We thus summarized the evidence related to specific biological correlates associated with childhood trauma in individuals affected by first episode psychosis. Specifically, we reviewed evidence on the role of 1) HPA axis functioning and cytokines levels, 2) gene × environment interaction, epigenetic and gene expression modifications and on 3) the levels of metabolic biomarkers within the association childhood trauma-psychosis.

Results

Hypothalamic-pituitary-adrenal (HPA) axis & cytokines levels

It has been clearly identified a key role for stress in the development and course of many psychiatric disorders, including psychosis. A dysfunctional activation of the immune system may in fact represent a potential biological mechanism connecting childhood trauma to psychopathology [11]. An altered HPA axis functioning has been found significantly associated with both childhood trauma and psychosis. HPA axis is in fact a key element of the body system that modulates the response to stress [12]: in physiological conditions, cortisol, which is the primary hormone released by the HPA axis in response to stress, functions to maintain homeostasis [13]. In case, however, of prolonged or abnormal stimulation this homeostatic mechanism may fail, resulting in increased levels of circulating corticosteroid hormones, due to an altered HPA cortisol-axis negative feedback mechanism and mediated, at least in part, by glucocorticoid receptor resistance. To date, our understanding about HPA axis functioning in FEP patients exposed to childhood trauma is hampered by mixed findings, possibly due to heterogeneous samples, different assay cortisol methodology (saliva or blood), as well as the broad definition of childhood trauma (subtype, timing, duration) [14]. HPA-axis dysfunction was proven associated to first episode psychosis itself. Specifically, HPA-axis hyperactivity, characterized by high cortisol levels in basal condition, and a blunted HPA axis response to stress (hypo-reactivity), have been both found to characterized psychosis [7,15-17]. This basal overactivity of the HPA axis in FEP patients was found in several studies, but not in all [7,15-17]. Moreover, in a recent meta-analysis [18], elevated blood levels of cortisol were demonstrated in individuals with FEP, providing further evidence for abnormal HPA axis function in early psychosis. Both HPA axis hyper- [19-21] and hypo-activation [12] and hyper- [22] and hypo-reactivity to stress [23, 24] have been significantly associated to childhood traumatic experiences. Regarding childhood trauma in FEP, a less reactive HPA axis, characterized by a blunted cortisol awakening response, might represent one of the biological mechanisms involved in the development of psychosis in individuals exposed to severe childhood trauma [25]. However, whether HPA axis dysfunction mediates the childhood trauma-FEP association or represents a trait of illness is still a matter of debate. Nonetheless, several findings [19-21] indicate that abnormalities in the stress response system, and the subsequent increased inflammation, originate in childhood and might be considered a 'biological scar' of the early exposure to high levels of stress [11].

Enhanced peripheral immune activation potentially plays a key role too in the pathogenesis of psychosis. An intricate network of interactions exists between the immune system and the central and peripheral nervous systems [26]. Inflammatory cytokines, including IL-1, IL-6 and TNF-α, represent the main mediators of this network. Cytokines are in fact responsible not only for the

organization of the cellular response to the pathogenic stimulus, but also for the behavioral changes necessary to healing. In physiological conditions, an acute stress activates the secretion of pro-inflammatory cytokines. The physiological cytokine-mediated pro-inflammatory response is temporary and strictly regulated by a balanced anti-inflammatory mechanism. Indeed, under normal conditions a neuro-immuno-endocrine anti-inflammatory response occurs. An adaptive behavioral response also takes place; it is usually temporary and placed under the control of CNS. Thus, a very complex, two-way neuro-immuno-endocrine interaction between the central and peripheral stress system and the immune axis takes place [27-29]. However, if the phlogistic stimulus becomes chronic and/or excessive it can lead to an out-of-control reaction of the inflammatory system, resulting in the development of immune-endocrine disorders (eg excessive production of proinflammatory cytokines and/or HPA axis malfunction) and contributing to the occurrence of non-functional behaviors. They therefore lose their adaptive purpose and sometimes become clinically relevant and attributable to psychiatric syndromes [26]. Cytokines are able to reach the brain through humoral, neural and cellular mechanisms [30], spreading the effect of peripherally produced cytokines on the CNS. Neurons, microglia and astrocytes, are therefore activated and an inflammatory state established. These neural inflammatory subjects, organized in complex systems, seem potentially involved in the development of psychiatric syndromes [31]. A meta-analysis of FEP studies [32] suggests the presence of an inflammatory syndrome in first episode psychosis, characterized by increased levels of IL-1α, IL-6, IL-12, IL-17, sIL-2R, interferon (IFN)-α, TNF-α, (TGF-α). Some cytokines (IL-1α, IL-6, and TGF-α) may represent state markers for acute exacerbations, and others (IL-12, IFN-c, TNF-α, sIL-2R) can be considered trait markers of psychosis [32]. Most interestingly, inflammatory markers were demonstrated particularly higher in those FEP patients who had also experienced childhood trauma [33,34]. Indeed, childhood trauma appears to be an independent risk factor for peripheral immune dysregulation and long-term, low-grade inflammation in adulthood [35]. A state of sustained peripheral inflammation follows exposure to childhood trauma [11], resulting in a chronic immune activation throughout adult life [21]. A recent meta-analysis [11] reported significantly higher levels of CRP, IL-6, and TNF-α in individuals exposed to childhood trauma, when compared with non-exposed controls. Diverse types of traumatic experience impacted differently on inflammatory markers' levels: increased TNF-α and IL-6 were found associated with physical and sexual abuse, while increased CRP levels appeared to be related to parental absence during childhood [11]. Cytokines levels in FEP patients traumatized during childhood were proven to differ significantly from those of both patients without childhood trauma [33,34] and healthy controls [34]. FEP patients with childhood trauma had significantly higher serum levels of TNF-α [33] and CRP [34] when compared with patients without childhood trauma. In particular, the association between childhood trauma and CRP was found to be specific for severe sexual abuse. Specifically, patients who had experienced severe sexual abuse showed higher levels of CRP when compared with both patients without such experience and with healthy controls [34].

Epigenetic modifications/gene expression

It has been demonstrated that childhood traumatic events may interact with genetic vulnerability or shape gene expression via epigenetic mechanisms, contributing to the development of psychiatric disorders [36,37].

Several studies have looked at G × E interactions as a putative missing link between childhood trauma and the development of psychosis. Specifically, several studies have focused on the effects of single nucleotide polymorphisms (SNPs) in the FK506 binding protein 5 (FKBP5) gene, finding that the A allele at two SNPs (rs4713916 and rs9296158) in the FKBP5 gene are a risk factor for psychosis in traumatized individuals [38]. Moreover, individuals who are TT homozygotes at the SNP rs1360780 in the FKBP5 gene and have been exposed to childhood trauma presented higher levels of positive psychotic experiences compared to the CC homozygotes [39]. Regarding the catechol-O-methyltransferase (COMT) gene polymorphism (Val158Met) [40], two studies found that Val/Val homozygotes had significantly higher levels of psychotic experiences after exposure to childhood trauma [41,42].

Epigenetic modifications, like cytosine residues methylation, are known to determine whether a DNA region is compacted and transcriptionally repressed/silent or open and transcriptionally active [43]; they regulate functional expression of genes by decreasing, silencing or increasing gene expression. Epigenetics, has been proven to participate in transducing environmental experiences in both genome and brain structure modifications, potentially underlining the association between childhood trauma and the development of psychosis [44]. Childhood trauma could thus influence gene expression and individuals' capacity of adaptation through epigenetic modifications [45]. Evidence concerning genome-wide methylation and gene expression modifications in FEP [46] shows a global DNA hypo-methylation in FEP patients when compared with controls [47], in line with available knowledge proving global DNA hypo-methylation in schizophrenia [48,49]. Moreover, genes related to transduction, RNA processing, lipid/glucose/protein metabolism, and mitochondrion functioning were prov-

en differently methylated or expressed in FEP patients when compared with healthy controls. In terms of gene expression profile, MPB, NDEL1, AKT1 and DICER1 were found hyper-expressed, while GCH1, DROSHA, COMT, and DISC1 resulted hypo-expressed in FEP patients in comparison with healthy controls. These genes and their proteins are all involved in a variety of CNS functions including neurodevelopment, plasticity and neurotransmission [50,51]. Such alterations could be considered both a direct (expression of a true biological difference) and an indirect (for example related to environmental exposures) manifestation of the psychosis. Childhood trauma per sé has also been proven associated to epigenetic and gene expression modifications in healthy individuals [46]. In terms of genome wide DNA methylation, genes related to central nervous system development [52,53], plasticity and degeneration [52,53], immune system and inflammatory response [53] were found differently methylated in healthy children and adolescents exposed to childhood trauma. When looking at target gene methylation related to childhood trauma in healthy subjects, SLC6A4, NR3C1, KITLG and OXTR [54] promoter regions were found hyper-methylated, while FKBP5 [55,56] and IL-6 [57,58] promoter regions and BDNF gene body [56] were demonstrated hypo-methylated in comparison to controls. Being methylation within promoter regions negatively correlated with gene expression, it is possible to speculate that childhood trauma leads to reduction in SLC6A4, NR3C1, KITLG and OXTR gene expression, favoring a dysfunctional serotonergic system (SLC6A4), an altered stress-reactivity (NR3C1, KITLG) and impaired social behavior and bonding (OXTR). In line with this hypothesis, healthy individuals with childhood trauma had reduced SLC6A4 gene expression [54], while no evidence is available demonstrating a reduction of NR3C1, KITLG or OXTR gene expression in association with childhood trauma. Given the reduced methylation within their promoter regions, it is also possible to hypothesize an increase in FKBP5 and IL-6 gene expression [59] in association with childhood trauma. Both genes encode proteins involved in the stress response system and their hyper-expression could favor a pro-inflammatory, stress-vulnerable phenotype. On the contrary, a gene is less expressed when hypomethylated in its body [60]. As mentioned above, BDNF gene was found significantly hypo-methylated within its body in healthy subjects with childhood trauma [56]; a reduced BDNF gene transcription could thus be a consequence. Despite the known impact of childhood traumatic experiences on FEP individuals [61] and the attention paid recently to epigenetics and gene expression, available studies relating to the epigenetic /gene expression modifications associated with childhood trauma in FEP patients were only three [33,62,63]. Out of them, one study investigated genome wide DNA methylation patterns, while the other two explored gene targets gene expression profile in FEP in relation to childhood trauma [33,63]. As reviewed before [46], the first study [62] indicates that childhood trauma, and specifically emotional abuse and total trauma score, entails global DNA hypo-methylation. However, as mentioned above, similar global DNA hypo-methylation has been also found in FEP patients [47] when compared with controls, not taking into account the presence of childhood trauma. This trauma-associated lower DNA methylation could have a functional relevance to gene regulation and/or be responsible for genomic instability, which has been previously observed in schizophrenia [49]. Further investigations are therefore required to elucidate whether the global hypo-methylation is to be considered as an epigenetic consequence of childhood trauma or a trait of psychosis [46]. The second study [33] found no differences in IL-1α, IL-1β, IL-6, IL-8, MCP-1, VEGF, EGF, INF-γ and TNF-α gene expression between patients with and without childhood trauma, while the third one [63] found a negative correlation between BDNF gene expression and the number of traumatic experiences. Reduced BDNF mRNA levels associated with childhood trauma in FEP [63] could result in altered neuroplasticity, since in this study FEP patients were also characterized by a smaller left hippocampal volume. However, the same study found no association between childhood trauma and BDNF gene expression in healthy controls [63]. Conversely, it was demonstrated that BDNF gene was significantly hypo-methylated within its body, and thus potentially reduced in its expression, also in healthy subjects with a history of childhood trauma [56]. Evidence on the topic appears inconsistent and it stands unclear whether the reduced BDNF gene expression is to be ascribable to a specific effect of childhood trauma per sé, independently from the presence of psychosis. Notably, there are not available replicated findings for methylation and childhood trauma neither in FEP, nor for gene expression and childhood trauma in both FEP and healthy individuals [46]. Large, well-designed case-control studies enrolling FEP subjects both with and without childhood trauma are warranted.

Metabolic dysregulation

Confirming the long-term effects of early life stress on the body, several studies [19] have linked childhood trauma to detrimental changes in physiological functions, including metabolism.

It is in fact worth mentioning that the stress system is closely interconnected with metabolism. HPA axis interacts with glucose metabolism hormones, like insulin, glucagon, gastric-inhibitor-peptide (GIP) and glucagon-like peptide-1 (GLP-1) [64] increasing the likelihood to develop metabolic dysfunctions. Insulin has an in-

hibitory activity on HPA axis, while glucagon, GIP and GLP-1 have an enhancing one, inducing the release of corticotrophin release hormone (CRH)/adrenocorticotrophic hormone (ACTH) [64]. Moreover, glucocorticoid hormones such as cortisol, stimulate gluconeogenesis and facilitate insulin-resistance, whereby chronic HPA axis activation might be at the bottom of the development of alterations in glycemic control [65]. In turn, an increase of fat mass due to glucocorticoids worsens insulin-resistance and glycemic control, triggering a vicious circle consisting of hyper-glycaemia, hyper-lipidemia and insulin-resistance [65]. The activation of the HPA axis activation may also induce alterations in the inflammatory response, which themselves could influence glucose metabolism. Individuals with schizophrenia are at higher risk of developing type 2 diabetes which is twice that of the general population [66]. Controversial results concerning insulin resistance have been reported in drug-naïve individuals with first-episode psychosis: some studies reported higher levels of insulin [67,68], insulin-resistance [67-69], increased levels of insulin-related peptides [70] as c-peptide [71] when compared to controls. In a large cohort of FEP patients recruited by our group decreased levels of glucagon and GLP-1 in compared to controls [72] have been found. Since visceral obesity can contribute to insulin resistance [73], several studies have investigated the role of appetite regulating hormones in FEP [74] reporting lower levels of leptin in drug-naïve FEP patients compared to controls. Taken together, this evidence suggests that other factors, a part from antipsychotic medications, can play a role in the metabolic alterations observed at psychosis onset. Among these, a possible role in the genesis of metabolic alterations could be covered by childhood trauma since it increases the risk for the onset of both psychosis and metabolic dysfunctions [5,75]. Individuals exposed to child sexual and physical abuse are in fact more likely to be obese or to show three or even more symptoms of metabolic syndrome when compared with non-victims [75]. Evidence suggests that individuals who reported an exposure of childhood trauma had an increased risk of the 32% to develop later in life type 2 diabetes [76] and of the 20-50% to develop obesity [77]. Furthermore, individuals with childhood trauma have decreased HDL and increased LDL levels with lower HDL/LDL ratio [78,79], higher triglyceride levels [80], reduced T3 levels and abnormal metabolism of thyroid hormones [81], and higher prevalence of metabolic syndrome [78,82] in later life. To date, evidence whether childhood trauma is involved in the development of abnormal glucose metabolism in FEP is very limited. Only two studies [83,84] have so far explored this relationship. The first one found [83] higher levels of glycated hemoglobin in FEP patients who were physically abused during childhood compared to those were not. The second one found that c-peptide and insulin levels are higher in patients exposed to childhood trauma, suggesting that hyperinsulinemia occurs early in the course of psychosis [84]. These findings underline the importance of monitoring metabolic alterations from the onset, especially in those patients who report childhood trauma, in order to carry out therapeutic interventions aimed at recovering from the negative outcomes of both hyperinsulinemia and trauma. It is still unclear to date whether markers related to glucose metabolism may be used to prevent treatment-induced weight gain in FEP patients [85].

Conclusions

Although evidence highlights a causal relation between childhood trauma and biological maladjustment in later life, the precise developmental trajectories and their temporal coincidence have not been elucidated yet[14].

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Review

Early traumatic experiences and eating disorders: a focus on the endogenous stress response system

Francesca Marciello[1], Alessio Maria Monteleone[2], Giammarco Cascino[1,2], Giuseppina Patriciello[2], Francesca Pellegrino[2], Gianmarco Fiorenza[1], Palmiero Monteleone[1]

[1] Department of Medicine, Surgery and Dentistry, "Scuola Medica Salernitana", University of Salerno, Salerno, Italy; [2] Department of Psychiatry, University of Campania L. Vanvitelli, Naples, Italy.

SUMMARY

Exposure to trauma during childhood is believed to be a major risk factor for lifelong psychiatric disorders, including eating disorders (EDs). Moreover, both an association between stressful life events and the onset/maintenance of EDs and higher presence of traumatic experiences in people with EDs have been documented. The aim of this review was to summarize the current knowledge concerning mechanisms involved in the connection between early trauma exposure and the risk to develop an ED by focusing on body stress response system. Several researches confirm that childhood trauma impairs the biological response to stress so dysregulations of the activity of the hypothalamic-pituitary adrenal (HPA) axis have been proposed as one of the main mechanisms underlying the early trauma-related risk for EDs across the life span. The data presented in this review support the existence of a "maltreated ecophenotype" in EDs characterized by specific clinic and neurobiological features resulting from early stressful environmental experiences. This concept may have important implications in treatment programming for such a type of patients.

Key words: eating disorders, anorexia nervosa, bulimia nervosa, trauma, stress response, hypothalamic-pituitary-adrenal axis

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Correspondence
Francesca Marciello
Department of Medicine, Surgery and Dentistry, "Scuola Medica Salernitana", University of Salerno, Salerno, Italy
Tel. +39 089 672833
E-mail: francescamarciello81@gmail.com

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Introduction

Existing literature has widely documented that exposure to childhood maltreatment increases the risk for development of different psychiatric disorders, including mood disorders, anxiety disorders, psychosis, alcohol and drug use disorders, disruptive and antisocial behavior disorders and eating disorders (EDs) later in life [1,2]. On the other hand, epidemiological research has suggested that the onset of psychiatric disorders across the life course is associated to adverse childhood experiences in nearly a third of cases, underscoring the public health significance of that exposure [3-5]. The reported association of childhood maltreatment with different psychiatric disorders suggests that early maltreatment can be considered a non-specific risk factor for psychopathology.

Anorexia nervosa (AN) and bulimia nervosa (BN) are complex psychiatric disorders predisposing to several severe medical and psychological complications associated with high morbidity and mortality. There is a general agreement on considering behavioural anomalies of EDs as secondary epiphenomena to a more profound psychopathological core, defined by excessive concerns about body shape and weight [6]. Thus, the core psychopathology of these disorders is characterized by a pathological fear of weight gain and alterations in the perception of body shape, thus individuals develop aberrant eating behaviors aiming at maintaining

a low body weight. In particular, subjects with AN restrict food intake and/or perform physical hyperactivity in order to obtain and maintain a low body weight, although in some cases binge eating followed by compensatory purging or non-purging behaviors also occurs. For this reason, two types of AN are identified: the AN restrictive subtype (ANR) and the AN binge-purging subtype (ANBP) [7]. BN, instead, is characterized by binge eating episodes followed by compensatory behaviors such as self-induced vomiting, misuse of laxatives and diuretics, prolonged starvation and restriction of food intake.

Although a conclusive etiopathogenesis of EDs is still unknown, it is widely acknowledged that biological, sociocultural and psychological factors likely influence their development, progression and outcome. Moreover, an association between stressful life events and the onset/maintenance of EDs has been clearly demonstrated [8-11] and individuals with EDs have been shown to have experienced greater adversity over their life course. For instance, case register studies have identified specific associations between later AN diagnosis and obstetric complications such as anxiety during pregnancy, pregnancy complications, childbirth complications, infant parameters/prematurity [12,13]. Moreover, during childhood, distinct types of child maltreatment, such as sexual, physical and emotional abuse or neglect, traumatic loss, and interpersonal stressors have been associated to both the onset and the maintenance of many EDs [2,14,15].

In this review we summarize the current knowledge suggesting potential mechanisms moderating the relationship between early trauma exposure and the risk to develop an ED by first describing one of humans' basic functions: response to stressors. Moreover, we will present evidence that a "maltreated ecophenotype" can be proposed for people with EDs.

Biological mechanisms regulating the body stress response

Body response to real or perceived environmental stressors is regulated by an endogenous biological system, which includes the sympatho-adreno-medullary (SAM) system and the hypothalamic-pituitary-adrenal (HPA) axis.

The SAM component of the stress response provides rapid physiological responses to potentially dangerous situations, which are responsible for the increase in heart rate and blood pressure, redistribution of blood flow to the brain and major muscle groups, and a decrease in vegetative function referred to as the "fight of flight" response [16]. The reaction of the HPA axis to stress consists in a slower, sustained, and amplified physiological response through the synthesis and secretion of glucocorticoids from the adrenal cortex. Glucocorticoids increase gluconeogenesis and lipolysis, inducing mobilization of fuel from liver and from white adipose tissue in order to provide the energy necessary to cope with the stressor [17]. Moreover, glucocorticoids exert a negative feedback on the HPA axis activity favouring the termination of the stress response. This feedback limits the time of tissue exposure to glucocorticoids, minimizing their catabolic, lipogenic, anti-reproductive and immunosuppressive effects [18,19].

The hypothalamic paraventricular nucleus (PVN) has a key role within the circuits regulating the endogenous stress response, since it integrates signals coming from brainstem (nucleus of the solitary tract) and forebrain limbic structures (prefrontal cortex, hippocampus, and amygdala), which are activated in response to threats to physiological homeostasis or psychogenic stressors, respectively [20]. PVN neurons lead to catecholaminergic stimulation of peripheral tissues, via the sympathetic nervous system, inducing the release of catecholamines into systemic circulation by the adrenal medulla. Moreover, PVN neurons release corticotropin-releasing hormone (CRH) and arginine vasopressin from their terminals in the median eminence into the portal circulation. CRH stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior hypophysis into systemic circulation, and ACTH stimulates the synthesis and secretion of glucocorticoids from the adrenal cortex.

The hippocampus, via projections to the PVN nuclei in the hypothalamus, has an inhibitory role on the HPA axis activity, intervening in the glucocorticoid-mediated termination of the endogenous stress response [20].

Childhood maltreatment and HPA axis dysregulation in mental disorders

Understanding the processes and mechanisms that contribute to the development of mental disorders in maltreated children appears to be an essential challenge of research in order to implement efficient interventions for both prevention and treatment of psychopathological disorders.

The biological background through which trauma exposure in the childhood may predispose to the development of psychiatric disorders later in life is still unknown. In last decades, scientific research has made enormous strides in trying to clarify the potential neurobiological consequence of childhood adverse experiences. A potential picture emerging involves the relationship between early traumatic events and alterations in stress-susceptible brain regions leading to long-lasting dysregulation in the neuroendocrine stress response system [21,22]. In particular, the role of the HPA axis has

been widely studied as a key determinant of psychiatric disorders onset associated with childhood trauma. Indeed, exposure to early adversities is considered a major determinant for enduring alterations of the HPA axis functioning leading to an increased sensitivity for the development of trauma-related symptoms [23,24]. The hypothesis is that the childhood trauma-related alterations of HPA axis functioning reflects aspects of a biological pathway that may contributes to psychopathological dimensions in adulthood.

Recent studies have attempted to clarify how the human endogenous response system reacts to early life stressors reporting long-lasting neurobiological modifications. In particular, most studies have focused on the epigenetic processes of DNA methylation (i.e. the chemical modification of DNA based at CpG islands, close to or within gene promoters) and has explored alterations in HPA axis activity in response to changes in stress-related genes' methylation levels. In fact, regards DNA methylations levels, specific CG sites within the NR3C1 exon 1F were found positively associated to childhood emotional abuse severity. Since this was associated to higher basal HPA axis activity, authors suggested that it may reflect an acquired glucocorticoid receptor resistance [25]. Therefore, early life experiences can influence stress sensitivity through epigenetic changes in stress-related genes, which may explain why some genetically at-risk individuals are more susceptible to some types of stress-reactive psychopathologies [26].

In addition, Teicher and Samson [27] have suggested that a developmental phenotype, the "maltreated ecophenotype", may result from structural and/or functional alterations in the brain as a consequence of early stressful environmental experiences. It has been reported that adults with a history of maltreatment had smaller hippocampi [21] and variations in the size of the amygdala, depending on the timing of stress exposure [21,28]. Furthermore, frontal cortical regions and the anterior cingulate cortex volumes are reduced in individuals with a history of maltreatment. This may contribute to the impairment in the regulation of the endogenous stress response [29].

A controversy still exists with respect to the direction of trauma-induced changes in HPA axis functioning, since both increased and decreased HPA axis activity has been described in individuals exposed to early maltreatment [30,31]. Indeed, a history of childhood maltreatment has been associated with HPA axis hyperactivity in subjects who developed depression or anxiety in adulthood as well as in healthy individuals. Therefore, higher circulating cortisol levels, enhanced cortisol awakening response (CAR), increased adrenocorticotropic hormone (ACTH) and cortisol responses to psychosocial stress or endocrine challenges (i.e. dexamethasone suppression test, DST) have been described in populations characterized by the presence of traumatic events in early life age [31-39]. The biological explanation of these findings could be that chronic hyperactivation of the stress system is related to hypersecretion of CRH by the hypothalamus and ACTH hypersecretion by the pituitary, resulting in higher circulating cortisol levels and to an "insensitive" negative glucocorticoid feedback of the HPA axis loop.

In contrast, other authors were in favor of a HPA axis hypoactivity in response to childhood traumatic events in psychiatric populations, reporting lower circulating cortisol levels and blunted cortisol stress responses to psychosocial stress or endocrine tests (DST, CRH test) in psychiatric patients with a history of childhood maltreatment [40-45]. This diminished activity could represent a compensatory physiologic adaptation possibly related to a negative feedback hypersensitivity of glucocorticoids or a long-lasting glucocorticoid catabolism drop leading to higher active cortisol persistence in liver and kidney without elevation in the periphery [46].

A significant factor modulating the impact of childhood maltreatment on future HPA axis activity may be its exact timing, suggesting a degree of developmental programming through glucocorticoid signaling, that is childhood traumatic experiences are probably associated with a differential impact on HPA activity according to the specific developmental period of exposure. Most researches, instead, proposed that the opposite polarities of HPA axis dysregulation could be explained by the time since the trauma exposure [47]. In fact, recent trauma exposure has been related to an enhanced HPA axis activity whereas HPA axis hypoactivity has been associated with remote trauma exposure [46]. As a matter of fact, children (8-12 years old) with aggressive behavior and personal history of trauma exhibited enhanced cortisol reactivity to laboratory stress [48] that, instead, resulted reduced in female youths (12-16 years old) exposed to childhood maltreatment [49,50]. Also, different types of childhood trauma have been related to distinct anomalies in HPA-axis functioning [51]. Finally, a dose-dependent effect of traumatic experiences on different measures of HPA axis activity, such as hair cortisol, salivary cortisol, CAR, has been described by some the authors, suggesting a higher impairment of HPA axis functioning with increasing traumatic load [47,52-55].

Childhood maltreatment and eating disorders

Early maltreatment has been found significantly more frequent in people with EDs than in general population [2,8,56,57]. The overall odds of having an ED has been estimated to be 3.21 time higher (95% CI [2.29, 4.51], p = 0.001) in individuals reporting a childhood trauma [2]. A recent meta-analysis found that the prevalence of childhood maltreatment was higher in each type of EDs

relative to both healthy controls and psychiatric control groups [57]. Moreover, current literature suggests that the experience of distinct forms of childhood maltreatment is differentially associated with different EDs [59-62].
Higher levels of childhood trauma have been found to be associated with higher levels of ED symptoms and lower daily functioning, and this association seems to be independent from psychiatric comorbidities [63]. Moreover, a significant dose-response effect between the number of experienced trauma and ED symptoms severity has been demonstrated [63]. Finally, compared to ED patients without a history of childhood trauma exposure those who were exposed to early traumatic events have been shown to exhibit a higher drop-out rate from psychotherapies [64] as well as a poorer response to cognitive behavioral therapy at 3-year follow-up [65], although this response has been found to be similar at 1-year follow-up between AN patients with or without childhood sexual abuse [66].

HPA axis activity in EDs

HPA axis and, in particular cortisol, have been the focus of an extensive research in EDs [67]. Briefly, almost all studies agree in indicating that subjects with AN have elevated basal or mean daily cortisol levels [68] due to the well-known effects of starvation and weight status on HPA axis functioning [69], whereas more variability exists in results on basal and mean daily cortisol levels in women with BN [68]. In fact, biological mechanisms underlying cortisol alterations in BN are less clear, although several studies suggested that binge-purging episodes may cause elevated basal and mean daily cortisol levels [70,71]. However, when the HPA axis activity has been studied by dynamic measures, such as the CAR, controversial findings have emerged. As a matter of fact, some studies showed that subjects with AN had an enhanced CAR compared to BN ones and controls [72] whereas others reported no significant differences among groups [73]. Another line of research has focused on cortisol reactivity to physical and psychosocial stressors in order to explore the reactivity of the of HPA axis to an acute stress. These studies have suggested the occurrence of both a blunted or an enhanced or a normal HPA axis reactivity to stressor exposure [74,75]. So additional research is needed to verify which variables could explain those discrepancies, and, in this line, recent studies have explored the impact of childhood maltreatment on HPA axis activity in people with EDs.

Early traumatic experiences and HPA axis functioning in EDs

In order to assess the HPA axis functioning in maltreated subjects with EDs, some authors have investigated the cortisol response to the dexamethasone suppression test (DST). Basurte et al. [76] found a significant relationship between cortisol suppression to low-dose (0.5 mg) DST and traumatic history in subjects diagnosed with ED. Similarly, Díaz-Marsá M et al. [77] reported that cortisol suppression to very low dose (0.25 mg) DST was significantly correlated with intensity of childhood traumatic experiences highlighting a hypersensitive HPA axis response to DST in maltreated ED subjects. As for BN, Yilmaz et al. [78] have shown no differences in cortisol suppression following a DST in bulimic patients with or without a history of childhood traumatic event and reported that Childhood Trauma Questionnaire (CTQ) scores were not associated with cortisol levels following DST. Cortisol response to oral administration of the partial 5-HT agonist meta-chlorophenylpiperazine (m-CPP) was studied in bulimic women in relation to the presence of childhood abuse: BN individuals reporting childhood abuse showed a decreased plasma cortisol response to mCPP than normal eater non-abused women [79].
Several studies have been conducted in order to examine the effect of childhood trauma experiences on HPA axis activity in ED by measuring salivary CAR. Monteleone AM et al. [80] reported that non-maltreated women with AN exhibited an enhanced CAR compared with controls and non-maltreated BN while subjects with AN or BN with positive history of childhood trauma exhibited statistically significant blunting of CAR than non-maltreated groups. These findings support the hypothesis that malnutrition and childhood trauma exert opposite effects (increase/blunting) on CAR in AN. Evidence for a dose-dependent effect of the traumatic load on HPA axis in women with ED were described [52]. In fact, AN and BN subjects with history of early trauma exhibited a progressive impairment of CAR with increasing the number of reported trauma. More importantly, that study showed that although significant negative correlations emerged between the overall cortisol secretion at awakening and the different types of childhood trauma such as emotional neglect, emotional abuse, physical neglect, physical abuse and sexual abuse, those correlations disappeared when a multiple regression analysis, including the number of trauma each patient was exposed to, was run. Indeed, only the number of experienced trauma persisted significantly and negatively associated to the CAR, suggesting that the number and not the type of childhood trauma is a major determinant of the impaired CAR in adult ED patients.
The effects of early trauma on HPA response to an acute psychosocial stress were also investigated in AN women with history of childhood maltreatment [81]. A blunted cortisol response to the Trier Social Stress Test (TSST) was detected in AN women exposed to childhood trauma as compared to both healthy controls and

non-maltreated AN women. Moreover, Mal AN women, compared to the other two groups, displayed a significantly reduced overall cortisol increase after the TSST, but a similar amount of the overall cortisol production. Since the overall cortisol increase is an index of the sensitivity of the HPA axis to a challenge test, those results suggest that childhood trauma exposure has detrimental effects on the HPA axis reactivity to a psychosocial stressor in adults with AN.

The diminished cortisol response to an acute psychosocial stressor in adult women with AN reporting childhood maltreatment is not easy to explain, although some hypotheses have been proposed [81]. The first one suggests that, according to the allostatic theory [82], a prolonged hyperstimulation of the HPA axis, due to repeated stressful events during early development, may lead to a state of chronic HPA axis hypoactivity and/or hypo-reactivity. Alternatively, since a specific deficit in social information processing in maltreated children has been proposed [83], it has been proposed that such a deficit may be responsible for a hypo-activation of the HPA axis in maltreatd AN women during the TSST, which specifically requires the use of this ability.

Taken together, all these studies suggest that exposure to childhood maltreatment may be associated with long-lasting neuro-endocrine modifications, which may account for its increasing risk for ED psychopathology.

Clinical implications and conclusions

It seems likely from the above that exposure to trauma in the childhood may be responsible of long-lasting effects on the activity of the HPA axis, which could represent the biological background of an intrinsic vulnerability to deal with potential stressful life events favoring the development/maintenance of an ED. Obviously, other risk factors likely interact with this vulnerability to precipitate or maintain an ED. Anyway, the data presented in this review support the existence in EDs of a "maltreated ecophenotype" characterized by specific clinic and neurobiological features. This may have consequences on the treatment programming for those patients. Indeed, although there are few studies in literature and the results are not really consistent, it seems that childhood trauma exposure has an impact on the outcome of psychotherapeutic interventions in people with EDs. Calugi et al. reported that the 6- and 12-month clinical outcomes of an enhanced-cognitive behavioural therapy (CBT) did not significantly differ between adult AN women with childhood sexual abuse and those without such an abuse [66]. Instead, another research group has recently reported that ED patients with childhood physical abuse had not only a more complex clinical presentation at admission but also lower ED psychopathology improvement and especially lower comorbidity remission three years after completion of a CBT programme compared to patients without a history of abuse [65]. Furthermore, dropping out for treatment occurred more rapidly in patients with abuse than in those without abuse, and the time to drop-out resulted even shorter in those patients who have experienced both abuse and neglect in their childhood. These data are in line with a previous study showing a dose-dependent effect of the traumatic load on the drop-out from psychotherapeutic treatment in BN with an increasing dropping-out as the number of childhood trauma increased [64].

These findings let us to suggest a lower efficacy of the current therapies primarily focused on ED symptoms in the presence of an history of childhood maltreatment and corroborate the importance of an integrated approach for the treatment of people with EDs especially in the presence of a childhood maltreatment history. In particular, it may be important to extend intervention strategies beyond ED core symptoms, focusing on the person's self-esteem development, abilities to recognize inner body states and emotions and on their mediating role between childhood maltreatment and ED symptoms.

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Review

Metabolic dysfunctions in people with post-traumatic stress disorder

Francesco Bartoli[1,2], Cristina Crocamo[1], Giuseppe Carrà[1-3]

[1] Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy; [2] Department of Mental Health & Addiction. Bassini Hospital. ASST Nord Milano, Italy; [3] Division of Psychiatry, University College, London, UK

SUMMARY

Objectives

The association between post-traumatic stress disorder (PTSD) and metabolic dysfunctions has attracted growing attention in recent years. Understanding and identifying common inflammatory and neuroendocrine mechanisms can help clinicians to improve the treatment and prognosis of these co-occurring conditions.

Methods

We conducted an overview, summarizing biological mechanisms and related biomarkers underlying the relationship between PTSD and metabolic dysfunctions

Results

Evidence suggests that PTSD may be associated with metabolic abnormalities. Metabolic syndrome in PTSD may impact both cardiovascular health and central nervous system functions. The role of traumatic events in influencing inflammatory and immuno-metabolic systems seems supported by available studies. Exposure to trauma may determine neuroendocrine responses and long-lasting changes in the regulation of the hypothalamic-pituitary-adrenal axis, affecting its physiological activity

Conclusions

Dysfunctional adaptation to stress may increase the vulnerability to metabolic abnormalities which, in turn, may favor the occurrence of psychopathological features after traumatic experiences. Approaching PTSD as a systemic condition by assessing, monitoring, and treating metabolic variations may lead to a significant improvement in its management and prognosis. Further research is needed to test novel treatments for PTSD, targeting neuroendocrine and immune-metabolic systems.

Key words: PTSD, metabolic, trauma, neuroendocrinology, inflammation, biomarkers

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Correspondence
Francesco Bartoli
Department of Medicine and Surgery, University of Milano-Bicocca, Piazza dell'Ateneo Nuovo 1, 20126, Milan, Italy
E-mail: francesco.bartoli@unimib.it

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Introduction

Posttraumatic stress disorder (PTSD) is a mental health condition related to the exposure to traumatic events and characterized by different post-traumatic symptom clusters, including intrusion symptoms, avoidance of trauma-related stimuli, negative changes in cognitions and mood, alterations in arousal and reactivity [1]. These symptoms are associated with significant distress and functional impairment. Data from 36,309 adults in the 2012-2013 National Epidemiologic Survey on Alcohol and Related Conditions-III, showed past-year and lifetime prevalence rates of 4.7 and 6.1%, respectively, with higher rates among females and younger subjects [2]. A comprehensive epidemiological study based on participants from the Environmental Risk Longitudinal Twin Study, a population-representative cohort of 2232 children born in England and Wales in 1994-95, found that about one third of participants reported trauma exposure and 7.8% experienced PTSD by the age of 18 years [3]. Recently, there has been consid-

erable attention on the relationship between metabolic dysfunctions and mental disorders [4], including PTSD that may represent a risk condition in terms of metabolic and cardiovascular health [5 6]. Subjects with a history of trauma have higher risk of heart failure, angina pectoris, and stroke [7]. Meta-analytic data pointed that PTSD was independently associated with increased risk for incident coronary heart diseases, recurrent cardiac events, and mortality [8,9]. An increasing body of literature actually suggests that the effects of traumatic stress equally impact on both physical and psychological health and should be considered a major clinical challenge given this dual perspective [10]. Metabolic changes observed in PTSD, such as hypertension, dyslipidemia, and obesity, may be the expression of an individual pattern of increasing sensitivity to environmental load [10], with this complex phenotype emerging from interactions among genetic, environmental, and biological factors [11]. Along with healthy risk behaviors, underlying biological mechanisms linking traumatic experiences and PTSD to metabolic abnormalities have been proposed, possibly including an increased autonomic nervous system activity, dysfunctions of the hypothalamic-pituitary-adrenal (HPA) axis system, and a systemic low-grade inflammatory state [11-13]. In this overview, we summarize epidemiological data on the association between metabolic disorders and PTSD, analyzing the potential biological vulnerability underlying this relationship.

PTSD and metabolic disorders

Although a large body of literature is available on the increased vulnerability to metabolic abnormalities in various mental disorders [4 14-17], there are fewer studies exploring this issue in PTSD. Metabolic syndrome is characterized by a cluster of metabolic abnormalities and cardiovascular risk factors. It is defined by the occurrence of at least three out of five conditions, including waist circumference ≥ 102 cm in men and ≥ 88 cm in women (with cut-offs varying according to geographical area and population), fasting serum glucose ≥ 100 mg/dl, serum triglycerides ≥ 150 mg/dl, high density lipoprotein (HDL) cholesterol level < 40 mg/dl in men and < 50 mg/dl in women, and blood pressure ≥130/85 mmHg [18]. A body mass index > 28.8 can be used as a substitutive criterion when information on abdominal circumference is not available [19,20]. Metabolic syndrome has attracted increasing attention in PTSD, even if most of studies have been conducted on war veterans [21-23], with less data available from community samples. Findings from meta-analytic studies, estimated significant associations of PTSD with both metabolic syndrome and obesity [24,25]. The prevalence of metabolic syndrome is estimated between 32.1 and 45.6%, with high rates also considering relevant subcomponents, i.e., abdominal obesity (29.7 to 69.0%), hyperglycemia (18.8 to 55.6%), hypertriglyceridemia (12.2 to 81.9%), low high density-lipoprotein-cholesterol (26.4 to 67.0%), and hypertension (67.9 to 84.8%) [26]. Prospective data analyzing the longitudinal association between PTSD symptoms and metabolic syndrome are also available. In 1,355 male and female U.S. Army or Marine Corps veterans, military deployed to the wars in Iraq and/or Afghanistan, cross-lagged panel models estimated that PTSD severity predicted subsequent increases in metabolic syndrome severity, whilst metabolic syndrome did not predict subsequent PTSD symptoms [27]. Metabolic syndrome in PTSD may impact also central nervous system (CNS). A neuroimaging study, based on 274 US military veterans, estimated that PTSD predicted metabolic syndrome which, in turn, was associated with reduced cortical thickness [28]. In particular, the authors found an association between metabolic syndrome and cortical thickness in: (a) bilateral temporal lobe, including temporal pole, fusiform gyrus, and insula, and extending into occipital cortex (left hemisphere) and orbitofrontal cortex (right hemisphere); (b) bilateral precuneus, posterior cingulate, calcarine, and occipital-parietal cortex; and (c) right rostral anterior cingulate cortex and central sulcus/postcentral gyrus. In addition, data from 204 male veterans aged 55-89 showed that veterans with metabolic syndrome may have poorer performance on tasks of executive function and immediate verbal memory regardless of PTSD status [29].

High rates of metabolic dysfunctions in PTSD increased the interest on possible mechanisms underlying this relationship that seems determined by three possible interconnections. First, lifestyle and health risk behaviors or specific treatments for PTSD may explain metabolic dysfunctions observed in PTSD. Several health risk behaviors, including poor diet, sedentary lifestyle, and smoking, may contribute to the increased risk of cardiovascular and metabolic disorders [30]. On the other hand, physical exercise seems to improve, along with individual metabolic health, also PTSD symptoms [31]. In addition, possible metabolic effects of treatments should be taken into account. Antidepressants are effective in PTSD [32], but they may be associated with weight gain [33]. Moreover, the off-label use of antipsychotics in PTSD does not seem rare [34,35] and antipsychotic-induced metabolic side effects [36,37] may at least partly explain the greater likelihood of weight gain, hyperglycemia, and dyslipidemia in PTSD. Nevertheless, Weiss et al. [38] highlighted that the association between current PTSD and metabolic syndrome seems independent to the use of antipsychotic drugs. It should be noted that stressful life events themselves may represent indicators of poor metabolic health, being associated with insulin resistance, obesity, and dyslipidemia [39]. It seems plausible to

hypothesizing a role of biological vulnerability to stress that may determine both the likelihood of developing PTSD and metabolic dysfunctions after the exposure to traumatic experiences. Metabolic syndrome might thus represents the consequence of individual neuroendocrinal adaptations to chronic stress [40].

Biological and neuroendocrine mechanisms underlying metabolic dysfunctions in PTSD

Available clinical and translational data seem to support the notion that PTSD itself is a metabolic disorder and suggest that dysfunctions of the inflammatory responses may be the common underlying mechanism [41]. Abnormalities involving neuroendocrine and inflammatory systems in PTSD seem similar to those occurring in metabolic disorders, such as metabolic syndrome, obesity, and diabetes [41]. In particular, increasing evidence has supported the hypothesis that traumatic events may be associated with a pattern of immune activation and inflammatory markers that may explain immunometabolic abnormalities in subjects with PTSD [11-13]. A relatively recent systematic review and meta-analysis [42] highlighted that several inflammatory cytokines are increased in subjects with PTSD. In particular, data showed that interleukin (IL) 6 (standardized mean difference [SMD]: 0.88), IL-1β (SMD: 1.42), and interferon γ (SMD: 0.49) levels in individuals with PTSD were higher than in healthy controls. In addition, subgroup analyses based on subjects who were not receiving any treatment, estimated higher tumor necrosis factor α (TNF-α) levels (SMD: 0.69) in PTSD subjects. Cytokines levels in PTSD were increased also after excluding individuals with co-occurring major depressive disorder. This is worth of mention considering that subjects with co-occurring PTSD and major depressive disorders, are generally considered at higher risk of metabolic disorders [43]. Consistently, the possible role of chronic low-grade inflammation as a potential target of PTSD treatment or biomarker of stress-related disorders, has been analyzed. In a large prospective study on war zone-deployed US Marines [44], the authors found that baseline plasma C-Reactive Protein (CRP) levels were significant predictors of post-deployment PTSD-related symptoms scores, after adjusting for relevant covariates. In particular, each 10-fold increment in CRP concentration was associated with an OR of 1.51 of any PTSD symptoms. Interestingly, the relationship between traumatic experiences and inflammatory biomarkers seems transdiagnostic. A previous meta-analysis [45], including 36 independent samples and based on 14,991 participants, showed that trauma exposure was positively associated with CRP, IL-1β, IL-6, and TNF-α, whereas no association was found for fibrinogen, IL-2, IL-4, IL-8, or IL-10. Meta-regression analyses estimated that psychiatric symptoms were significant predictors of increased effect sizes for IL-1β and IL-6, and positive correlations between inflammation and trauma exposure across different mental disorders were found. These results confirmed the hypothesis that chronic inflammation might represent one of possible mechanisms underlying the risk of health problems [46] also in trauma survivors. Exposure to trauma seems to determine neuroendocrine responses and long-lasting changes in the regulation of the HPA axis compromising its physiological activity [47]. In particular, abnormal functions in the sympathetic-adrenergic nervous system influencing the release of hormones via the endocrine HPA axis, may play a role in metabolic dysfunctions in subjects with PTSD [48]. Cortisol stimulation may contribute to changes in inflammatory biomarkers such as CRP and may facilitate the development of central obesity and metabolic syndrome [48]. However, mixed support of this hypothesis has been provided by previous research, showing a decrease or no variations of cortisol levels in individuals with PTSD. Pooled data from 37 studies including 828 individuals with PTSD and 800 relevant controls did not show any differences in plasma/serum cortisol levels in PTSD, whereas decreased levels were found in samples including females, as well as in studies testing traumatic experiences related to physical or sexual abuse [49]. In addition, a subsequent systematic review and meta-analysis [50] estimated salivary cortisol levels in PTSD lower than in healthy controls (SMD = -0.28). It has been suggested that these might be a vulnerability marker for PTSD development after trauma exposure [51]. In particular, a hypoactive HPA axis prior to trauma may predispose to PTSD, possibly leading to failure in mobilizing adequate energy resources to cope with stressors induced by traumatic experiences, and in restoring homeostasis after the challenge has subsided [52]. Lower levels of cortisol may lead to an adaptation of the HPA axis to increase sensitivity of glucocorticoid receptors in the pituitary gland [53]. Along with cortisol, despite generally less studied than cortisol, the dehydroepiandrosterone (DHEA) and its sulfate form DHEA-S, secreted by the adrenal cortex, are important factors for clarifying the role of HPA axis dysfunctions in PTSD [54]. While low concentrations of DHEA and DHEA-S can be neuroprotective, high concentrations of DHEA can be ineffective or neurotoxic [55]. A relatively recent systematic review and meta-analysis [56] did not show any significant differences in DHEA or DHEA-S levels between PTSD and control groups, despite DHEA levels in trauma-exposed controls were higher than in controls not exposed to trauma, suggesting that trauma exposure, irrespective of PTSD development, might increase steroid hormones.

Another important issue involves possible variations of appetite regulating hormones in PTSD. Adipokines, such as adiponectin and leptin, have been shown to be important factors in different mental disorders, including psychotic and depressive disorders [57-59]. Adiponectin, also called gelatin-binding protein-28 (GBP28), AdipoQ, adipocyte complement-related protein (ACRP30) or apM1 [60], is one of most abundant plasma adipokine [61] synthesized by adipose tissue. It plays a key role in the homeostasis of glucose and lipid metabolism [62], influencing insulin sensitivity [63] (with anti-inflammatory properties [64]. Consistently, meta-analytic data have shown that higher levels of adiponectin are associated with a lower risk of type 2 diabetes with a dose-response relationship [65] and that adiponectin may be an useful biomarker for metabolic syndrome [66]. In addition, entering the brain through the peripheral circulation and interacting with AdipoR1 and AdipoR2 receptors, adiponectin may influence important CNS functions, including energy homeostasis and synaptic plasticity [67]. Recently, variations of appetite regulation have been found in subjects with PTSD. A study sampling in Korea [68] estimated that, among 507 male firefighters, those with PTSD symptoms had adiponectin plasma levels lower than those without PTSD. In addition, severity of PTSD was inversely correlated with adiponectin levels. Consistently, adiponectin effects on extinction of contextual fear and intrinsic excitability of dentate gyrus granule neurons were found in animal models, suggesting that drugs targeting adiponectin may be used to strength extinction-based exposure therapies for PTSD [69]

Similarly, leptin resistance has been involved in the pathogenesis of metabolic disorders in PTSD. Although in physiological conditions leptin reduces appetite as a circulating signal, inhibiting hypothalamic neuropeptide Y (NPY) and activating the release of α-MSH from proopiomelanocortin (POMC) neurons in the hypothalamic arcuate nucleus [70], resistance to leptin induces increasing levels of leptin, with failure in hunger control and weight modulation [71]. In addition, resistance to leptin may contribute to abnormal hypothalamic and CNS functions, leading to dysfunctional reward signaling and uncontrolled appetite [48]. A previous study [72], analyzing the relationship between post-disaster psychiatric symptoms and serum leptin levels, showed a direct relationship between stress-related symptoms and serum leptin levels. In particular, hyperarousal predicted higher leptin levels, suggesting a role for leptin as a neuroendocrinological marker for the hypervigilant state of PTSD. Moreover, paranoid, anxiety, and depressive symptoms have been all positively associated with leptin levels. Consistently, NPY, a hypothalamic hormone regulating feeding behaviors, has also been linked with PTSD [73]. NPY is abundantly expressed in forebrain limbic and brainstem areas that regulate stress and emotional behaviors [74], lowering the stress-signaling hormones norepinephrine and corticotropin-releasing hormone [75]. Multiple lines of evidence supported the relevance of NPY as a potential 'resilience-to-stress' factor involved in the pathophysiology of PTSD [76]. Levels of NPY in cerebrospinal fluid has been negatively correlated with PTSD symptoms, especially intrusive ones [77]. In particular, it has been hypothesized that suboptimal NPY levels in different brain regions, including amygdala, hippocampus, prefrontal cortex, hypothalamus, and brain stem, may represent the biological substrate of the PTSD clinical features [76]. Individuals with lower levels of NPY expression, or who are less capable of activating the NPY system in response to trauma, would be more vulnerable to PTSD and other trauma-related disorders [76].

Main variations of immune-metabolic profile in subjects with PTSD are summarized in Table I.

Conclusions

PTSD and metabolic disorders are both associated with increased cardiovascular risk, and may have similar underlying biological mechanisms. It is likely that changes of inflammatory and neuroendocrine systems may be involved in PTSD, although the direction of this relationship remains unknown. It seems plausible hypothesize that a dysfunctional individual adaptation to stress may increase the vulnerability to metabolic dysfunctions that, in turn, may favor the occurrence of psychopathological features after traumatic experiences. Approaching PTSD as a systemic condition, involving low-grade inflammation, HPA axis dysfunctions, and metabolic abnormalities, along with important psychological burden, has important implications in terms of treatment, man-

TABLE I. *Main variations of immuno-metabolic profile in PTSD.*

Inflammatory markers	
CRP	↑
IL-1β	↑
IL-6	↑
INF-γ	↑
TNF-α	↑
HPA axis	
Cortisol	↓
NPY	↓
Adipokines	
Adiponectin	↓
Leptin	↑

CRP: C-reactive protein; IL: Interleukin; INF-γ: Interferon-γ; HPA axis: hypothalamic-pituitary-adrenal axis; NPY: Neuropeptide Y; TNF-α: Tumor Necrosis Factor-α.

agement, and prognosis. Clinicians should regularly assess, monitor, and treat metabolic abnormalities in subjects with PTSD. Further research is needed to test novel treatments for PTSD, targeting neuroendocrine and immune-metabolic systems.

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Review

Sleep, stress and trauma

Valentina Socci[1], Rodolfo Rossi[2], Dalila Talevi[1], Claudio Crescini[1], Daniela Tempesta[1], Francesca Pacitti[1]

[1] Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, Italy;
[2] Department of System Medicine, University of Rome Tor Vergata, Italy;

SUMMARY

The potential impact of sleep and sleep disorders on stress responses has received increasing interest particularly in the context of Post-traumatic Stress Disorder (PTSD). This review aims at synthesizing current evidence concerning the link between trauma exposure, sleep, emotional regulation and stress. In the last decades, experimental investigations suggested a critical role of sleep on emotional memory formation and emotional reactivity; similarly, animal and human studies highlighted the relations between sleep and fear responses, supporting the notion that sleep disturbance plays an important role in PTSD-relevant processes such as fear learning and extinction. Although some crucial aspects of these interactions need further clarification, convincing evidence now suggests a complex physiological interaction of stress response and sleep. In the context of trauma-related disorders, sleep alterations have been suggested as core symptoms as well as risk and prognostic factors; importantly, sleep may also represent an important therapeutic target in mental health. However, evidence accumulated so far points to sleep disturbance as a marker not only of PTSD, but also of increased vulnerability to maladaptive stress responses. Novel models conceptualize sleep disturbance as a modifiable, transdiagnostic risk factor for mental disorders, with important theoretical and clinical implications.

Key words: sleep disturbances, trauma, emotional processing, post-traumatic stress disorder

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Correspondence
Francesca Pacitti
Department of Biotechnological and Applied Clinical Sciences (DISCAB), University of L'Aquila, via G. di Vincenzo 16/B, 67100 L'Aquila, Italy
E-mail francesca.pacitti@univaq.it

Conflict of interest
The Authors declare no conflict of interest.

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Introduction

In the last years, the potential relation between sleep and trauma has received increasing interest, particularly in the context of trauma and stress-related disorders such as Post-traumatic Stress Disorder (PTSD). In the last two decades, experimental investigations have progressively highlighted the importance of sleep for cognitive as well as emotional functioning [1,2]. A critical implication of sleep in emotional memory formation as well as emotional homeostasis is well documented, also leading to important implications for trauma-related disorders. Similarly, animal and human studies have probed the relationship between sleep, particularly Rapid Eye Movement (REM) sleep and fear responses, also providing strong support for the hypothesis that sleep disturbance plays an important role in trauma-related processes. Alterations of sleep pattern represent a typical behavioral consequence of acute stressful/traumatic exposure and a core symptom of PTSD. In this context, while sleep disorders could have a pathoplastic role in PTSD, the emotional hyper-reactivity associated with a traumatic experience itself may, in turn, affect subsequent sleep quality. A complex, bidirectional relation between sleep and stress/trauma emerges, whereby emotional processes can progressively affect and be affected by sleep disturbances. Overall, recent literature suggests that disturbed sleep can contribute to maladaptive stress and trauma responses and may constitute a modifiable, transdiagnostic vulnerability factor for poor psychiatric outcomes [3,4]. Importantly, sleep disturbance is a modifiable vulnerability factor, and sleep restoration through effective

targeted sleep treatments may accelerate recovery from trauma exposure and PTSD. Further clarifying the neural substrate and the behavioral implications of the relation between sleep and trauma is a critical issue for the development of innovative strategies for risk management and treatment.
The aim of this review is to summarize relevant evidence on the relations between stress exposure and trauma, sleep and emotional regulation. Potential critical implications of sleep in the context of stress exposure, trauma-related disorders and interventions will be discussed. Further, critical issues for future research will be suggested.

Sleep disturbance in PTSD

Post-traumatic Stress Disorder is a psychiatric illness that can occur after the exposure to traumatic events Lifetime prevalence of PTSD is estimated between 2.3 [5] and 6.1% [6] in civilians and 30% in veterans [5]. PTSD symptoms include four psychopathological dimensions, i.e. avoidance, negative affect, intrusions (including nightmares) and hyperarousal. In the 5th Edition of the Diagnostic and Statistical Manual of Mental Disorders [7], sleep disorders are included among the criteria for PTSD as re-experiences of traumatic symptoms (nightmares, criteria B) as well as alterations in arousal and reactivity (sleep disturbance, criteria E). Difficulties in falling asleep, frequent awakenings, reduced sleep duration, restless sleep and fatigue represent typical complaints of PTSD patients. Particularly, nightmares and anxiety dreams, a Rapid-eye Movement (REM) sleep phenomenon, appear consistently associated with PTSD [8], so that they are commonly considered a core symptom of PTSD [9]. Accordingly, disturbed sleep, particularly REM sleep disturbances and nightmares, have been considered as the hallmark of PTSD [10]. Although the presence of sleep disturbance is a diagnostic criterion for the disorder, a clear consensus regarding the link between sleep disorders and the development of PTSD is still lacking. Findings concerning objective sleep alterations in PTSD are contrasting. A meta-analytic review [11] showed more stage 1 sleep, less slow-wave sleep, and greater REM density in PTSD patients compared to controls. Conversely, REM sleep reduction or fragmentation has been observed both in the acute aftermath of trauma exposure and in subjects with PTSD several years after the onset of PTSD [12,13]. Nevertheless, insomnia and REM sleep fragmentation following traumatic events are predictive of later development of PTSD [14]. Also, self-reported sleep disturbances have been showed to increase the likelihood of developing PTSD following a natural disaster [15], thus also indicating a potential proactive role of sleep disturbance on the PTSD vulnerability. Moreover, sleep-focused treatments can significantly improve both sleep and PTSD symptoms [16,17].
A recent general population survey conducted in 24 countries reported a lifetime prevalence of trauma exposure of approximately 70% [18]. An even higher lifetime rate of traumatic events has been estimated in clinical populations, with a lifetime prevalence of 90% [19]. Particularly, compared to the general population, the exposure to interpersonal traumatic events such as physical and sexual violence is higher in individuals with a severe mental illness [20], with a significant impact on personal and social functioning of patients with mental disorders [21,22]. Although the exposure to traumatic events is common in both clinical samples and general population, only a minority of individuals will develop PTSD. In addition to trauma exposure, increasing evidence suggests alterations in emotional memory processing and emotional modulation as critical to PTSD and complex PTSD development and maintenance [23]; in this context, evidence also exists in support of a causal role of sleep disturbance in such alterations.

Sleep and emotional processing: implications for trauma-related disorders

In the last two decades sleep research strongly supported a crucial relationship between sleep and learning/memory consolidation [2]. Accumulating evidence suggests that sleep-related consolidation processes are essential for the long-term maintenance of emotional information [1]. Behavioral investigations showed that post-learning sleep selectively favored the retention of negative emotional texts compared to neutral texts and this emotional memory enhancement may persist for several years [24,25]. Similarly, napping may facilitate the consolidation and the post-sleep encoding of declarative emotional and neutral memories [26] or may promote preferential memory consolidation for negative emotional information [27]. Furthermore, sleep deprivation literature converges at indicating that the sleeping brain provides ideal conditions for episodic memory consolidation, while sleep loss negatively affects emotional memory processing [1,28-31].
Importantly, accumulating evidence pointed to REM as the sleep stage specifically involved in emotional memory processing. Indeed, REM sleep stage is typically associated with reports of emotionally intense dreams [32]. REM sleep is accompanied by specific hyperactivity within brain areas implicated in memory functions during wake [33]. A large literature now suggests that the link between the REM sleep neuroanatomophysiology and the emotional domain is not coincidental [34]. During REM sleep, memories within

the neocortex are subjected to a plasticity-related cholinergic activity while remaining free from arousal-related noradrenergic interference, thus they potentially recombine each other and integrate into preexisting memory networks [35].

However, while a crucial implication of sleep in all stages of emotional memory formation is well documented [30,31], the specific impact of sleep on the next-day emotional reactivity is still controversial. According to Wagner and coworkers (2001) the REM sleep-mediated emotional memory consolidation is paralleled by the strengthening of the associated emotional charge. Consequently, REM sleep deprivation should prevent sleep-dependent neural reactivation assumed to be necessary for the consolidation of new memory traces, thus impairing the consolidation of a memory and of its associated emotional tone. In line with these assumptions, the use of sleep deprivation as a potential preventive therapeutic measure to hinder the long-term retention of traumatic events has been suggested [24,25].

In contrast to the previous hypothesis, the 'Sleep to remember, sleep to forget' model [34] posits that the inherent neurobiological state of REM sleep could support a de-potentiation of the emotional charge of a memory. Specifically, during REM sleep the activation of brain areas implicated in memory function, such as the amygdala and the hippocampus, would support the overnight reprocessing and long-term retention of emotional memories ('Sleep to remember') [36]. Contextually, the suppressed adrenergic activity would gradually dissipate the autonomic charge associated with the emotional experiences ('Sleep to forget'). In this way, REM sleep could represent an 'overnight therapy' to adaptively preserve the salient aspects of a memory, dissipating at the same time the associated emotional tone, eventually promoting an accurate separation of the emotional charge from the declarative content of the mnesic trace [36]. Neuroimaging as well as behavioral studies offer support to this assumption. Indeed, after sleep loss, an amplified limbic activation in response to negative emotional stimuli has been observed, in association with a reduced functional connectivity between the amygdala and the ventro-medial prefrontal cortex (vmPFC). These alterations are suggestive of a dysfunction of the vmPFC-amygdala circuitry and a lack of top-down control by the prefrontal cortex (PFC) on the limbic system [37]. Therefore, at the behavioral level, sleep loss may impose a more negative affective tone to memories [38]. Within this framework, REM sleep has also been indicated as a preventive therapeutic measure for emotional brain homeostasis to preserve an effective functional PFC-limbic connectivity [36].

On the whole, investigations on the relationship between sleep and emotional reactivity produced contrasting results, with evidence supporting both enhanced and diminished REM-related emotional reactivity, as well as no effect specifically associated with REM sleep [1]. Although the specific direction of the sleep-dependent emotional modulation needs to be further clarified, these results support the importance of sleep for appropriate emotional memory processing and next-day emotional reactivity.

The complex relationship between sleep and trauma

Increasing evidence is providing important insight into the relationship between sleep and trauma. Such link is relevant in light of the robust relations between sleep disorders, adverse life events and mental disorders. While daytime affective symptoms can adversely affect sleep, there is growing evidence that sleep disturbances can reciprocally impact daytime symptoms [39].

In the last years, fear conditioning paradigms in mammals [40] confirmed that sleep plays a critical role in the encoding and long-term retention of fearful memories. Research in this field showed that an experimentally induced fear response can affect subsequent sleep, as well as sleep manipulation can influence subsequent fear conditioning/extinction processes. Fear conditioning investigations have linked post-learning sleep to the consolidation of both fear conditioning and fear extinction in humans [1]. Although the specific direction of sleep-mediated modulation of fear remains unclear, sleep seems to promote the appropriate recognition of salient stimuli and the discrimination between fear and safety relevant stimuli, thus fostering the most appropriate response to the environment. This could be relevant since the dysfunctional persistence of fear conditioning and poor fear extinction has been implicated in the pathogenesis and maintenance of stress-related disorders and anxiety disorders. Indeed, dysfunctional fear expression in anxiety disorder may result from abnormally strong fear response or alterations of the inhibitory system modulating fear [41,42]. In this respect, a dysfunctional activation of brain areas implicated in fear extinction has been shown to differentiate trauma-exposed individuals with and without PTSD; at the behavioral level, such alterations were associated with impaired recall of extinction memory [42-44]. Importantly, in clinical populations such as spider-fearing women, sleep after exposure therapy may promote the retention and generalization of extinction learning with the potential to enhance the efficacy of the treatment, possibly preventing sensitization to threat and fear generalization [45,46]. Conversely, disturbed sleep may negatively influence the optimal processing of fear and extinction-related memory traces.

On the other hand, sleep disturbance represents a common behavioral consequence of acute and chronic

stress response [47]. In the animal model, different types of inescapable experimental stress were associated with subsequent REM sleep fragmentation; furthermore, conditioned reminders have been shown to produce similar stress-induced alterations in sleep architecture that may persist long after the initial stressful experience, while extinction learning seems to reverse these alterations [48]. Acute trauma-related hyperarousal itself could produce sleep disturbances that may lead, in turn, to a paradoxical hypervigilance response, thus perpetuating the stress response [39]. Moreover, sleep disruption may further impair the sleep-dependent memory processing, hindering an adaptive emotional regulation. Accordingly, at the neuroendocrine level, a complex mutually interactive physiology of stress response and sleep has been suggested, whereby traumatic experience may prevent a subsequent appropriate sleep-dependent emotional homeostasis (i.e. reduction in catecholamine levels, sympathetic tone, hypothalamic pituitary adrenal (HPA) axis and central corticotropin releasing factor (CRF)-ergic activity) resulting in an abnormal daytime stress response [39]. In the context of trauma-related disorders, these findings suggest that sleep alterations possess the potential to directly exacerbate initial symptoms end/or to impair the subsequent consolidation of appropriate extinction learning, thus contributing to the maintenance of maladaptive stress response.

Sleep disturbance: a transdiagnostic risk factor

The importance of understanding the link between sleep and emotional processing is evident in light of the robust evidence demonstrating associations between sleep alterations and mental disorders [3,49]. Disturbed sleep represents both a core symptom and a potential pathophysiological factor of PTSD; however, in the DSM-5 sleep disturbance is a key symptom of many, if not all, psychiatric disorders. Accordingly, it has been suggested that sleep continuity disturbances imply a transdiagnostic imbalance in the arousal system that could represent a basic dimension of mental health [3].

As reported in epidemiological and prospective studies, pre-existing or peritraumatic sleep disturbance represents a risk factor not limited to PTSD, but also for mental disorders such as anxiety disorders, mood disorders and alcohol/substance use disorders [50–54]. Similarly, insomnia is a risk factor for incident depression [55]. In Major Depression, alterations in the sleep/wake cycle may emerge in a premorbid, symptoms-free age of life [56]; similarly, differences in circadian profiles can be found in subjects with Depression and Panic Disorders even before the clinical onset of the disorders [57]. The co-occurrence of sleep and psychiatric disorders tends to attenuate treatment response; further, sleep alterations may increase the risk of relapse, thus suggesting an important prognostic significance of sleep disturbance in mental disorders [58,59].

In addition to their specific implication in PTSD, increasing evidence to date support the hypothesis that sleep disturbances may reflect a broad index of maladaptive stress responses to trauma exposure. The predictive relationship between sleep alterations and an increased risk for a broad range of subsequent disorders strongly suggests that sleep disturbances could be important indices of compromised resilience [60]. In further support of this, the presence of consolidated sleep in trauma-exposed individuals [61], as well as sleep improvements during treatment for affective disorders [62,63], are associated with better mental health outcomes. These finding therefore have important implication for the implementation of preventive and therapeutic strategies in mental health settings.

Conclusions and future directions

In the last years, increasingly evidence supported an intimate relationship between sleep and trauma. A large number of experimental investigations have demonstrated a crucial role of sleep on the processing of emotional memories. Similarly, fear conditioning studies have implicated sleep, particularly REM sleep, in the adaptive consolidation of both fear and extinction memories, a process that could be specifically impaired in PTSD. Literature also suggests that treating sleep disturbances immediately after the trauma exposure may reduce the development or severity of PTSD via consolidation and generalization of extinction memories. However, some crucial aspect of the sleep-mediated overnight emotional modulation should be further clarified, with important theoretical and clinical implications for trauma-related disorders. Specifically, the role of sleep in emotional processing should be further addressed in clinical PTSD samples, in order to better elucidate the specific direction of such relationship. In this respect, while restoring REM sleep may be related to appropriate extinction learning in PTSD, it could also promote the initial consolidation of fear memories, thus exerting an opposite effect on the emotional reactivity in the early aftermath of a trauma. This suggest the individuation of a precise, strategical time window for sleep interventions as a critical issue for future research on trauma-related disorders.

Future studies investigating the link between sleep and trauma should advance our understanding on the specific impact of potential vulnerability or protective factors. For example, differences in REM sleep propensity could moderate the effects of stress and trauma exposure on behavioral and physiological

outcomes [64]. Sex-related differences in functional brain activity have been described in studies investigating emotional memory [65] and emotional reactivity [66,67]; also, physiological estrogenic fluctuations may influence some aspects of the emotional processing [68]. Moreover, a specific vulnerability of females to the detrimental effects of sleep loss [69] as well as to mood disorders [70] and sleep disturbances [71] has been reported, suggesting the need to further investigate the specific contribution of sex-related differences in modulating the relation between sleep and emotions.

Moreover, future studies investigating the relations between sleep, stress and trauma should further clarify the potential role of neurobiological markers such as brain-derived neurotrophic factor (BDNF). In this respect, alterations in BDNF levels have been linked with post-traumatic stress spectrum symptoms [72] and PTSD [73]. Moreover, changes in BDNF levels are associated with chronotype [74], sleep loss and sleep quality [75], with evidence also pointing to sleep as a key mediator in the relation between stress and BDNF regulation [76], thus encouraging further research.

Future research should also be dedicated to a better understanding of the relations between sleep, trauma exposure and trauma-related disorders across different life stages. Retrospective studies suggested that childhood trauma could be particularly associated with sleep disturbances later in life [77,78]. Also, sleep problems in children or adolescents predict subsequent anxiety and depression disorders [79]. Early adverse experiences may have long-lasting effects on REM sleep and brain development [80]. These findings also raise the possibility that trauma exposure and altered sleep patterns during critical developmental stages may crucially interact in representing a significant transdiagnostic risk factor for subsequent mental illness.

Taken together, evidence accumulated so far supports the notion that sleep disturbance represents a sensitive index of heightened vulnerability to maladaptive stress responses and compromised resilience. In the context of trauma-related disorders, evidence-based sleep interventions have the potential to significantly advance clinical care. More generally, sleep disturbances should be conceptualized as a modifiable risk factor for poor psychiatric outcomes and therefore an important target for prevention and early intervention; novel models emphasize the transdiagnostic nature of sleep disturbance as a dimension for brain and mental health [3,4,81]. Addressing sleep quality through accurate sleep assessment and interventions in populations at risk may represent an important preventive and therapeutic strategy in mental health.

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Review

PTSD in the aftermath of a natural disaster: what we learned from the Pisa-L'Aquila Collaboration Project

Claudia Carmassi[1], Alessandro Rossi[2], Virginia Pedrinelli[1], Ivan Mirko Cremone[1], Valerio Dell'Oste[1], Paolo Stratta[2], Carlo Antonio Bertelloni[1], Liliana Dell'Osso[1]

[1] Department of Clinical and Experimental Medicine, University of Pisa, Italy; [2] Department of Clinical and Experimental Medicine, University of L'Aquila, Italy

SUMMARY

Objectives

Several studies have shown that survivors of natural disasters present high PTSD rates. On 6th April 2009, L'Aquila (Central Italy) was jolted by a 6.3 Richter scale magnitude earthquake causing a massive destruction of the town. More than 300 individuals died, 1,600 were injured and about 65,000 displaced. The aim of this paper is to review the researches conducted on survivors to this earthquake in the context of the Pisa-L'Aquila Collaboration Project which is going on since 2009, in order to assess post-traumatic stress spectrum psychopathology and its correlates.

Methods

An overall sample of more than 2000 earthquake survivors was assessed by means of the Trauma and Loss Spectrum-Self Report (TALS-SR), a questionnaire exploring post-traumatic stress spectrum symptoms. The TALS-SR offers a multidimensional approach that considers three major dimensions: potentially traumatic events, including losses and the so-called low magnitude events; symptoms of the acute/peri-traumatic reaction; post-traumatic spectrum symptoms. Survivors were also assessed by means of Mood Spectrum-Self Report (MOODS-SR), to detect correlations between post-traumatic stress spectrum and mood spectrum symptoms.

Results

High prevalence rates of both full and partial PTSD were found, as well as several factors (e.g. younger age, female gender, degree of exposure, bereavement experiences) associated with an increased likelihood of post-traumatic stress symptoms. Survivors with PTSD also reported significantly higher prevalence rates of specific symptoms, such as maladaptive behaviors including suicidality, and impairment in eating behaviors and somatic symptoms.

Conclusions

These studies highlighted the heavy burden of PTSD in the aftermath of the earthquake, even months after exposure, and a close relationship between post-traumatic stress spectrum and mood spectrum symptoms, suggesting the need of additional research.

Key words: PTSD, post-traumatic stress spectrum, mood spectrum, earthquake, natural disaster

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Correspondence
Virginia Pedrinelli
Section of Psychiatry, Department of Clinical and Experimental Medicine, University of Pisa, via Roma 55, 56126 Pisa, Italy
E-mail: virginiapedrinelli@gmail.com

Conflict of interest
The Authors declare no conflict of interest

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Introduction

Earthquakes represent, above all, one of the most frightening and frequent natural disasters a person can experience, bringing not only damage to one's properties and physical health, but also significant psychological distress [1,2]. These mass trauma, indeed, happen without warning all around the world, causing massive destruction and major damage in populated areas, being often responsible of other natural disasters (e.g.

tsunami and landslides), causing death or injuries instantaneously or rapidly and widespread [3-5]. Earthquakes have the characteristics to strike suddenly and affect a large amount of people simultaneously, representing a particular setting for interplay between risk and vulnerability factors for trauma-related psychopathology. For all these reasons, over the past several decades, seismic events gained a growing attention of researchers and clinicians [6,7]. Increasing attention to mental health has been paid, trying to find effective interventions, to provide high standard prevention and rehabilitation services in affected populations, given that there's now agreement that earthquakes survivors need mental health professionals' support [3,8].

Extensive research, especially over the past twenty years, has been focusing on mental disorders development after earthquakes. Indeed, the psychopathological sequelae associated with these experiences represent a challenge for healthcare systems throughout the world [9-13]. High rates of many mental disorders can be detected in the aftermath of these traumatic events. Among them, post-traumatic stress reactions, especially Post-Traumatic Stress Disorder (PTSD) both in its full-blown and partial manifestations, are the most frequently reported and are often characterized by a chronic course and high risk for suicide [4,14,15]. Post-traumatic stress reactions are a challenge for mental health professionals, as they have consequences impacting affected individuals not only in the phase immediately after trauma exposure, but also in the long term. Moreover, even if the symptoms' onset is usually in the first month after the traumatic event, in a minority of cases, there can be a delay of months or years before symptoms start to appear [16,17].

Italy is one of the highest seismic risk countries in Europe, but luckily deadly earthquakes occur rarely. In the last ten years, three massive destructive earthquakes affected the Country: the one happened in L'Aquila in 2009, the one that struck the Emilia-Romagna region (Northern Italy), in 2012 and, more recently, the one that hit Amatrice (Central Italy), in 2016. On April 6th 2009, at 03:32 hours, Central European Time, a terrific 6.3 magnitude seism jolted L'Aquila and its province. L'Aquila is a town with 72,000 inhabitants in the Abruzzo, region of Central Italy: the town was massively destroyed, more than 100,000 buildings were severely damaged, 309 people were killed at 19 different localities, 66,000 individuals were left homeless and 1600 were injured, among whom more than 200 seriously. Marks of this event are still visible: today, the town is still under reconstruction and about 10,000 people are still displaced, living in temporary accomodations. The historic centre of L'Aquila, which was home to around 20,000 people before the earthquake, is a tale of two cities: one still emerging from the rubble, the other resiliently trying to return to normal.

In this context, a collaboration between researchers of the Universities of Pisa and L'Aquila has given the chance to conduct studies on the impact of L'Aquila earthquake on mental health. Large-scale surveys on a total of over 2,000 people affected have been carried out, with a focus on post-traumatic stress spectrum and its correlates. Survivors were assessed by means of a specific instrument developed to assess post-traumatic stress spectrum symptoms: the Trauma and Loss Spectrum-Self Report (TALS-SR) [18], referred to the earthquake exposure.

The TALS-SR is an instrument developed in the framework of an international collaborative research project called *Spectrum Project* going on since 1995, exploring common clinical features that accompany each disorder, as it is classified through DSM diagnostic criteria [19,20]. According to this view, the spectrum approach refers to a dimensional view of psychopathology that takes into account, besides the core and most severe DSM symptoms, a wide number of atypical and sub-threshold manifestations, as well as temperamental traits, that might be prodromals, precursors or sequelae of the target disorder. A Structured Clinical Interview for Trauma and Loss Spectrum (SCI-TALS) [21], and its Self Report (TALS-SR) [18], have been developed and validated. The TALS-SR consists of 116 dichotomous items (yes/no), grouped in nine domains that explore the trauma and loss spectrum through a multidimensional approach. This approach refers to three major dimensions: the one of lifetime exposure to several potentially traumatic events (included the so-called "low magnitude" and loss events), that of the acute/peri-traumatic reactions and that of post-traumatic stress and/or Complicated Grief (CG) spectrum symptoms.

Through this paper, we aimed to re-examine the lessons we have learned from the results of the researches conducted on survivors to the L'Aquila earthquake, assessed by means of the TALS-SR, showing the data gave a relevant contribution to understand post-traumatic stress symptomatology related to the exposure to a natural disaster.

Full and partial symptomatological PTSD: the impact of nosographic evolution in the DSM-5

The rates of full and partial symptomatological PTSD, as well as the role of specific risk factors, were assessed at 10 and 21 months after the event. In later studies, the impact on PTSD diagnosis of the changes in the DSM diagnostic criteria from the fourth to the fifth edition were also investigated, as the TALS-SR included a wide range of post-traumatic stress spectrum symp-

toms comprising also those that had been later acknowledged among DSM-5 criteria for PTSD. In particular, symptomatological PTSD, according to DSM-IV-TR criteria, emerged in 37,5% of 512 survivors attending the last year of high school assessed ten months after the event; a further 29,9% reported partial PTSD[2]. After twenty-one months rates of full and partial PTSD resulted to be of 30,7 and 31,4%, respectively, according to literature data [4,6,11,22]. After DSM-5 was published, we first adopted the new diagnostic criteria by means of an algorithm including symptomatic criteria for PTSD diagnosis encoded by TALS-SR items [13], showing full- blown PTSD rates as high as 39,8%. Moreover, an accurate analysis of the differences in the criteria endorsed was performed.

Our findings on L'Aquila survivors also confirmed the higher vulnerability of females to the impact of traumatic events, both in terms of PTSD prevalence rates, as well as severity of symptoms. In the above mentioned study [2], in fact, a significant difference was found between females and males in PTSD prevalence rates, with about double rates in female sex, in line with prior studies [22,23]. On the contrary, no significant differences between genders ware reported in partial PTSD rates. Consistently, females showed higher TALS-SR domain scores and symptoms with respect to males. Data were confirmed according to DSM-5 criteria [24], also on a larger sample of more than 900 survivors, demonstrating the main effect of gender on development of post-traumatic stress symptoms after a natural disaster [12].

Our findings also add up on the weight of age effect as a vulnerability factor element on development of PTSD: age differences emerged only among females, with younger ones being the most affected [12,25]. A significant interaction between exposure*age and gender*age of TALS-SR symptoms emerged, these latter being higher in young subjects than in unexposed elderly ones, and in young females with respect to the older ones [12]. In line with some authors [26,27], these results suggest that females and younger individuals are more prone to the development of post-traumatic stress symptomatology when exposed to trauma, even if we found an impact of age only within the less affected ones and among females.

The impact of the characteristics of the "trauma"

In the past decades increasing literature has highlighted the role of the kind of trauma and/or severity of exposure as risk factor for PTSD [28]. In this regard, the DSM-5 has risen the threshold for defining an event as traumatic. However, studies on survivors to the 9/11 terroristic attack pointed out PTSD reactions even in subjects far from the epicenter of the event [29,30]. In the aftermath of an earthquake, the degree of exposure, in terms of distance from the seismic epicenter, has been suggested as a major risk factor, with higher symptom levels being reported in individuals who were closer to the seismic epicenter at the time of the earthquake [3,5]. We explored two samples of a total of more than 1,500 survivors to the L'Aquila earthquake, located at different distances from the epicenter at the time of the event. Results confirmed significantly higher post-traumatic stress spectrum symptoms in survivors located in the closest area to the epicenter, corroborating a close relationship between degree of exposure and severity of the psychopathological sequelae [12,25]. Another interesting finding regarded traumatic loss, as a risk factor for post-traumatic stress symptoms. It is well known that significant losses in the framework of earthquakes are considered to be a contributory factor to PTSD development, both in adolescents and adults [3,31]. Pathological grief reactions (variously described as CG, Traumatic Grief or Prolonged Grief Disorder), have been widely studied, since they have been associated with persistent impairment of global functioning and with a higher suicidal risk in people affected [32-34]. Loss of beloved one represents a possible contributor to the traumatic impact of an event leading to an increased risk of PTSD development. In L'Aquila, the 2009 earthquake caused the death of more than 300 people and the weight of loss had an impact on affected individuals; in a sample of 475 young adult survivors, 15,2% reported a loss and these showed significantly higher PTSD rates and post-traumatic symptoms levels with respect to not bereaved ones[11].

Suicidality and maladaptive behaviors

Not surprisingly, earthquakes are the most studied natural disasters for their impact on suicidal attempts [35], with increasing data showing high rates of suicidality in people survived, especially after highly destructive events [36,37], and PTSD was found to be one of the principal mediators between mass traumas and suicidality [38-40]. Data on L'Aquila earthquake survivors, reported significantly higher rates of suicidal ideation and attempts related to PTSD diagnosis, with rates of suicidal ideation present in about 7-14% of the sample and rates of suicidal attempts ranging between 2 and 5%. [2,41]. This variability could be explained by many factors, such as age, gender, concomitant mood symptoms and different coping strategies. In particular, our results demonstrated a significant association between suicidality and male gender in PTSD survivors, suggesting, as others have highlighted [27,42], that men tend to express psychological disturbances through acting out and external behavior, whilst women tend to express their distress

by turning their feelings inwards, leading to depression and anxiety [43].

In this regard, the DSM-5 included a new set of symptoms for PTSD diagnosis, among which the so-called maladaptive behaviors. These are defined as volitional behaviors whose outcome and negative consequences impact everyday activities [25,42,44,45]. Reckless or self-destructive behaviors are one of the three new criteria included in DSM-5 for PTSD diagnosis as part of criterion E. As for pathological grief reactions, the *Spectrum approach* of TALS-SR [18,46], that includes a specific domain addicted to maladaptive behaviors, allowed to explore these psychopathological traits years before the DSM-5 acknowledgement [47]. Maladaptive symptoms encompass behaviors such as reckless driving, promiscuous sex, self- injuring behaviors, alcohol, substance or drug use, ceasing to take care of oneself or to take prescribed therapies and suicidal behaviors [44-48].

Many interesting evidences came out in L'Aquila survivors' samples: in all the studies emerged survivors with PTSD reported significantly higher prevalence rates of maladaptive behaviors than those without [2,49,50]. On the impulse of previous studies [51,52], 512 high school students were recruited ten months after the event and screened for these behaviors by means of TALS-SR. A significantly higher number (almost double) of females with respect to males reported they had stopped taking care of themselves; males, on the contrary, reported significantly higher percentage for other maladaptive behaviors, such as use of alcohol or substance use and promiscuous sex [2]. Gender differences in the context of maladaptive symptoms were investigated also in a larger sample of 900 survivors, including adult individuals [50]. A statistically significant association between male gender and a presence of at least one maladaptive behavior among PTSD survivors was reported. Data showed significantly higher rates of alcohol or substance use among earthquake survivors with PTSD, with rates as high as more than 20%, compared to the ones who did not report PTSD, presenting rates around 10%. These evidences were confirmed by other studies among young people exposed to this same event, with marked increase in levels of abuse compared to prior to the trauma [53]. Furthermore, almost half of individuals with PTSD, also reported a decrease in self-care (e.g. not getting enough rest, not eating properly), with more than 10% reporting suspension of on-going treatments or medical recommendations. In line with other studies on the same sample [54], we reported significantly higher rates of risk-taking behaviors, including self-injuring and suicide attempts, among survivors with PTSD. Moreover, in this group, emerged significant correlations between maladaptive coping and symptoms of re-experiencing, avoidance and numbing and arousal in women, while only between maladaptive coping and avoidance and numbing in men. Finally, age showed to be an influential factor in the former sample, besides gender: males with respect to females, reacted to trauma with more maladaptive coping behaviors, particularly evident in the younger ones (< 40 years), suggesting the need to take into consideration age and gender on post-traumatic stress symptoms, in order to identify high-risk subjects.

More recently, these data have been reanalyzed according to the new DSM-5 PTSD criteria. Exploring the TALS-SR main scores of the senior high school students, maladaptive behaviors were found to be endorsed by 36.8% of PTSD cases and were found to be essential in satisfying DSM-5 E2 diagnostic criterion threshold in 14.2% of PTSD diagnosis. Maladaptive behaviors were also critical in almost half of the PTSD diagnoses in males, but only in about one-fourth in females [13,24].

Maladaptive behaviors were additionally studied from a new perspective that hypothesized an interplay with guilt and shame PTSD symptoms (new PTSD DSM-5 D3 symptom): among 869 L'Aquila earthquake survivors, 11,6% endorsed at least one guilt/shame symptoms, with significantly higher rates in PTSD with respect to no-PTSD ones and the presence of guilt or shame symptoms being positively correlated with maladaptive behaviors [55].

These constructs have also been investigated as to their possible relationships with lifetime mood spectrum, by means of the Mood Spectrum-Self Report (MOODS-SR) [56], upon the evidence of a strong relationship between bipolar comorbidity and increased PTSD severity [57-59]. In particular, lifetime manic spectrum symptoms were strongly related to TALS-SR "potentially traumatic events" and "maladaptive coping" domains, suggesting their notable role for PTSD development [60].

On the other hand, the role of resilience factors has also been explored. Religion and spirituality are often seen as a source of comfort, meaning and hope, but findings about their role in dealing with psychological distress in the aftermath of trauma exposure have been equivocal [61]. On a sample of 901 survivors to the L'Aquila earthquake [62], religiosity was reported to provide resilience against post-traumatic stress symptomatology, as a value for ritualistic than for spiritual religiosity. In a second study on 426 survivors, the same authors reported higher rates of suicidal ideation among survivors with negative religious coping, suggesting a more important role of positive versus negative religious coping rather than the presence of religiosity itself as a possible risk factor for suicidality [37]. In 2016, on the sample of 475 high school students recruited 21 month after the L'Aquila seism, correlations between Spirituality/Mysticism/Psychoticism dimension of the MOODS-SR (including symptoms such as ecstatic experiences and

psychotic symptoms of mania) and suicidality were explored: higher rates of each of the Spirituality/Mysticism/Psychoticism item among subjects with PTSD diagnosis with respect to those without emerged and subjects with suicidal ideation (as well as suicide attempt), reported significantly higher scores in the MOODS-SR Spirituality items [41,62]. Stratta et al. [37], suggested that separating religious coping from spirituality might represent a possible key of explanation for the conflicting results presented in literature: if rituals and social support derived from belonging to a religious community seem to provide resilience, on the other hand spirituality may have a role in increasing the risk of developing post-traumatic stress symptoms and even suicidality.

A new perspective: the interplay between trauma and eating behaviors and somatic complaints

Even if there's unanimous content about the linkage between PTSD and alterations of neurovegetative functions, literature mostly focused on some of them, such as sleep disturbancy (e.g., recurrent nightmares, frequent awakenings, disruptive nocturnal behaviors), finding greater rates in trauma exposed samples than in general population [63,64].

The co-somministration of the TALS-SR and MOODS-SR (that includes a rhytmicity and vegetative functions domain) has allowed to investigate the interplay between trauma and other neurovegetative functions, such as eating behaviors and somatic complaints in young adult survivors of L'Aquila earthquake.

Most recently, there has been growing interest on the correlations between eating disorders and somatic complaints and PTSD [65,66]. Among the traumatic events more strongly associated with eating disorders have been reported interpersonal traumas such as childhood abuse, parental break-up and loss of a family member, but changings in eating habits and eventually the onset of eating disorders is a neglected area in the field of post-traumatic stress symptoms in the aftermath of a mass trauma. The study [67] enlighted impaired eating behaviors in up to 12,3% of survivors 21 months after trauma, with significant higher rates in women with respect to men in all eating behaviors explored. Moreover, significant higher rates of impaired eating among survivors with DSM-5 symptomatological PTSD diagnosis with respect to those without were found. An other noteworthy finding is that not only women, but also men with PTSD, reported significant higher levels of impaired eating behaviors with respect to those without, corroborating the need to accurately explore the influence of trauma exposure and PTSD on dietary habits in both genders. These behaviors could be encoded as an atypical manifestation of stress exposure being part of maladaptive symptoms.

Similar to eating behaviors, even if complaints of somatic symptoms have been correlated to stressful life events and PTSD [62,63], they have been poorly investigated in the setting of natural disasters. In this regard, a recent research on the same sample of survivors, emphasized the strong link between PTSD and somatic symptoms burden, finding up to 14% survivors complaining somatic symptoms 21 months after the exposure, with the PTSD group showing higher ratio of endorsing at least one MOODS-SR somatic symptom than the no-PTSD group [68]. These data are in line with prior evidence in children and adolescents exposed to Lushuan 2013 earthquake [65]. The physical disorders most frequently lamented were chronic pain, gastrointestinal disorders, headaches and thermal/painful stimuli hypo-hypersensitivity. Further, higher rates of somatic symptoms were shown in females rather than in males. Moreover, the latter were positively correlated to TALS-SR maladaptive coping domain (including "having stopped to take care of themselves" and "the use of drugs or over the counter medications to relief symptoms"), in line with previous studies on adolescents exposed to trauma, showing higher rates of use of drugs or medications to relieve emotive and physical pain [51,52].

This issue deserves more scientific and clinical attention, since, as demonstrated, these clinical features have an impact not only in the short term but also over the long term after the traumatic experience.

Conclusions

Albeit additional researches on larger and more representative samples are essential in understanding the nature and the course of post-traumatic stress symptoms in the aftermath of mass disasters, the studies reported on L'Aquila earthquake survivors highlighted the heavy burden of these symptoms, suggesting the necessity of effective preventive and treatment strategies. The *Spectrum approach* adopted by the TALS-SR allowed a more accurate assessment of trauma-exposed people. Further, the co-somministration of MOODS-SR allowed us to explore the trauma-related psychopathological features from a different angle, focusing on the close relationship between post-traumatic and mood spectrum symptoms. Indeed, from this perspective, the trauma-exposure psychopathological sequelae can be interpreted as the intersection of symptoms belonging to different pathological matrices, ending in a common final pathway. Increasing neurobiological and clinical evidences about the impact of post-traumatic stress symptoms on alterations of neurovegetative functions have been confirmed by surveys in our samples, that highlighted higher rates of them in PTSD patients, such

as impaired eating behaviors and somatic symptoms. These findings suggest that more studies are warranted to detect these symptoms in high-risk populations, in order to provide a proper clinical management of affected individuals.

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Review

Oxytocin in the prevention and the treatment of post-traumatic stress disorder: a systematic review of randomized controlled trials

Giorgio Di Lorenzo[1,2], Lucia Longo[1,2], Tommaso B. Jannini[1,2], Cinzia Niolu[1,2], Rodolfo Rossi[1], Alberto Siracusano[1,2]

[1] Chair of Psychiatry, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy; [2] Psychiatry and Clinical Psychology Unit, Fondazione Policlinico Tor Vergata, Rome, Italy

SUMMARY

Recent evidences are revealing the role of oxytocin in the pathophysiology of post-traumatic stress disorder (PTSD) and its possible application in prevention and the treatment of PTSD. Aim of the present article is to provide a systematic review of randomized controlled trials (RCT) of clinical effects of oxytocin in PTSD and trauma-related disorders was conducted. Only six articles were selected after applying the inclusion and exclusion criteria. We compared acute and long clinical effects of oxytocin administration on acute trauma symptomatology and PTSD. The acute clinical effects of oxytocin remain unclear, despite some studies show a reduction of global or single cluster of PTSD and of others clinical symptomatology. The long clinical effects of oxytocin administration show a non-statistically reduction of PTSD, although effect of oxytocin seem to be correlated to the severity on acute PTSD symptom. In fact, the presence of high acute PTSD symptoms showed significantly lower PTSD symptom severity across follow-up, indicating a long-term protective effect of oxytocin administration. Future clinical studies, with accurate psychopathological assessments and a structured clinical follow-up, are mandatory to understand the clinical efficacy of oxytocin administration in patients with PTSD or in patients with acute distress and an increasing risk in developing PTSD.

Key words: oxytocin, post-traumatic stress disorder, trauma-related disorder, psychopharmacology, treatment

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Correspondence
Giorgio Di Lorenzo
Department of Systems Medicine, University of Rome Tor Vergata, via Montpellier 1, 00133 Rome
E-mail: di.lorenzo@med.uniroma2.it

Conflict of interest
The Authors declare no conflict of interest

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Introduction

Post-traumatic stress disorder (PTSD) is an invalidating psychiatric illness caused by psychological trauma, with aberrantly consolidated and persistent traumatic memories, and failing in fear extinction [1]. Despite psychological traumatic experiences are common in the general population, the prevalence of trauma-related disorders, including PTSD, is relatively low, around to 2 to 6%, expect for veteran population where the percentage reaches 30% [2]. The clinical picture in PTSD is heterogeneous, mainly characterized by re-experiencing phenomena of traumatic experience, avoidance thoughts and behaviours, hyperarousal symptoms, emotional mumbling, cognitive impairment and, sometimes, severe dissociative symptoms, self-harm and suicidality [3-7]. The psychotherapeutic approaches are relevant in alleviating of psychopathology of trauma-related disorders and PTSD [2,8]. However, psychopharmacological treatment has a relevant role in managing the PTSD symptoms [9]. Several neurobiological mechanisms are implicated in the PTSD pharmacological strategies [10].

Recent evidences are revealing the role of oxytocin (OXT) in the pathophysiology of PTSD and its possible application in prevention and

the treatment of PTSD. Aim of the present article is to provide a brief description of OXT effects on biological systems implicated in the pathophysiology of trauma-related disorders and to conduct a systematic review of randomized controlled trials (RCT) of clinical effects of oxytocin in PTSD and trauma-related disorders.

Pathophysiology of oxytocin in stress-related disorders

The stress response features many physiological processes, such as cognitive and behavioral ones, that are able to ensure survival and restore homeostasis. Perceived unexpected threats or aversive situations can elicit cardiovascular, immune and neuroendocrine processes, leading to adaptive or maladaptive responses [11,12].

Trauma exposure can have enduring and overwhelming psycho-physiological consequences. On one hand, the risk of psychiatric conditions such as anxiety disorders, depression, alcohol abuse and, most of all, PTSD is highly enhanced [13]. On a physiological level instead trauma exposure can lead to disruptions of the neuroendocrine system, most frequently with regard to the hypothalamic-pituitary-adrenal (HPA) axis. Being able to respond either to internal and external stimuli, e.g. many life stressors, is one of the HPA axis' fundamental role [14-16]. Many stressful events, mostly during early life, could impact on HPA axis' homeostasis, resulting to be either hyperactivated or hypoactivated. This may lead to multiple pathophysiological effects, ranging from the vulnerability to many physical and mental disorders to the weakening of the immune system [17 19]. Many factors are well known to affect the function of the HPA axis and among them the neurotransmitter OXT plays a significant role. OXT is a neurohormone produced in the central nervous system (CNS), specifically by the hypothalamus in the supraoptic (SON) and paraventricular (PVN) nuclei, and is deeply involved in affecting social behaviors [20]. Through axons projections, hypothalamic neurons send OXT to the posterior hypophysis, or neurohypophysis, and, from there, to the bloodstream. When stressful experiences occur, the central OXT secretion exerts the function of maintaining and modulating cortisol levels, minimizing the response of the HPA axis and therefore allowing the body to uphold its prestress homeostasis [21-23].

Other than modulating the HPA pathway, OXT is an important regulator of anxiety for further reasons. Existing evidence suggests that this neuropeptide wields anxiolytic effects acting on the main stress-related and salience network in the brain. In humans, in fact, many regions express the oxytocin receptor (OR). These include the brainstem, olfactory nucleus, anterior cingulate cortex and both central and basolateral amygdala [24]. The OR-mediated anxiolytic effect features a intracellular activation of mitogen-activated protein kinase signaling pathways, which leads to long

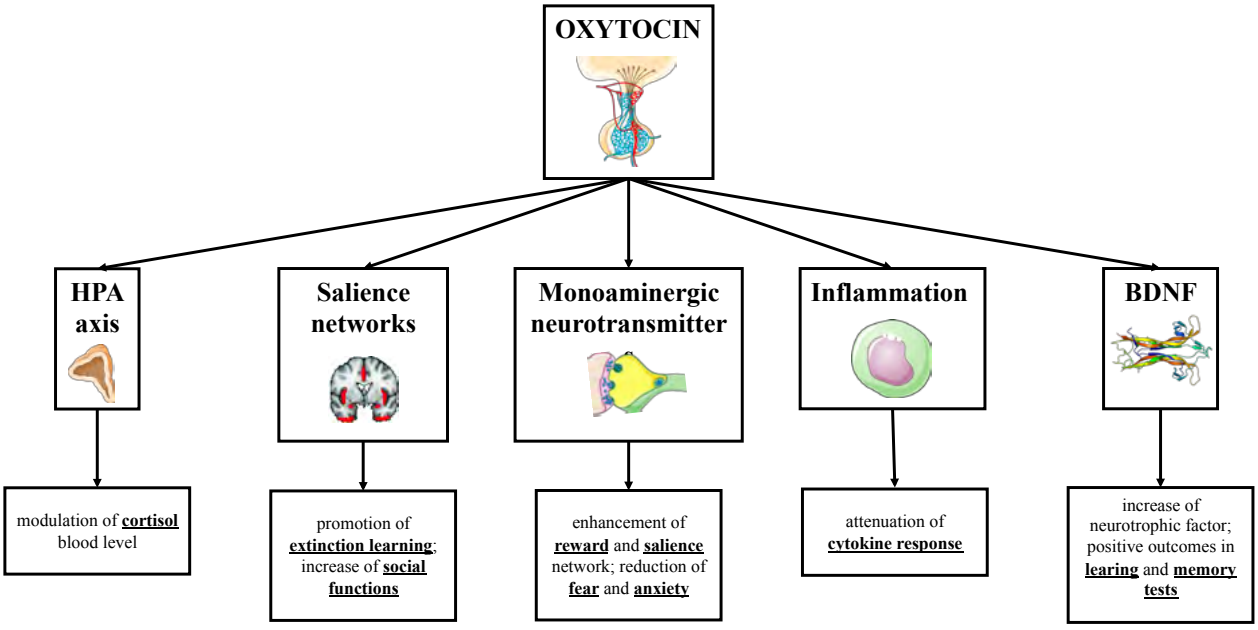

FIGURE 1. *Schematic representation of oxytocin effects on biological systems implicated in the pathophysiology of trauma-related disorders.*

term behavioral adaptations through differential gene expression [25,26]. In addition, oxytocin-related neural activity is deeply connected to other neurotransmitters of the salience and reward regions, with evidence of its effects on norepinephrine, serotonin and dopamine systems [27-29].

A growing research suggests that OXT has anti-inflammatory effects, which encourages future studies, given the evidence of high pro-inflammatory cytokine levels in patients with stress-related disorders. Intravenous administration of OXT in humans demonstrated to dampen cytokine effects in healthy individuals and, on the other hand, in hamsters enhanced wound healing [30,31].

Although preliminary, promising data show that OXT enhances BDNF levels in chronic stress rat models [32,33]. BDNF is a key factor that participate in neural development, growth and plasticity whereas its

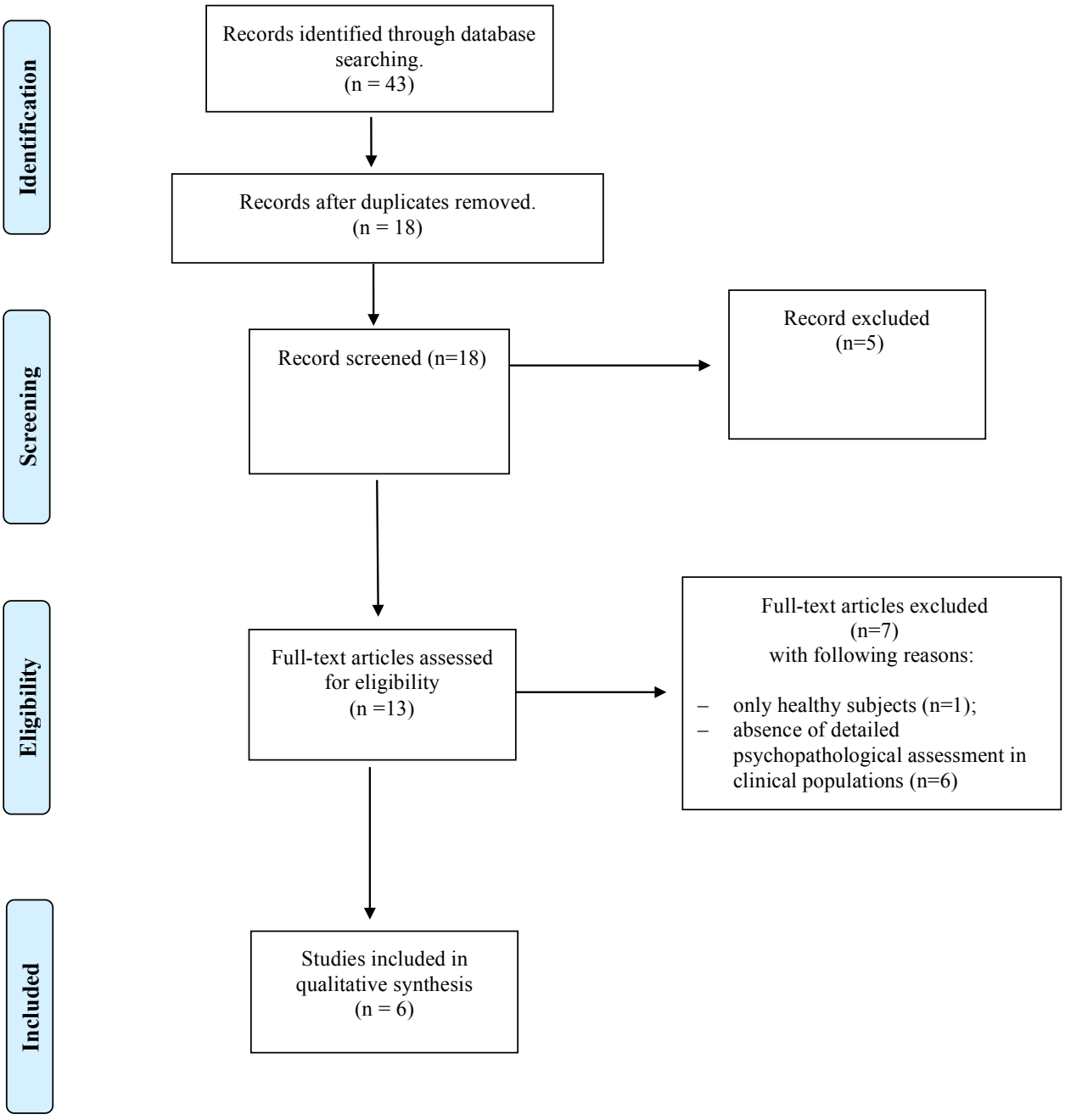

FIGURE 2. *Stages of the screening process applied in the selection of studies.*

TABLE I. *Acute clinical effect of intranasal oxytocin administration.*

Author/ Year	N/sex	Sample	Trauma characteristics	PTSD assessment scale
Koch et al., 2019	Interest sample (P/O)	CAPS ETI IES-R	MINI-plus SCID AUDIT HADS fMRI, WMT	40IU
	15F 21M 36T	PP with PTSD	W-RTE and CTE	
	Interest sample (P/O)			
	20F 20M 40T	PP trauma-exposed	W-RTE and CTE	
Sack et al., 2017	Interest sample (O+P)	SKID IES	SCID-D DES RSDI Second study (TSST challenge experiment) : M-CIDI	24 IU
	35 F	PTSD outpatients Psychosomatic Clinic	17 SV by a family member, 6 non-SV by a family member, 4 accident, 3 organized SV, 2 SV by a stranger 1 natural disaster	
	Comparison sample (O+P) (second study)			
	10 F	HS	No traumatic history	
Frijling et al., 2016 B	Interest sample (O)	TSQ PDI CAPS ETI	MINI RSDI Script driven imagery and resting state fMRI	40IU
	15F 9M 24T	ED, patients with AD and increasing risk of PTSD	12 traffic accident, 5 accident at work/ home, 6 interpersonal trauma, 1 other	
	Comparison sample (P)			
	9F 9M 18T	ED, patients with AD and increasing risk of PTSD	14 traffic accident, 3 accident at work/ home, 3 interpersonal trauma	
Koch et al., 2016	Interest sample (O/P or P/O)	CAPS	MINI-plus SCID VAS fMRI	40 IU

Other variables/ Instrument	Dose	Other drugs/ placebo	Adverse events	Clinical findings
Placebo (0.9% saline)	N.E.	Severity of PTSD, anxiety and depression symptoms did not differ between scanning sessions.		
Placebo	N.E.	Intranasal oxytocin treatment significantly attenuated PTSD symptoms triggered by trauma-script exposure. Oxytocin-mediated reduction in dissociative and re -experiencing symptoms was not significant. Oxytocin treatment attenuated avoidance with a trend for statistical significance.		
Placebo (0.8% NaCl)	N.E.	Treatment effects on RSDI scores after the trauma script were considered statistically significant. O-treated participants specifically reported higher flashback intensity during RS-trauma than P-treated participants.		
Placebo (NaCl 0.9%)	N.E.	Compared with placebo, O administration in PTSD patients was associated with lower ratings of subjective anxiety and nominally lower ratings of nervousness but not happiness and sadness.		

follows **TABLE I.** *Acute clinical effect of intranasal oxytocin administration.*

Author/ year	N/sex	Sample	Trauma characteristics	PTSD assessment scale
	16F 21M 37T	PP with PTSD	Early trauma and W-RTE, non-specified	
	Comparison sample (P/O or O/P)			
	20F 20M 40T	PP trauma-exposed without PTSD	Early trauma and W-RTE, non-specified	

Legend of sample: Acute Distress (AD), Childhood traumatic events (CTE), Emergency Department (ED), Healthy Subjects (HS), Police Personnel (PP), Sexual Violence (SV), Work-related traumatic event (W-RTE).
Legend of PTSD assessment scale: Clinician Administered PTSD Scale for DSM-5 (CAPS), Early Trauma Inventory, short version (ETI), German translation of the Structured Clinical Interview for DSM-IV (SKID-PTSD), Impact of Event Scale (IES), Impact of Event Scale-Revised (IES-R), Peritraumatic Distress Inventory (PDI), Posttraumatic diagnostic Scale (PDS), Trauma Screening Questionnaire (TSQ).

deficiency can cause aggressive behavior and anxiety disorders [34,35], including PTSD [36].
Having these evidences in mind, it is easily comprehensible why this hormone has an important role in social behaviors. This in fact has a powerful evolutionary significance, since interactions like mating, nursing, sex and lactation are situations where stress must be dramatically avoided.
Figure 1 summarizes schematically main actions of OXT on biological systems that are involved in the pathophysiology of trauma-related disorders and PTSD.

Methods

The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA - Moher et al., 2009) were adopted as the methodological framework of this study.
The electronic database PsycINFO, PubMed, Scopus, Web of Science were searched with limitation in terms of type of articles (randomized controlled trials). The following keywords were used followed by "AND" or "OR" oxytocin; PTSD; post-traumatic stress disorder; traumatic events; trauma-related disorder, acute trauma. Textbooks on psychiatry were also consulted.
The selection of papers suitable for this review was restricted to articles published in English peer-reviewed journals and those that added an original contribution to the literature. Studies on healthy samples were excluded from our research. At the same way, studies of neural responses or specific task with no clinical correlates were excluded (see Fig. 2 for search results as well the reasons for article exclusion).
Two reviewers (L.L., T.B.J.) independently inspected all citations of studies identified by the search and grouped them according to the topic of the papers. Reviewers acquired the full-text article for all papers located. Where disagreement occurred, this was resolved by discussion with the senior author (G.D.L.) who also independently inspected all articles located and grouped them following the major areas of interest identified by the reviewers.

Results

A total of 43 articles were found, but only 6 articles were selected after applying the inclusion and exclusion criteria (Fig. 2).
The studies were divided into two groups, based on the number of intranasal oxytocin administrations: four studies with less than 2 OXT administrations were included in the "acute clinical effects of oxytocin administration" group (Tab. I); studies with more than 2 OXT administrations were included in the "long clinical effects of oxytocin administration" group (Tab. II).
The major results of each study group are presented below.

Acute clinical effects of oxytocin administration

In a recent study [37] of 36 PTSD police officers and 40 police officers trauma-exposed controls Koch *and colleagues* showed that after oxytocin administration (40 IU) or placebo (0.9% saline) on average 83.48 (± 4.21) minutes before task performance; severity of PTSD, anxiety and depression symptoms did not differ between scanning session (all $p > 0.05$).
In contrast, Sack *and colleagues* [38], in a study of 35 PTSD women (outpatients of Psychosomatic Clinic) and

Other variables/ Instrument	Dose	Other drugs/ placebo	Adverse events	Clinical Findings

Legend of other variables/ Instrument: Alcohol use disorder identification test (AUDIT), Dissociative Experiences Scale (DES), Hospital Anxiety and Depression Scale (HADS), Mini International Neuropsychiatric Interview (MINI), Munich Composite International Diagnostic Interview (M-CIDI), neutral script condition (RS-neutral), Profile of Mood States (POMS), Responses to Script-Driven Imagery Scale (RSDI), Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D), trauma script condition (RS-trauma), Trier Social Stress Test (TSST),Visual analog scale (VAS), Working memory task (WMT).

10 healthy women, showed that after 1 dose (24 IU) of oxytocin or placebo administered, Responses to Script-Driven Imagery Scale (RSDI) was significantly reduced in oxytocin-treated patients (p = 0.012). Consequently, intranasal oxytocin treatment significantly attenuated PTSD symptoms triggered by trauma-script exposure. Furthermore, oxytocin treatment attenuated avoidance, at least with a trend for statistical significance (p = 0.093). Contrarily oxytocin-mediated reduction in dissociative and re-experiencing symptoms was not significant (respectively p = 0.26 and p = 0.15).

Also Frijling *and colleagues* [39], in a study of 42 subjects with acute distress and increasing risk of PTSD (TSQ ≥ 5, PDI ≥ 17), showed that, after 40 IU of oxytocin (24 patients) or placebo (0.8% NaCl, 18 patients) administered forty-five minutes before script driven imagery and resting state fMRI, treatment effects on Responses to Script-Driven Imagery Scale (RSDI) were considered statistically significant. In particular, the study showed that Sleepiness attenuation from RS-neutral to RS-trauma was significantly higher in oxytocin-treated participants than in placebo-treated participants (p = 0.03). Sleepiness during RS-trauma was significantly lower in oxytocin-treated participants (p = 0.04). Furthermore, the study showed no group differences on RSDI subscale scores after the trauma script (i.e., PTSD symptoms during RS trauma) (p = 0.45), but oxytocin-treated participants specifically reported higher flashback intensity during RS-trauma than placebo-treated participants (p = 0.046). CAPS re-experiencing scores were associated with RSDI flashback intensity scores (p = 0.018), but did not explain the observed group difference. Adjusting for duration between intranasal administration and scanning, the oxytocin effect on lowering sleepiness during RS-trauma became marginally significant (p = 0.053), and adjusting for lifetime PTSD, oxytocin-treated participants had marginally higher flashback intensity scores during RS-trauma than placebo-treated participants (p = 0.07). Moreover, the study concluded that all other results were unaltered.

Also Koch *and colleagues* [40], in a study on 37 police personnel with PTSD and 40 police personnel trauma exposed without PTSD, with randomized administration of oxytocin (40 IU) during one fMRI session and placebo (NaCl 0.9%) during another fMRI session (or the contrary), showed lower ratings of subjective anxiety (p = 0.044) and nominally lower ratings of nervousness (p = 0.055) but not happiness and sadness (all p > 0.05) in patients with oxytocin administration in PTSD sample.

Long clinical effects of oxytocin administration group

Only two studies of long clinical effects of oxytocin were found.

In a recent study, Flanagan *and colleagues* [41] has evaluated the effects of 8 doses of oxytocin (40 IU for dose, 8 subjects) or placebo (8 doses, 9 subjects) administered 45 minutes prior to each weekly of Prolonged Exposure (PE) therapy session in 17 patients with PTSD. The study concluded that the oxytocin group show lower PTSD and depression symptoms during PE, and had higher working alliance scores, although these differences did not reach statistical significance. Furthermore, the oxytocin group had a marginally lower estimated mean PCL-5 score at end of treatment as compared to the placebo group (31.0 *vs* 40.9, p = 0.09). Between-group differences in the trajectory

TABLE II. *Long clinical effect of intranasal oxytocin administration.*

Author/ year	N/sex	Sample	Trauma characteristics	PTSD assessment scale
Flanagan et al., 2018	Interest sample (O)	Global sample: 8 trauma related to combat exposure 4 sexual assault 5 other trauma	CAPS PCL-5	MINI HAQ-II CSQ BDI-II
	1 F 7 M 8T	PTSD sample (5 veterans)		
	Comparison sample (P)			
	2 W 7 M 9 T	PTSD sample (5 veterans)		
Van Zuiden et al., 2017	Interest sample (O)	TSQ PDI CAPS PDEQ IES-R ETI	MINI HADS PSS	40 UI twice daily for 8 days
	27F 26M 53T	Adult ED patients with current trauma	43 accidents 10 assault	
	Comparison sample (P)			
	26F 28M 54T	Adult ED patients with current trauma	48 accidents 6 assault	

Legend of sample: Emergency Department (ED),
Legend of PTSD assessment scale: Clinician Administered PTSD Scale for DSM-5 (CAPS), Early Trauma Inventory, short version (ETI), Impact of Event Scale (IES), I mpact of Event Scale-Revised (IES-R), Peritraumatic Dissociation Experience Questionnaire (PDEQ), Peritraumatic Distress Inventory (PDI), PTSD Checklist for DSM-5 (PCL-5), Trauma Screening Questionnaire (TSQ).
Legend of other variables/ Instrument: Beck Depression Inventory, second edition (BDI-II), Client Satisfaction Questionnaire (CSQ), Hospital Anxiety and Depression Scale (HADS) Helping Alliance Questionnaire (HAQ-II), Mini International Neuropsychiatric Interview (MINI), Perceived Stress Scale (PSS).

Other variables/ Instrument	Dose	Other drugs/ placebo	Adverse events	Clinical findings
40 IU (8 doses)	Placebo (8 doses)	NO	The oxytocin group demonstrated lower PTSD and depression symptoms during PE, and had higher working alliance scores, although these differences did not reach statistical significance. Between-group differences in the trajectory of symptom improvement, session 3 PCL-5 scores showed a statistically significant group difference.	
Placebo (0.9% NaCl)	Yes (see results section for details)	An effect of oxytocin dependent on acute PTSD symptom severity was found, as assessed at baseline within 10 days post trauma. Oxytocin- treated participants with high acute PTSD symptoms had significantly lower PTSD symptom severity across the complete follow-up period up to 6 months post trauma. IES, HAD-anxiety and HAD-depression scores at follow-up significantly decreased over time, without significant group differences in overall symptom severity or symptom decrease over time.		

of symptom improvement, PCL-5 scores showed a statistically significant group difference (O = 30.3 *vs* P = 45.4, p = 0.03).

Van Zuiden *and colleagues* [42] in a study of adult emergency department patients with current trauma (with TSQ ≥ 5 and PDI ≥ 17), 12 days after trauma, administered 40 IU of oxytocin twice daily for 8 days (53 subjects) or placebo (0.9%) with the same scheme (54 subjects). Participants recorded their self-reported administration time and potential adverse effects in a diary. Patients treated with oxytocin showed the following adverse events: ear, nose, and/or throat symptoms (12), headache (4), gastrointestinal symptoms (4), neurological symptoms (3), sleep problems (4), positive sensation/feeling (1), light-headedness and/or dizziness (1), planned surgery (10), fatigue (1), pulmonary symptoms (1), neck and back pain (1), dermatological symptoms (1), traffic accident without hospital admission (1), deep venous thrombosis (1), suicidal ideation (1), other (8), gynaecological women symptoms (3) [42]. In all participants, oxytocin administration did not result in significantly lower clinician rated PTSD symptom severity compared to placebo at 1.5 months post-trauma or across follow-up compared to placebo-controls. Nevertheless, the study showed that effect of oxytocin dependent on acute PTSD symptom severity, as assessed at baseline within 10 days post-trauma. Relative to placebo-treated individuals with high acute PTSD symptoms, oxytocin- treated participants with high acute PTSD symptoms had significantly lower PTSD symptom severity across the complete follow-up period up to 6 months post trauma, indicating a long-term protective effect. In contrast, oxytocin administration had no effect on follow-up PTSD symptoms for individuals with relatively low acute PTSD symptom severity. Furthermore, IES, HAD-anxiety and HAD-depression scores at follow-up significantly decreased over time, without significant group differences in overall symptom severity or symptom decrease over time.

Discussion

Very few RCT were found for this review. The results of our review are exiguous and presents different limitations.

The group "Acute clinical effects of oxytocin administration" consists of four studies. For two studies, the sample consists in police officers with PTSD or trauma-exposed controls [37,40]. One study's sample it's composed only by women with PTSD or healthy subjects [38], and the last study analyzed not PTSD patients, but patients with acute distress and increasing risk of PTSD [39]. Furthermore, also the characteristics of trauma are different: work-related traumatic event and childhood traumatic events [37,40], different traumas with a prevalence of violence [38] and different traumas with a prevalence of traffic accidents [39]. The PTSD assessment and the other instruments utilized are also different (Tab. I). Different doses of oxytocin were administered: three studies administered 40 IU [37,39,40], one study 24 IU [38]. No psychological treatment was implemented in the analyzed studies and no adverse events are reported in the full-text papers.

The results of acute clinical effects of oxytocin administration were in contrast. After administration of oxytocin, it was reported a reduction of levels of PTSD global symptomatology [38,39], anxiety [40], sleepiness [39] and nervousness [40]. For specific cluster of PTSD symptomatology, Sack *and colleagues* showed that only avoidance was attenuated with a trend for statistical significance, while reduction of dissociative and re-experiencing symptoms was not statistically significant [38]. In contrast, a recent study [37] did not show differences in PTSD symptomatology, anxiety and depression. Furthermore, Frinjling *and colleagues* [39] showed that after oxytocin administration, patients specifically reported higher flashback intensity at trauma script condition (RS-trauma) respect to the placebo controls.

The "long clinical effects of intranasal oxytocin administration" group consists of only two articles. Also in this group, the samples of the studies were different for clinical features. In particular, one study [41] consists of PTSD patients (10 of 17 patients were veterans), the other study consists of patients with acute distress and increasing risk of PTSD [42]. Moreover, the trauma characteristics were different: different traumas with a relative prevalence of trauma related to combat exposure in one study [38] and different traumas with a prevalence of traffic accidents in the other study [39]. The PTSD assessment and the other instruments utilized are also different (Tab. II) but both the studies utilized the CAPS for PTSD assessment scale. The dose of oxytocin administered were different: 40 IU for 8 doses [41] and 40 IU twice daily for 8 days [42] 12 days after trauma exposure. Furthermore, in one study the single dose was administered before each weekly of Prolonged Exposure therapy [41] while in the other study, no psychological treatment was provided. One study, report reports several side effects (see results section for details). During Prolonged Exposure, patients treated with oxytocin show a non-statistically significant reduction of PTSD global and depression symptomatology, only in session-3 the authors found a significant group difference [41]. In contrast, Van Zuiden *and colleagues* [42] showed that oxytocin administration did not result in significantly lower clinician rated PTSD symptom severity compared to placebo at 1.5 months post-trauma or across follow-up compared to placebo-

controls. But the same study [42] showed that the effect of oxytocin depends on acute PTSD symptom severity, as assessed at baseline within 10 days post trauma. In particular, participant with high acute PTSD symptoms had significantly lower PTSD symptom severity across the complete follow-up period up to 6 months post trauma, indicating a long-term protective effect, while oxytocin administration had no effect on follow-up PTSD symptoms for individuals with relatively low acute PTSD symptom severity. Furthermore, at follow-up, scores of Impact of Event Scale (IES), Hamilton Rating Scale for Anxiety (HAM-A) and Hamilton Rating Scale for Depression (HAM-D) decreased significantly over time, without significant group differences in overall symptom severity or symptom decrease over time.

Conclusions

The studies analyzed for this systematic review present a small number of patients included and are highly heterogeneous for clinical features, presenting differences in the samples for types of traumas and clinical assessment, as well as for dosages of oxytocin. Furthermore, in one study the use of oxytocin was analyzed in add-on other specific treatment (psychotherapy). Future clinical studies, with accurate psychopathological assessments and a structured clinical follow-up, are mandatory to understand the clinical efficacy of oxytocin administration in patients with PTSD or in patients with acute distress and an increasing risk in developing PTSD.

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