UNIVERSITY OF PISA

RESEARCH DOCTORATE IN NEUROBIOLOGY AND CLINIC OF AFFECTIVE DISORDERS

DEPARTMENT OF PSYCHIATRY, NEUROBIOLOGY, PHARMACHOLOGY AND BIOTECNOLOGIES

Thesis:

MULTICENTER NATIONAL STUDY IN PATIENTS WITH POST-TRAUMATIC STRESS DISORDER AND/OR COMPLICATED GRIEF VERSUS CONTROLS: VALIDATION OF THE STRUCTURED CLINICAL INTERVIEW FOR TRAUMA AND LOSS SPECTRUM (SCI-TALS) AND NEUROBIOLOGICAL CORRELATIONS TO MOOD SPECTRUM

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YEARS 2004-2006

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1. SYNOPSIS

Clinicians and researchers are increasingly interested in a better characterization of psychiatric disorders than that provided by the DSM IV-TR (Kupfer, 2005; Maj, 2005; Maser & Akiskal, 2002). Despite debates and different perspectives concerning diagnostic nomenclature have been vital in psychology and psychiatry through the last 40-50 years, the forthcoming DSM-V is challenging the current categorical conceptualization. New data emerging from basic and clinical neurosciences, genetics, cognitive and behavioural sciences, clinical research (rising issues such as that of "comorbidity"), as well as the increasing need to provide more sophisticated examination of development across the lifespan, have increased the debate on the essential need of incorporating a dimensional model directly into the diagnostic nomenclature. Inevitably, this process has also involved post-traumatic stress conditions, that have recently risen progressive interest after the emerging increasing rates of exposure to trauma in the general population, either related to urban or domestic violence, or to great disasters, such as happened for the Twin Towers terrorist attack, the Tsunami or the New Orleans hurricane.

Post-Traumatic Stress Disorder (PTSD) is a severe and often chronic disorder with a typical onset following exposure to traumatic events (Kessler et al., 1995), that has been only recently carefully investigated in general population samples (Breslau et al., 1991; Kessler et al., 1995). Originally

described as a war related disorder it was first coded in DSM only in 1980 (DSM-III) and its characteristics and diagnostic criteria have been progressively defined, both for what concerns the definition of the trauma and of the symptomatology. Current diagnostic criteria (DSM-IV-TR, 2000) stipulate exposure to an event that threatens serious physical injury or death, and that is accompanied by feelings of intense fear, helplessness, or horror, the diagnosis then requires development of symptoms in 3 domains, re-experiencing, avoidance and hyperarousal, that persist for at least a month.

Recently, investigators have emphasized the importance of a further evolution in the definition of whether the event is shocking to the individual or not, regardless of its form, in order to define it as traumatic, i.e. able to produce symptoms of traumatic stress (intrusion, numbing and arousal) (Galea et al., 2005). Although greater degrees of trauma are expected to yield higher rates of PTSD than less extreme ones (Engdahl et al., 1997), increasing evidence documents the importance of the so-called "low-magnitude" events (e.g., divorce, serious illness and financial reverses) in determining post-traumatic stress reactions (Breslau & Davis, 1987; Solomon & Canino, 1990; Moreau & Zisook, 2002). Moreover, several studies reported significant functional impairment and seek for treatment in a large number of victims who, even if exposed to a DSM-IV-qualified trauma, did not fulfil all the other criteria (B,C and D) for PTSD (Stein et al., 1997; Marshall et al., 2001; Hepp et al., 2005), leading some authors to introduced the concepts of partial, subthreshold or subsyndromal PTSD, in order to better investigate the clinical relevance of

these forms (Weiss et al., 1992; Carlier & Gersons, 1995; Stein et al., 1997). In line with these data, a first multidimensional model approach to PTSD has been developed, exploring the symptom severity, the nature of the stressor and the possible responses to trauma (Moreau & Zisook, 2002).

As part of an international collaboration project, named the "Spectrum Project", ongoing since 1995 between researchers form the University of Pisa (G.B. Cassano, L. Dell'Osso, M. Mauri), the Western Psychiatric Institute and Clinic of the University of Pittsburgh (E. Frank, D.J. Kupfer), the Columbia University of New York (J. Endicott, M.K. Shear) and of the University of California San Diego (J.D. Maser), a new concept of trauma and loss spectrum has been developed. This concept is based on a spectrum model (Cassano et al., 1997) that emphasizes soft signs, low-grade symptoms, subthreshold syndromes, as well as temperamental and personality traits comprising the clinical and subsyndromal manifestations, that targets PTSD and prolonged grief disorder. This latest, also sometimes called Complicated Grief (CG), has been recently explored as an independent form of stress response (Prigerson et al., 1995, 1996; Horowitz et al., 1997).

In line with an increasing number of studies interested in a better characterization of psychiatric disorders than that provided in DSM IV-TR (Kupfer, 2005; Maser & Akiskal, 2002), the "Spectrum Project" is aimed at developing and testing a set of instruments that assess a broad array of clinical features associated with different DSM conditions (Fagiolini et al., 1999; Cassano et al., 1999; Mauri et al., 2000; Dell'Osso et al., 2000; Dell'Osso et

al., 2002a, 2002b; Sbrana et al., 2003; Sbrana et al., 2005). The latest of this series of spectrum assessment is represented by the Structured Clinical Interview for Trauma and Loss Spectrum (SCI-TALS), whose development process and validation study is reported in the present thesis.

When developing a spectrum assessment of this condition, we included a continuum of potentially triggering events, a range of symptoms that comprise an acute reaction, and an array of persistent symptoms. We also included loss events as highly stressful experiences capable of evoking a specific constellation of grief symptoms, in line with recent work identifying a syndrome of complicated grief as a form of stress response (Prigerson et al., 1996; 1999; Horowitz et al 1997; Shear & Smith-Caroff, 2002; Langner & Maercker, 2005; Shear & Shair, 2005). The instrument includes two specific sections that apply the "spectrum" concept to the definition of the trauma: one exploring the exposure to a spectrum of losses, including either those of relatives or close friend or of important relationships or situations; the other exploring a spectrum of traumas ranging form DSM-IV-qualifying ones to less severe experiences. The items of the interview include, in addition to a subset of the DSM-IV criteria for PTSD, a number of features derived from clinical experience and from a review of the phenomenological descriptions of post-traumatic syndromes including CG.

Primary aim of the present thesis is to document the acceptability, reliability and validity of the Structured Clinical Interview for Trauma and Loss Spectrum (SCI-TALS), that was investigated through a national

multicenter validation study, involving 6 Italian Academic Departments of Psychiatry (Pisa, Cagliari, Milano, Napoli, Sassari and Siena), coordinated by the 2nd Psychiatric University Clinic of the University of Pisa (Prof. L. Dell'Osso, Dr. C. Carmassi). Study participants included a consecutive sample of 186 subjects, divided in three diagnostic groups (patients with PTSD, patients with CG and Controls), data from a sub-sample of 140 subjects, without comorbid diagnosis of PTSD and CG, were analyzed for the validation study of the SCI-TALS reported in the present thesis. The final sample included 48 consecutive patients with PTSD (DSM-IV-TR, 2000), 44 with CG (Prigerson et al., 1999), and 48 comparison individuals, without current or lifetime psychiatric history. All subjects were assessed by: SCID, for DSM-IV diagnosis (number of items endorsed in re-experiencing, avoidance and arousal criteria were listed), Impact of Event Scale, for PTSD severity, and Inventory of Complicated Grief, for CG diagnosis .

Results showed that SCI-TALS significantly discriminated subjects with PTSD or CG from controls. As expected, the instrument did not discriminate between those with PTSD and CG, except on the domain of grief reactions. Validity and reliability of the instrument were confirmed as substantial and internal consistency was good. Acceptability was excellent. The SCI-TALS showed to be user friendly to both clinicians and patients.

Besides progresses in clinical assessments, recent studies attempting to arrive at a clear-cut demarcation of the PTSD syndrome and to delineate clear-cut diagnostic criteria for PTSD, have suggested the relevance of biological

markers of PTSD. Although the findings have been highly variable (de Kloet et al., 2006), a great number of data have suggested the presence of characteristic alterations in the function of hypothalamic-pituitary-adrenal (HPA) axis (Yehuda et al., 2000; Nemeroff et al, 2006), the network which coordinates steroid metabolism during the physiological responses.

The steroid biosynthesis occurs mainly in the adrenal gland, but also in the brain glial cells, in which the so-called neurosteroids are synthesized. In both tissues, the pivotal limiting step in the synthesis is the cholesterol transport within mitochondria which is realized through a mitochondrial pore. The mitochondrial translocator protein (Peripheral Benzodiazepine Receptor, PBR), a protein complex mainly localized in the outer membranes of the mitochondria, has been demonstrated to be a component of such pore, essential for the cholesterol crossing through the outer mitochondrial membrane, behaving either as a channel or as a chaperon (Culty et al., 1999; Lacapere & Papadopoulos, 2003).

The PBR density has been found altered in many psychiatric disorders (Papadopoulos et al, 2006) as well as in stress responses: up-regulation has been shown in acute stress conditions while down-regulation in repeated or chronic stress (Weizman et al., 1994; Gavish et al., 1996; Droogleever et al., 2004; Veenman & Gavish, 2006).

Studies on PTSD have investigated platelet PBR levels only in veteran populations during or after chronic war stress (Weizman et al., 1994; Gavish et al., 1996), in which lower receptor levels have been reported.

Since mitochondrial PBR is a key element in the steroidogenesis rate-limiting step, and alterations in the HPA axis seem to represent a characteristic finding of PTSD patients, secondary aim of the present thesis was to explore lymphomonocyte mitochondrial PBR alterations in Italian civilian patients with PTSD (DSM-IV), exposed to non-combat related traumas, versus controls.

Increasing data in the literature have shown higher vulnerability for PTSD development in patients with bipolar disorder (BD) (Otto et al., 2004), and authors are debating whether BD might represent a risk factor for PTSD (Pollack et al., 2006) or if this comorbidity might be due to the fact that patients with BD frequently present characteristics that have been identified as risk factors for PTSD, such as: trauma exposure (Darves-Bornoz et al., 1995; Mueser et al., 1998; Neria et al., 2002), depression and hypomania (Schnurr et al., 1993), comorbid anxiety disorders (Pollack et al., 2006). Recently Pollock and collaborators (Pollack et al., 2006), examining PTSD onset following indirect exposure to the September 11, 2001, terrorist attacks, in a cohort of patients with BD (enrolled in the on-going longitudinal study Systematic Treatment Enhancement Program for Bipolar Disorder, STEP-BD), have suggested the presence of manic state at the time of exposure as the most critical risk factor for the onset of persistent PTSD.

Since increasing data have reported the possibility of a relevant correlation between the presence of a manic or hypomanic state during exposure to traumatic events and the subsequent onset of PTSD (Otto et al., 2004), secondary aim of the present study was to investigate if the number of

lifetime manic/hypomanic spectrum symptoms reported by the patient could be correlated with PBR density decrease in civil patients with PTSD. Correlations between PBR changes and lifetime subthreshold mania in patients with PTSD diagnosis were investigated in order to corroborate the role of mood alterations as risk factors for adverse sequel following exposure to trauma.

Until now, no difference has been reported in platelet PBR density of subjects with major depression, with respect to controls. Moreover, no studies are available about PBR in bipolar disorders, although abnormalities of the HPA axis functions are well documented in this psychiatric disorder (Gavish et al., 1999; Watson et al., 2004).

Subjects enrolled for the national multicenter validation study at the Pisa site were asked to complete this second phase of the study. Patients who consented to participate gave a blood sample (16 ml) after all procedures were explained to them and a written consent was obtained. Blood samples were then processed to assess PBR binding characteristics in lymphomonocyte mitochondrial membranes. Patients were also assessed by the MOODS-SR (Dell'Osso et al., 2002), a sharpened assessing the mood spectrum symptomatology.

These results showed, for the first time, a significant decrease in mitochondrial PBR density in the lymphomonocytes of civilian trauma victims with diagnosis of PTSD with respect to controls, according to data obtained in war-related samples. PBR alterations presented a significant correlation to full-blown Axis I PTSD diagnosis, enhancing the possible relevance of PBR for

diagnostic implications in PTSD. We did not also evidenced any correlation between the receptor density and IES scores, in line with previous findings (Weizman R. et al., 1994). Further, a significant correlation between PBR alterations and the presence of lifetime manic spectrum symptoms was found. We enhanced a significant correlation between PBR Bmax and total Mania values of the MOODS-SR. In particular, patients with PTSD presenting the highest number of lifetime manic/hypomanic items showed the lowest PBR density. This data corroborated the relevance of an accurate assessment of manic-hypomanic spectrum symptoms as risk factor for PTSD onset.

In conclusion, post-traumatic stress conditions are showing increasing prevalence in the general population and subclinical and subsyndromal forms are showing their clinical relevance. The results of the present thesis demonstrate the validity of a new assessment instrument, the Structured clinical interview for Trauma and Loss Spectrum, corroborating the relevance of a spectrum approach to post-traumatic stress conditions, including CG.

The SCI-TALS showed to be a valid and reliable instrument, able to provide a more specific description of patients' clinical features giving information on a broad spectrum of trauma, loss events and related symptoms beyond those covered by existing instruments. A less restrictive approach to the definition of the potentially traumatic events than that defined in DSM-IV, as reported by SCI-TALS, would particularly help clinicians to more accurately explore post-traumatic stress conditions. Moreover, the evidence of a different profile for those suffering the consequences of trauma versus loss

suggests that the spectrum approach might help identify specific phenotypes to be used in clinical, neurobiological and genetic studies.

Further, in line with studies enhancing the need for neurobiological markers for a better understanding of either full blown and subsyndromal forms, the significant decrease in platelet PBR levels found in civilian patients with PTSD supports a role for this biochemical parameter in clinical assessments. Moreover, the correlation between this alteration and the presence of lifetime manic spectrum symptoms enhances the possible role of mood spectrum symptomatology on PTSD onset, and corroborates the relevance of an accurate assessment of manic-hypomanic spectrum symptoms as risk factors for PTSD onset.

To our knowledge, this is the first study investigating PBR alterations in a group of civilian patients that reported a PTSD diagnosis not related to war traumas, comparing the receptor among subjects with chronic PTSD arisen after exposure to different types of traumas. Moreover, this is the first study in which PBR density determination was conduced only on mitochondrial membranes, assuring the PBR amount estimated is involved in the biosynthesis of steroids.

Further studies are warranted to assess the potential utility of this spectrum approach to PTSD and CG in clinical practice and to confirm the role of biological markers, such as PBR, in helping to increase the knowledge on the pathogenesis of these disorders.

2. INTRODUCTION

STRESS AND PSYCHIATRIC ILLNESS

Historically, the conceptualization of mental disorders had been ascribed to an imbalance in bodily humours, to the influence of external spiritual or other supernatural forces, and to moral or somatic deficiency. In the early nineteenth century, a new school of thought emerged in France, led by Philippe Pinel of the Salpetriere in Paris, and in the United States, led by Amariah Brigham, conceptualizing that the expression of mental illness was affected by life circumstances and, more broadly, by societal factors. These various influences were further elaborated an later converged in the bio-psychosocial models.

This orientation has progressively held to the modern concept that individual's response to stress can be modified and modulated by a number of intrinsic factors (e.g., genetic vulnerability, pre-morbid personality) and extrinsic factors (e.g., social support). Further models have incorporated individual temperamental and experiential characteristics, such as potential vulnerability (or resiliency) factors, stressful life events as initiating or exacerbating factors, and a variety of support networks as potentially modifying factors for the occurrence of mental illness. For the most part, this

multideterminate model of mental illness has dominated modern psychiatric thinking. Nevertheless, the current diagnostic nomenclature (the Diagnostic and Statistical Manual of Mental Disorders fourth edition revised, DSM-IV-TR) does not emphasize this bio-psychosocial model of the nature and genesis of psychiatric disorders for its structure that is proposed to be descriptive and phenomenological. Thus, in DSM-IV-TR, major depression is major depression, whether it appears in the context of job loss, divorce, or for no apparent reason. There are interesting inconsistencies in this approach, for example when a major depressive episode occurs in the context of bereavement it may not be coded as major depression in accordance to DSM-IV-TR, as there is agreement on the fact that loss events may induce, in most case, depressive "like" reactions. Interestingly, we can argue whether if individuals develop major depression after the loss of their home as consequence of a traumatic event. In this case, according to DSM-IV-TR, it should rather be diagnosed as an adjustment disorder (if short-lived), but if persistent, then a diagnosis of major depression would apply. The question rises on weather the two episodes should be considered differently just as correlate with re provoking or triggering event.

It is a given of human existence to be exposed to life-threatening events, and epidemiological studies confirm that a large majority of the population report such exposure. However, a substantial unlucky minority goes on to develop posttraumatic stress disorder (PTSD) and even if attention to this

debilitating condition has increased dramatically over the past decade, yet little is known on risk factors and psychopathology of PTSD.

The recent increasing attention to PTSD rises the relevance of a new focus on the impact of life events over the development of psychopathology. The increased risk for exposure in the modern countries, besides the documented need for treatment required by people expressing subthreshold form of post-traumatic stress reactions increases the need for researches oriented to a new dimensional approach to these conditions.

Although PTSD is another exception to the DSM-IV-TR rule that the nomenclature should be atheoretical (it is one of several disorders for which the occurrence of a stressful life event is pivotal for diagnosis), it has its own characteristic symptoms (e.g., reexperiencing symptoms), nevertheless, as it is happening for other disorders in the classification revision for the forthcoming DSM-V, multidimensional perspectives have been suggested to succeed struggling potentially stressful life events, acute reaction and persistent symptomatology into diagnosis.

In line with the progresses in this increasingly actual debate, further research is needed in order to sharpen the thinking about the relationship between life events, stress and psychiatric illness.

POST-TRAUMATIC STRESS DISORDER (PTSD)

Diagnostic Evolution and Epidemiology

The concept of Post-Traumatic Stress Disorder (PTSD) is well known nowadays, after its introduction in DSM-III in 1980 (APA, 1980). However, the relationship between life events and psychopathology has long been described in medicine, and many names and concepts have preceded the actual definition (Kinzie & Goetz, 1996).

In the most recent centuries it's possible to find descriptions of psychopathological reactions with a typical onset after exposure to a traumatic event that resemble the symptomatological features of what is now called PTSD (DSM-IV-TR, 2000).

The first anecdotic evidences of post-traumatic reactions can be found around the sixteenth century and were described in relationship to combat events (Holmes, 1985); later on, symptoms related to non combat trauma have also been described. In 1666, in fact, a case of post-traumatic syndrome has been described as consequence of the Great London Fire (Daly, 1983); two centuries later, even the famous writer Charles Dickens seemed to have experienced many post-traumatic symptoms after having witnessed a railway accident outside London (Trimble, 1981).

In 1838, Esquirol already described, in his "Traitè des maladies mentales", the possible role of certain life events as "moral" causes of mental illness in a systematic manner, enhancing the distinction between "psychological" and "physical" causes of insanity.

Subsequently, many different names were reported in the medical literature in order to define the clinical states developed after trauma exposure: in 1867 Ericksen defined the syndrome of "railway spine" (Ericksen, 1867; Trimble, 1981) to describe the varying mixture of neurological damages, psychological arousal and conversion symptoms that originated after the many railway accidents of that time; in 1871, de Costa, an American army physician, described the syndrome of "irritable hearth" (De Costa, 1871; Paul, 1987), enhancing the role of cardiovascular symptoms in these reactions. Other diagnostic entities were later created, especially in the context of military settings, in order to define these presentations of post-traumatic syndromes in a culturally acceptable manner. Particularly, names such as "weakness of the heart", "disordered action of the heart", "valvular disease of the heart", "trench syndrome", "shell shock syndrome" and "combat fatigue" were reported (Skerrit, 1983; Paul, 1987).

This concepts were later elaborated by authors at the turn between the XVIII and XIX century, but it is only at the end of the nineteenth century that Oppenheim first expressed the concept of psychic trauma, coining the word "traumatic neurosis", in order to describe the anxiety states rising after the exposure to emotional trauma. Also Kraepelin, in his Psychiatric Treatise

(1896), included the description of the “Schreckneurose”, or “fright neurosis”, as an independent clinical disorder with a typical onset related to severe trauma such as railway accidents, fire, or any other kind of disaster.

Nevertheless, it’s only with the World War I that the concept of traumatic neurosis, particularly as “war neurosis”, became a widely used term also outside the restricted group of experts. It’s in fact during the World War I that military physicians had to face an increasing number of soldiers presenting with this syndrome. Probably, the characteristics of a long lasting trench warfare, with respect to the battles of the military tradition of the eighteenth century, played a relevant role. Just at the end of the World War I, in fact, Ernst Simmel (1918) published the “Kriegsneurosen und psychisches Trauma” in which he fully treated the “war neurosis” syndrome suggesting a psychopathological onset of it. The observation of the inseparable presence of physical symptoms in psycho-traumatic disorders, performed during the World War I, led also Kadiner, an American army psychiatrist treating many veterans from World War I, to designate post-traumatic neurosis as a “physioneurosis” in 1941 (Kardiner, 1941).

It’s important to notice that in military life, a notion of psychological distress was not acceptable in general until very recently. In the case of “traumatic neurosis” in fact, the negative connotation in the sense of secondary gain, in both the Anglo-Saxon and the German ambit, was exemplary in this respect.

Anyway, after 1918, the interest recently arisen for these forms from the wide number of cases emerged to the attentions of military physicians, decreased rapidly for the natural decrease of the number of cases with the end of the war. This concept was then completely substituted with that of "reaction" (anxious or depressive) to traumatic or distressing events. It was only with the World War II that a new relevant number of cases was presented to the attention of clinicians.

A decisive impulse towards an accurate characterization of these disorders and to the acceptance of "post-traumatic stress disorder" as a formal diagnosis was given, with no doubt, in the United States by the effects of the Vietnam War and, in particular, by those post-traumatic syndromes that Vietnam veterans reported in the 60s and 80s. In those years, clinicians started to talk about a "post-Vietnam syndrome", which clinical descriptions fully meet the criteria for modern PTSD.

Despite the substantial evidences about the existence of a clinical syndrome developing as consequence of exposure to trauma of different kind and severity, no diagnostic category for disorders related to traumatic events was jet included neither in the Diagnostic and Statistical Manual of Mental Disorders (DSM), First Edition (APA, 1952) or Second Edition (APA, 1968). Only in 1980, with the third edition of the DSM, PTSD was fully included in the international psychiatric nomenclature, confirming the decisive role of Vientam war effects.

In DSM-III (APA, 1980), the term Post-Traumatic Stress Disorder was proposed by the American Psychiatric Association to describe, under a single definition, all the psychopathological syndromes typically developing after exposure to traumatic or distressing events that were "beyond the range of normal human experience", and characterized by prolonged psychic distress. In this way, the American Psychiatric Association tried to give an unitary nosographic approach to the different post-traumatic syndromes previously described by different authors.

From its first codification in the Diagnostic and Statistical Manual of Mental Disorders-IIIrd edition, in 1980, up to the latest DSM-IV-TR (APA, 2000), the characteristics of either the provoking trauma and of the symptomatology have been progressively more accurately described and defined.

One of the major evolutions has concerned the definition of the DSM Criterion A, that is the definition of the provoking trauma. While DSM-III defined trauma as an "event beyond the range of normal human experience and that can induce stress symptoms in most of the people", DSM-IV states as trauma "all the events that may threat one's physical integrity and that can induce feelings of intense fear, helplessness or horror, and that could directly involve the patient, or that the patient cold witness or learn about". This implies that the trauma is no more considered as an event outside the normal human experience, that is also a quite indefinite definition, but can include also very common experiences that can even happen in civilian population's

everyday experience. Moreover, DSM-IV does not specify that the trauma has to be an event that may have induced a severe post-traumatic reaction in almost everybody exposed (DSM-III, 1980), reducing the relevance given to the severity of the trauma for the syndrome onset and highlighting the role of subjective vulnerability.

In DSM-IV-TR (APA, 2000), no changes were reported to the criteria for PTSD diagnosis, in this latest version only un update of the associated features and of the comorbidity and familiarity were added. Although debate continues on whether an event could be defined as traumatic, that is able to elicit the onset of PTSD, the progressive evolution in the definition of the potentially traumatic events across DSM editions led to the actual definition (DSM-IV-TR, 2000) that includes either rare events (such as natural or human made disasters) and frighteningly common events (such as criminal victimization, rape or serious motor vehicle collision).

With this definition of trauma in place, recent surveys on the general population have reported increasing rates in the lifetime prevalence of the disorder, that is now placed at approximately 10%. The Epidemiologic Catchment Area (Helzer et al., 1987), the first epidemiological study assessing PTSD in the general population according to DSM-III criteria, reported rates of 0.9% (0.5% males and 1.3% females). More recently, adopting the DSM-IV criteria for PTSD, rates of 9.2% (6% males and 11.3% females) were reported in the Random Community Survey (Breslau et al., 1991), while rates of 7.8% (5.0% males e 10.4% females), in the National Comorbidity Survey (Kessler et

al., 1995). Interestingly all studies agree on the characteristic higher risk for females for developing the disorder. Females show rates of prevalence of PTSD that are almost twice as much as those reported by males, even when corrected for type of exposure (Prigerson et a, 2001). On the other hand, studies on trauma exposure constantly show the opposite, with males being exposed twice as much than females, further confirming females higher vulnerability to PTSD (Kessler et al., 1995).

Despite the differences in prevalence rates, the occurrence of PTSD after severe psychological trauma provides the most persuasive evidence in favour of certain kinds of stress causing psychiatric illness. Nevertheless, it's important to remind that event most severe psychological stressors can not to result in the development of PTSD (or other forms of psychiatric illness), as it has been reported also for the terrorist attack to the Twin Towers on September 11, 2001, were PTSD resulted in only approximately one out of ten residents of Manhattan, New York (Galea et al., 2005). These data stand as testimony to the resilience of the human psyche.

Clinical Characteristics and Subthreshold PTSD

Post-Traumatic Stress Disorder is a severe and often chronic disorder characterized by the development of symptoms in 3 domains, re-experiencing, avoidance and hyperarousal, that persist for at least a month according to

DSM-IV-TR (2000). As already mentioned current diagnostic criteria stipulate exposure to an event that threatens serious physical injury or death, and that is accompanied by feelings of intense fear, helplessness, or horror. The diagnosis then requires

Traumatic events can be experienced directly by the patient or can be witnessed by the patient, such as an event that threatens one's death, injury, physical integrity, or can be learned about by the patient. DSM-IV-TR lists the traumatic events that could be experienced directly, including, even if they could be not limited to: military combat, violent personal assault (such as sexual assault, physical attack, robbery, mugging), being kidnapped, being taken in hostage, terrorist attack, torture, incarceration as a prisoner of war or in a concentration camp, natural or man made disasters, severe automobile accidents, or being diagnosed with life threatening illness. Witnessed events include, but are not limited to: observing the serious injury or the unnatural death of another person due to a violent assault, accident, war, or disaster or unexpectedly witnessing a dead body or body parts. The events experienced by others that are learned about include, even if they are not limited to: violent personal assault, serious accidents or serious injuries experienced by a family member or a close friend; learning about the sudden, unexpected death of a family member or of a close friend, or learning that one's child has a life threatening disease.

In accordance to DSM-IV-TR (Criterion A2), the person's response to the trauma must involve intense fear, helplessness, or horror in order to be able

to determine a post-traumatic stress disorder. The way people respond during acute exposure to trauma is crucial in explaining whether they recover or develop mental health symptoms.

DSM-IV-TR recognizes the existence of a different disorder than PTSD if the onset of the symptomatology lasts within the first month since the trauma has occurred: Acute Stress Disorder (ASD). As already reported PTSD can diagnosed only if symptoms last for at least one month. Acute Stress Disorder is denoted by the presence of prominent dissociative symptoms (e.g., derealization, numbing), and when it occurs after trauma, it usually identifies a subset of individuals who are at several fold increased risk for the subsequent development of PTSD (Bryant and Harvey 1998, Bryant, 2003). Nevertheless this time frame distinguishing between ASD and PTSD seems to be arbitrary and researcher are planning to reconsider the existence of ASD in the forthcoming DSM-V.

DSM-IV-TR criteria for PTSD include the development of symptoms in 3 domains, the first of whom is represented by reexperiencing. The traumatic event can be reexperienced in various ways. Commonly the person has recurrent intrusive recollections of the event, including images, thoughts or perceptions (Criterion B1 of the DSM-IV-TR, 2000) or recurrent distressing dreams during which the event is replayed (Criterion B2). In rare instances the person experiences dissociative states that last from a few seconds to several hours, or even days, during which components of the event are relieved and the person behaves as though experiencing the event at that moment (Criterion

B3), this may include a sense of relieving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated. Intense psychological distress (Criterion B4) or physiological reactivity (Criterion B5) often occurs when the person is exposed to triggering events that resemble or symbolize an aspect of the traumatic event (e.g. anniversaries of the traumatic event; cold, snowy weather or uniformed guards for survivors of death camps in cold climates; hot, humid weather for combat veterans of the South Pacific; entering any elevator for a woman who was raped in an elevator).

The second diagnostic domain for PTSD diagnosis in accordance to DSM-IV, includes avoidance and numbing symptoms. Stimuli associated with the trauma are, in fact, persistently avoided. The person commonly makes deliberate efforts to avoid thoughts, feeling or conversations about the traumatic event (Criterion C1) and to avoid activities, situations, or people who arouse recollections of it (Criterion C2). This avoidance of reminders may include amnesia for an important aspect of the traumatic event (Criterion C3). Diminished responsiveness to the external world, referred to as a "psychic numbing" or "emotional anaesthesia", usually begins soon after the traumatic event. The individual may complain of having markedly diminished interest or participation in previously enjoyed activities (Criterion C4), of feeling detached or estranged from other people (Criterion C5), or of having markedly reduced ability to feel emotions (especially those associated with intimacy, tenderness, and sexuality) (Criterion C6). The individual may have a sense of a

foreshortened future(e.g. not expecting to have a career, marriage, children, or a normal life span) (Criterion 7).

The third domain for PTSD diagnosis (DSM-IV-TR, 2000) includes the symptomatology related to increased arousal. The individual, in fact, usually reports persistent feeling of anxiety or increased arousal that were not present before the trauma. These symptoms may include difficulty falling or staying asleep that may be due to recurrent nightmares during which the traumatic event is relieved (Criterion D1), hypervigilance (Criterion D4), and exaggerated startle response (Criterion D5). Some individuals report irritability or outbursts of anger (Criterion D2) or difficulty concentrating or completing tasks (Criterion D3).

The symptoms of PTSD usually occur soon after the occurrence of the traumatic event, although, in some cases, the symptoms develop months or even years after the trauma, in this case we talk about "PTSD with delayed onset" (i.e., if symptoms onset at least 6 months after the trauma). The course of the disorder can be acute, if symptoms last less than 3 months, or chronic, they last over 3 months. In most cases the course is chronic, with the highest levels of symptomatology usually expressed within the first three months from the onset (Freedman et al., 1999; Shalev et al., 2000).

Authors have reported how certain characteristics of the traumatic stressor or the immediate post-exposure response, including the magnitude of and proximity to the stressor (Engdahl et al., 1997;Breslau et al. 1999; Progerson et al, 2001), the occurrence of physical injury (Norris et al., 2000),

and the occurrence of peritraumatic dissociation (Fullerton et al., 2001; Bryant, 2007), seem to increase the propensity to develop PTSD after exposure. However, individual differences also contribute to the variance in PTSD expression after trauma exposure, including female gender (Fullerton et al., 2001; Bryant, 2007), genetic vulnerability (Stein et al., 2002), and a history of exposure to early childhood trauma (Breslau et al., 1999). This latter finding has been both particularly intriguing and exceptionally controversial. The controversy has been spurred, in part, by the methodological difficulties inherent in assessing the nature and severity of childhood trauma. Concerns range from the possibility that some individuals might recall being sexually victimized in childhood when this has not actually occurred (i.e., the so-called false memory syndrome) to the possibility that some traumatized individuals might have suppressed the memories of childhood victimization and, therefore, may be unable to report that they were, indeed, traumatized. Nevertheless, a variety of studies suggest that early experiences of victimization predispose an individual to developing PTSD when later exposed to psychological trauma.

On the cutting edge of traumatic stress research are recent studies that suggest that psychological trauma may result in quantifiable abnormalities in neurocognition (e.g., executive function) and perhaps, neuroanatomy (e.g., hippocampal volume). If replicated, these studies promise to dramatically alter understanding of the effects of stress on psychiatric disorders and, ultimately, on normal and pathological brain development.

Most recently, in line with the ongoing debate over the definition of the potentially traumatic event, investigators have emphasized the importance of determining whether the event is shocking to the individual or not, regardless of its form, in order to define it as traumatic, i.e. able to produce symptoms of traumatic stress (intrusion, numbing and arousal) (Galea et al., 2005). Although greater degrees of trauma are expected to yield higher rates of PTSD than less extreme traumas (Engdahl et al., 1997), increasing evidence documents the importance the so-called "low-magnitude" events (e.g., divorce, serious illness and financial reverses) in determining post-traumatic stress reactions (Breslau & Davis, 1987; Solomon & Canino, 1990, Moreau & Zisook, 2002). Davidson and Foa (1991) state ''clinical observations seem to suggest that for some persons the loss of a job or marital separation may also give rise to this syndrome, leading to criteria B (re-experiencing), C (avoidance and numbing), and D (hyperarousal) symptoms of PTSD''. In the literature, two studies have assessed the impact of ''low-magnitude'' trauma, showing that events such as marital disruption, the death of a loved one, failed adoption plans, miscarriage, and poisoning may lead to PTSD (Burnstein, 1985; Heltzer et al., 1987). The nature of the stressor is believed to have considerable breadth, from the loss of a job or marital separation to the loss of a loved one or involvement in a serious accident or involvement in abuse or combat.

On the other hand, several studies on post-traumatic conditions have recently emphasized the fact that significant functional impairment and seek for treatment is reported by a large number of victims who, even if exposed to

a DSM-IV-qualified trauma, did not fulfil the other criteria (B,C and D) for PTSD diagnosis (Stein et al.,1997; Marshall et al., 2001; Hepp et al., 2005). Sin line with these findings, some authors have introduced the concepts of partial, subthreshold or subsyndromal PTSD in order to better investigate the clinical relevance of these forms (Weiss et al., 1992; Carlier and Gersons, 1995; Stein et al.,1997).

Marshall et al (2001) reviewed studies that demonstrated that subthreshold PTSD caused by various stressors was as common as full PTSD. In the National Vietnam Veterans Readjustment Study (Weiss et al., 1992), partial PTSD was defined by levels of dysfunction equivalent to PTSD, the presence of two of three symptom clusters, or meeting most criteria in each of the three clusters, and with this definition in place it was reported in 22.5% of men and 21.2% of women exposed to war-related trauma. In a longitudinal study of 132 persons involved in serious motor vehicle accidents, 28.5% met criteria for two symptom clusters 1 to 4 months after the accident (Blanchard et al., 1996). Carlier and Gersons (1995), in a study conducted on 136 survivors of a plane crash into two apartments, found that 20% of subject met criteria for two symptom clusters followed for 6 months. A community study that used standardized telephone interviews of 1002 persons asked about trauma, and positive replies were given a DSM-IV PTSD symptom checklist. Persons with partial PTSD had clinically meaningful levels of functional impairment in association with their symptoms (Stein et al., 1997). Impairment could not be directly attributed to PTSD symptoms in this sample, however, because there

was no control for comorbid conditions. Schutzwohl and Maercker (1999) compared 146 political prisoners in the former German Democratic Republic to subjects in that country who had not experienced trauma, of these 29% met criteria for partial PTSD, which was defined as satisfying criteria in the reexperiencing cluster and either hyperarousal or avoidance clusters. More recently, Marshall and collaborators (2001) found that 2608 of 9358 individuals on National Anxiety Disorders Screening Day 1997 had at least one PTSD symptom for at least 1 month's duration and impairment increased linearly with each increasing number of subthreshold PTSD symptoms. Even after controlling for the presence of major depressive disorder, individuals with subthreshold PTSD were at elevated risk for suicidal ideation. A limitation of this study includes the assessment of impairment by self-report and failure to assess for specific areas of impairment, such as occupational or social functioning.

Most recently, results from a latent class analysis of two large epidemiological samples suggested the existence of a three-class structure separating trauma exposed persons with pervasive disturbance from those with intermediate or no disturbance (Breslau et al., 2005).

In line with these studies on partial and subthreshold forms, Moreau & Zisook (2002) developed a first multidimensional model approach to PTSD where these forms were included in a continuum encompassing from subsyndromal forms of stress-related disorders to full blown expressions, also assessing the spectrum of the nature of the potentially provoking events.

In accordance to Yehuda (1998), Moreau & Zisook (2002) also highlighted an important issue over partial forms suggesting that: subthreshold symptoms may represent a prodrome of the full syndrome or residual symptoms of PTSD in partial remission. Regarding the first possibility, a prof is given from the fact that individuals who react to trauma with dissociation are at elevated risk for later developing the full syndrome of PTSD (Yehuda, 1998). For the second point, it's important to notice that for many patients, mild symptoms, such as numbing of affect and irritability limited to the recollection of trauma, may persist indefinitely. Even after treatment, many individuals with PTSD continue to suffer from residual symptoms years after the full syndrome is no longer present (Marshall et al. 2001). Although empirical validation is needed, we can argue from clinical practice that individuals with residual symptoms may be more susceptible to developing the full syndrome after subsequent traumatic exposure than individuals with full symptom and functional recovery. Further, an important issue is determined by the characteristic course of PTSD, which is usually fluctuating in symptom severity, with persons meeting full criteria for diagnosis intermittingly over the course of many years (van der Kolk et al., 1996).

Moreau & Zisook's spectrum concept (2002) also considered the severity of PTSD spectrum designing it with: uncomplicated PTSD in the middle of the spectrum, and PTSD complicated with multiple comorbidities on the other side of the severity spectrum. More than 80% of patients with chronic PTSD, in fact, have at least one comorbid psychiatric condition, most often

mood, anxiety, or substance use disorders (Kessler et al., 1995). When comorbidity is present, PTSD is often misdiagnosed, chronic, more severe and impairing, and more difficult to treat (Yehuda, 1998).

All these studies on subthreshold or partial forms of PTSD, and highlighting the ongoing issue of the definition of the trauma, have been determinant for the "Spectrum" concept developed by the researchers of the University of Pisa, within the international research collaboration project named "Spectrum Project", for trauma and loss, that will be further presented in this thesis.

COMPLICATED GRIEF

Life stressors usually entail exposure or confrontation with negative events that can often be represented by loss of positive events or situations. In PTSD diagnostic evolution across DSMs, there has been relevant point of interest in DSM-IV edition, represented by the fact that expanding the range of “qualifying” traumatic events (from the core category of traumas represented by military, combat and disaster and criminal violence), for the fist time also the death of a loved one from any cause, included natural causes, was included as a stressor (Breslau et al., 2001). DSM-IV, in fact, acknowledges the importance of life events that are life threatening by designating these as traumatic and loss is considered a trauma if it entails death that is “sudden” and “unexpected”.

Although the revised concept of the "A" criterion has opened the door for bereavement, the epidemiologic studies on community samples that have been held in recent years to broaden the scope of stressful life events, have not considered "normal" bereavement to be the kind of event warranting a diagnosis of PTSD. Most published studies thus far, in fact, have excluded normal bereavement as an etiologic event for PTSD. Not surprisingly, when the sudden unexpected death of a close friend or relative was included as “qualifying” event in epidemiological studies, it resulted to be the most common trauma found, with approximately 60% of men and women having

experienced an event of this type at some time in their lives. Further, the risk of PTSD associated with this trauma ranged around 16% in females and 13% in males (Breslau and Kessler, 1998).

Authors are now debating whether other forms of death, for example, the death of a loved one who died from a chronic illness or whose death had been anticipated, may also lead to a PTSD-like syndrome and, if so, whether this syndrome is unique from other forms of PTSD. In other words, weather PTSD might, like depression (Zisook & Suchter, 1993) or other anxiety disorders (Jacobs et al., 1990) represent a possible adverse complication of bereavement.

We can argue that if trauma has been described as entailing an event that violates strongly held beliefs about the security of the world and/or challenges the validity of existing mental models, the death of an attachment figure, even if not sudden and unexpected, would fully meet this criterion.

Lindemann first outlined a broad spectrum of grief phenomena in survivors and family members of victims of the Coconut Grove Fire (Lindemann, 1944), and described five pathognomonic symptom complexes of this grief experience: 1) somatic distress accompanied by waves of intense discomfort, a sense of unreality, and numbing and avoidance; 2) preoccupation with images of the deceased; 3) guilt about surviving, or about what could or should have been done; 4) hostility; and 5) loss of ordinary patterns of conduct. Despite we have to notice a certain degree of overlap with PTSD symptomatology, probably due to the fact that the event that caused the deaths

most probably met DSM-IV criteria for trauma, Lindemann's observations legitimized the biomedical study of grief and bereavement and led to a considerable number of empirical investigations of grief phenomena, course, and complications. Nevertheless, despite Lindemann's emphasis on stress-like experiences among the bereaved, most subsequent studies have emphasized the depressogenic aspects of bereavement (Gallagher et al., 1983; Jacobs et al., 1989; Zisook and Suchter, 1993), and relatively less attention has been devoted to looking at bereavement as a serious stressor, capable of resulting in a "traumatic stress disorder."

Some authors that have examined grief as a general stressor exploring the characteristics of the loss: Parkes (1990), for example, noted the increased life disruption, stress-like phenomena, and chronicity of bereavement when the death was sudden and unanticipated as opposed to insidious or expected, defining the "unexpected loss syndrome" as one of the pathologic forms of grief (Parkes, 1983). Lundin described unanticipated loss as associated with increased psychiatric morbidity, anxiety, grief reactions, and functional incapacity compared with grief following expected deaths (Lundin, 1987). Describing grief after homicide or suicide, Rynearson emphasized the traumatic aspects of the loss by describing ongoing themes of violation, victimization, and volition, and underscores the primacy of PTSD phenomena over grief phenomena in non-recovery (Rynearson, 1986).

More recently, authors have progressively investigated the correlations between PTSD and bereavement. Some of the few investigators to actually

describe the prevalence of PTSD after the death of a loved one, Schut and collaborators (1991) found rates from 20-31% over the first 2-years of spousal bereavement and that 9% met PTSD criteria at every stage throughout the 2 year data collection period (Schut et al., 1991). Zisook and collaborators (1998) examined the prevalence, course, comorbidity, and consequences of PTSD after spousal bereavement finding that that at 2 months after the spouse's death, criteria for PTSD were met by 10% of those whose spouses died after a chronic illness, by 9% of those whose spouses died unexpectedly, and by 36% of those whose spouses died from "unnatural" causes (suicide or accident) had PTSD. Moreover, symptoms tended to be chronic in at least 40% of the subjects, almost always were associated with comorbid depression and created substantial morbidity. Authors concluded that PTSD may occur after bereavement suggesting that the 'A' criterion of the official diagnostic system (DSM-IV) would need further examination.

In line with these concepts, more recently some authors have identified a syndrome of pathological response to bereavement, called “Traumatic” or “Complicated Grief” (CG), as a form of stress response (Prigerson et al., 1995, 1999; Horowitz et al 1997; Shear & Smith-Caroff, 2002; Langner & Maercker, 2005; Shear & Shair, 2005). Prigerson and collaborators (1996, 1997) first identified this syndrome as distinct from either bereavement-related depression or anxiety, and defined it as characterized by intense and prolonged preoccupation with thoughts of the deceased, yearning and searching behaviours, disbelief, and avoidance. Similarly to PTSD, only a subset of

people who experience a loss may develop a pathological response to bereavement such as CG (Horowitz et al, 1997; Maercker et al., 1998). This form of response to bereavement might also share features of response to a DSM-IV traumatic event, such as a sense of disorientation and confusion, and a tendency to intrusive thoughts oscillating with avoidance (Horowitz et al, 1997; Maercker et al., 1998), and entails separation distress with intense yearning, searching and longing for the person who died, and preoccupation with thoughts and memories of the deceased (Shear et al., 2005).

In line with these considerations, when looking at the spectrum of possible triggering events, while developing the Trauma and Loss Spectrum concept, both life threatening situations and bereavement were considered as potential triggers for a trauma response. Moreover, the way how either of these might be associated with long term clinically significant symptoms was explored.

3. THE TRAUMA AND LOSS SPECTRUM (SCI-TALS)

The Trauma and Loss Spectrum Concept

Clinicians and researchers are increasingly interested in better characterization of psychiatric disorders than that provided in DSM IV-TR (Kupfer, 2005; Maj, 2005; Maser & Akiskal 2002).

Current categorical methods of classification of mental disorders, such as the Research Diagnostic Criteria (RDC) (Spitzer et al., 1978), the Diagnostic and Statistical Manual of Mental Disorders 4th edition (APA, 1994) and the International Classification of Diseases 10th edition (ICD-10), have provided a reliable tool for epidemiologic, clinical and, especially, treatment outcome research. Nevertheless, despite adding specificity to the psychiatric nomenclature, their stereotypic rigidity in classification, the so-called "threshold psychiatry", has failed in identifying the full range of subthreshold, atypical and often enduring symptoms that encompass the core manifestations of full-blown mental disorders, thus leading to the misdiagnosis of atypical disorders. In fact, patients suffering from subsyndromal forms of axis I disorders, either alone or in comorbidity with other full-blow axis I disorders, cannot be easily accommodated within these rigidly structured nosological systems (Frank et al., 1998; Cassano et al., 1999). Despite this, these often

neglected spectra of symptoms may be as distressing and debilitating as the full-blown disorder and have unrecognized importance in seek for treatment (Galea et al., 2003). Recently, lifetime spectrum symptoms of a range of mood and anxiety disorders were also found to contribute to impairment (Bazzichi et al., 2005; Fagiolini et al., 2005), to represent a risk factor for suicidality (Balestrieri et al., 2006), and to influence treatment outcome (Frank et al., 2000; Frank et al., 2002; Dell'Osso et al., 2007). Furthermore, increasing evidence has been reported for a lack of correspondence between current classifications of mental disorders and psychopathological presentations, in both community and clinical settings and this has often led to an incomplete characterization of most patients (Cassano et al., 1999).

For what is concerned to PTSD, the relevance of these partial or subsyndromal forms, besides the importance of a multidimensional approach to this particular disorder typically related to a provoking event, has been already widely exposed in a previous sessions of the present thesis (see Clinical characteristics and subthreshold PTSD). Nevertheless, most recent data confirming these considerations derive from studies on the psychological sequelae and seek for treatment risen in Manhattan and New York residents, after the September 11- 2001 terrorist attack (Galea et al., 2003, Galea et al., 2005; Agronic et al., 2007).

Surely, the correct identification and recognition of these atypical and subsyndromal expression of psychopathology may lead to improved clinical characterization and more effective treatment for most patients. Probably, this

approach is required also to fill the gap that is present between the actual psycho-pathological expression of psychiatric disorders and the current diagnostic categories, in line with the perspectives of including dimensional approaches in the new edition of DSM-V.

Neurobiological studies also corroborate this hypothesis, suggesting the need for a better characterization of clinical phenotypes that may help, in a more efficacious way, understanding the patophysiology of psychiatric disorders.

In line with these considerations, researchers have worked towards a re-conceptualization and assessment of the spectrum phenomena, identifying these phenomena as mosaics comprising recognizable and treatable manifestations of the full-blown disorder. This has already led to the concepts of schizophrenia (Kety et al., 1968), bipolar (Akiskal, 1983), and obsessive-compulsive (Hollander, 1993) spectrums, although different authors have defined different meanings of the term "spectrum".

The need for a systematic identification and assessment of a broad array of symptoms and behavioural features related to Axis I disorders has induced a group of researchers from the Institute of Psychiatry at the Department of Psychiatry, Neurobiology, Pharmacology and Biotechnologies, of the University of Pisa (Italy), led by Prof. G.B. Cassano, to the conceptualization of a new "spectrum" model. With the term "spectrum" these authors (Cassano et al., 1997), include the core symptoms of current DSM diagnostic categories, not limiting to them but also referring to broad areas of psychiatric

phenomenology relating to a given axis I disorder including: (1) core, atypical, and subclinical symptoms of DSM's axis I disorder; (2) signs, isolated symptoms, symptoms clusters and behavioural patterns related to the core symptoms and (3) clinical features which have ordinarily been viewed as temperamental and/or personality traits.

This model has been developed within an international research collaborative group, named "the Spectrum Project", started in 1995 and is still ongoing, between researchers of the Psychiatric Clinic of the University of Pisa and researchers of the Western Psychiatric Institute and Clinic at the University of Pittsburgh, the University of California San Diego, and from the Columbia University of New York. This Project is aimed at the definition and assessment of the subthreshold and atypical phenomenology encompassing mental disorders. It first applied to panic agoraphobic (Cassano et al., 1999) and mood spectra (Dell'Osso et al., 2002; Cassano et al., 2004), it has been constructed by identifying different psychopathological symptoms and grouping them into clinical domains that comprise the conceptual organization incorporating and extending the Axis I disorders as described in DSM-IV.

Based on the same theoretical foundation, specific diagnostic instruments, developed to assess a broad array of clinical features associated with different DSM conditions, have been developed and tested within this Project. These "spectrum" instruments comprise a set of structured clinical interviews and self report questionnaires, that evaluate isolated criterion and non-criterion symptoms, behavioural tendencies and temperament-like traits

experienced over a lifetime, for most of the DSM-IV disorders (Fagiolini et al., 1999; Cassano et al., 1999; Mauri et al., 2000; Dell'Osso et al., 2000; Dell'Osso et al., 2002a, 2002b; Sbrana et al., 2003; Sbrana et al., 2005).

The latest of these spectrum assessment instruments is represented by the Structured Clinical Interview for Trauma and Loss Spectrum (SCI-TALS), that targets PTSD and CG, which validity is being evaluated in the study reported in the present thesis.

This trauma spectrum is based on the premise that PTSD symptoms are on a continuum with normal reactions to trauma exposure rather than being qualitatively different (Moreau & Zisook., 2002; Shear et al., 2002). This consideration is in line with the recent literature on subthreshold PTSD that have begun to demonstrate comparable impairment in individuals who experienced only some, but not all, symptoms of PTSD (Weiss et al., 1992; Carlier & Gersons, 1995; Stein et al., 1997; Schurzwohl & Maerker, 1999; Marshall et al., 2001; Ruscio et al., 2002; Hepp et al., 2005).

Nevertheless, PTSD requires a dual process of trauma exposure and response and recent dimensional approach to PTSD have highlighted the need for a multidimensional model (Moreau & Zisook, 2002; Breslau 2005). What constitutes trauma was hotly debated in the development of the DSM criteria since PTSD is unique in the DSM, as a disorder specifically tied to a life event. The conservative position that trauma requires exposure to an event that is threatening to physical integrity is sensible from many standpoints, but it is likely inaccurate with respect to the development of clinically significant

symptoms since this pattern of symptoms can be seen in response to other events (e.g., a lawsuit) (Shear, 2002). Thus, it is possible that a clinically significant condition may be produced by subthreshold trauma exposure (Breslau & Davis, 1987; Solomon & Canino, 1990; Moreau & Zisook, 2002) associated with threshold or subthreshold symptoms. If an important evolution in the diagnostic criteria for PTSD, has concerned the inclusion of the victim's appraisal of the event, recent literature emphasize how, for some persons, even "minor" events such as the loss of a job or marital separation, may also give rise to PTSD (Burnstein, 1985; Heltzer et al., 1987; Zisook et al., 1998; Pfefferbaum et al., 2000).

Given the requirements of DSM-IV-TR (2000) for PTSD diagnosis, that is the need for a threshold level of exposure and for criterion level symptoms, and in line with the literature addressing the role of subthreshold trauma and subthreshold PTSD, when developing a spectrum assessment of this condition (SCI-TALS), we included a continuum of potentially triggering events and a range of symptoms that comprise an acute reaction, and an array of persistent symptoms.

To provide a spectrum assessment for PTSD, we first created a list of possible triggering events where we included low magnitude, subthreshold events (e.g., divorce, serious illness and financial reverses) capable of producing clinically significant symptoms related to PTSD, in accordance to recent literature (Breslau & Davis, 1987; Solomon & Canino, 1990; Moreau & Zisook, 2002; Hepp et al., 2005). Moreover, we included loss events as highly

stressful experiences capable of evoking a specific constellation of grief symptoms, in line with recent work identifying a syndrome of complicated grief as a form of stress response (Prigerson et al., 1995; Horowitz et al 1997; Prigerson et al., 1999; Shear & Smith-Caroff, 2002; Langner & Maercker, 2005; Shear & Shair, 2005). In line with these studies, when developing a spectrum assessment for post-traumatic conditions, we decided to consider both life threatening situations and bereavement as potential triggers for a trauma response, and we considered how either of these might be associated with long term clinically significant symptoms. We considered that stressful life events can be broadly categorized as those that entail exposure to a threatening negative life event and those that entail loss of an important positive relationship or situation, not limiting the loss events only to death.

The SCI-TALS includes 116 items coded in a dichotomous way (yes/no answer) divided into IX domains. The spectrum of losses and potentially traumatic events are investigated into two different domains (I and III respectively).

In order to accommodate the different symptomatological manifestations that can be related to post-traumatic stress syndromes, we postulated a post-traumatic spectrum model to capture the continuum between the core symptoms of Axis I disorders and the associated prodromal, atypical and sub-clinical psycho-pathological expressions (Cassano et al., 1997). A first symptomatological domain was created in the SCI-TALS in order to assess acute reaction to either trauma and loss (Domain IV). Further, domains

assessing the spectrum of symptoms related to re-experiencing (Domain V), avoidance and numbing (Domain VI), and arousal (Domain VIII) were created. In order to allow a more accurate detection of grief responses a separate domain assessing these symptoms was added (Domain II). Two adjunctive domains were included: one assessing maladaptive coping (Domain VII) that may emerge since the trauma or the loss had happened; and one assessing personal characteristics or risk factors (Domain IX) that may account for post-traumatic symptoms onset.

In conclusion, the nine domains of the trauma and loss spectrum incorporate the typical symptomatology of Post-Traumatic Stress Disorder (PTSD) and complicated grief (CG), together with the array of subthreshold and atypical post-traumatic and grief symptoms which are less frequently linked to PTSD and CG. What follows is a systematic description of each domain of the Trauma and Loss Spectrum (SCI-TALS) from a psychopathological and clinical standpoint.

The SCI-TALS instrument

The SCI-TALS was developed by the international team of researchers belonging to the "Spectrum Project". Originally developed in English, the interview was then translated into Italian and then back translated into English in order to revise for inconsistencies between the two languages. In the validation study reported in the present thesis, the revised Italian version was utilised.

The SCI-TALS includes 116 items exploring lifetime traumatic events or losses and lifetime symptoms, behaviours and personal characteristics that might represent risk factors for the development of the disorder. The instrument is organized into 9 domains. Items responses are coded in a dichotomous way (yes/no) and domain scores are obtained by counting the number of positive answers.

Domain I: Loss Events (Items 1-10)

Life stressors usually entail exposure or confrontation with negative events that can often be represented by loss of positive events or situations. When developing a spectrum assessment for post-traumatic stress, both life threatening situations and bereavement were considered as potential triggers for a trauma response. In order to better distinguish bereavement and life threatening situations as potential triggers for a trauma response, and to consider how either of these might be associated with long term clinically

significant symptoms, two different domains of the SCI-TALS were created, Domain I and III respectively.

DSM-IV acknowledges the importance of life events that are life threatening by designating these as traumatic and loss is considered a trauma if it entails death that is sudden and unexpected. Nevertheless, trauma has also been described as entailing an event that violates strongly held beliefs about the security of the world and/or challenges the validity of existing mental models, and the death of an attachment figure, even if not sudden and unexpected, fully meets these criterion.

Even if the revised concept of criterion "A" in DSM-IV, with respect to DSM-III-R, opened the door for bereavement, not many epidemiological studies have considered "normal" bereavement to be the kind of event warranting a diagnosis of PTSD (Zisook et al., 1998). However, this convention is somewhat arbitrary and may not be consistent with emerging information. The first epidemiologic study using DSM-IV criteria for the "bereavement" stressor found high rates of PTSD in civilian populations, where it was previously considered relatively rare, especially when the sudden and unexpected death of a loved one was counted as a traumatic event (Breslau et al., 1998). Schut and collaborators (1991) first described the prevalence of PTSD after the death of a loved one, that was "normal bereavement", finding rates from 20-31% over the first two-years of spousal bereavement, with 9% meeting PTSD criteria at every stage throughout the 2-year data collection period. More recently, Zisook and collaborators (1998), examining the

prevalence, course comorbidity and consequences of PTSD after spousal bereavement, found even higher rates of the disorder, that is in: 10% of those whose spouse died after chronic illness, 9% of those whose spouses died unexpectedly, and in 36% of those who spouses died from "unnatural causes". Moreover, symptoms tended to be chronic in at least 40% of the subjects and almost always were associated with comorbid depression, and created substantial morbidity.

Besides considering the relevance of "normal" versus "sudden and unexpected" death in determining post-traumatic symptomatology, recently authors are debating that stressful life events can be broadly categorized as those that entail exposure also to loss of an important positive relationship or situation. In this concept, while developing the SCI-TALS, we wanted to apply the spectrum concept to loss events considering not only people's death but broadening the scope of stressful losses, that might count for the "A" criterion. For this reason this domain encounters a number of items referring to possible losses either related to the sudden and unexpected death of relatives or close friends, as it is encountered in DSM-IV criterion A for PTSD, or to normal bereavement, or either to the loss of relationships and/or events that may have been relevant for the patient.

Domain II: Grief Reactions Loss Events (Items 11-32)

A syndrome of pathological response to bereavement, named complicated or traumatic grief, has been recently defined (Prigerson et al.,

1995; Horowitz et al 1997; Shear and Shair, 2005). This grief response, that can develop after losses that may also not be as traumatic as it's required in DSM-IV criterion A for PTSD, has been identified as a form of stress response (Prigerson et al., 1995; Horowitz et al 1997; Prigerson et al., 1999; Shear & Smith-Caroff, 2002; Langner & Maercker, 2005; Shear & Shair, 2005). Similarly to what happens in PTSD, this pathological response to bereavement can be reported by only a subset of people who experience a loss (Horowitz et al, 1997; Maercker et al., 1998; Prigerson et al., 1995a), enhancing the relevance of the subjective traumatic response to a loss event.

Prigerson and collaborators (1997) identified the syndrome of Complicated Grief, distinct from either bereavement-related depression or anxiety, and described it as characterized by intense and prolonged preoccupation with thoughts of the deceased, yearning and searching behaviours, disbelief, and avoidance (Prigerson et al 1996, 1997). This pathological reaction to bereavement might also share features of response to a DSM-IV traumatic event, such as a sense of disorientation and confusion, and a tendency to intrusive thoughts oscillating with avoidance (Horowitz et al, 1997; Maercker et al., 1998). Entailed symptoms of separation distress are represented by intense yearning, searching and longing for the person who died, and preoccupation with thoughts and memories of the deceased (Shear et al., 2005).

In order to allow an accurate detection of grief responses Domain II has been developed.

Domain III: Potentially Traumatic Events (Items 33-58)

The essential feature of Post-Traumatic Stress Disorder is the development of characteristics symptoms of exposure following to an extreme traumatic stressor involving direct personal experience of an event that involves actual or threatened death or serious injury, or other threat to one's physical integrity; or witnessing an event that involves death, injury, or a treat to the physical integrity of another person; or learning about unexpected or violent death, serious harm, or threat of death, or injury experienced by a family member or other close associates (DSM-IV-TR Criterion A, 2000).

As previously introduced, Domain III is the second domain assessing the lifetime potential trauma experienced by the patient and particularly, it explores the lifetime presence of exposure to a broaden spectrum of potentially traumatic events than that presented in DSM-IV.

Although PTSD was not long ago considered to be a disorder of war veterans, it is now recognized as a highly prevalent disorder, affecting a much larger segment of the population, and this is mostly related to the progressive characterization of the potentially traumatic events. The definition of the criteria for the traumatic event has in fact evolved across the different DSM editions: while current diagnostic criteria (DSM-IV-TR, 2000) stipulate exposure to an event that threatens serious physical injury or death, and that is accompanied by feelings of intense fear, helplessness, or horror, DSM-III (1980) initially described trauma in relation to the degree of emotional impact

caused by an event that was "beyond the range of normal human experience". Consequently, although debate continues, it is now generally accepted that any life-threatening (or, perhaps, life-altering) event, however common (e.g., a serious motor vehicle collision), can be considered sufficiently traumatic, that it is capable of eliciting PTSD. With this definition in place, recent surveys have placed the lifetime prevalence of PTSD in the community at approximately 10%.

DSM-IV-TR lists the traumatic events that could be experienced directly, including, even if they could be not limited to: military combat, violent personal assault (such as sexual assault, physical attack, robbery, mugging), being kidnapped, being taken in hostage, terrorist attack, torture, incarceration as a prisoner of war or in a concentration camp, natural or man made disasters, severe automobile accidents, or being diagnosed with life threatening illness. Witnessed events include, but are not limited to: observing the serious injury or the unnatural death of another person due to a violent assault, accident, war, or disaster or unexpectedly witnessing a dead body or body parts. The events experienced by others that are learned about include, even if they are not limited to: violent personal assault, serious accident or serious injuries experienced by a family member or a close friend; learning about the sudden, unexpected death of a family member or of a close friend, or learning that one's child has a life threatening disease.

Investigators continue to consider how best to define the range of events that might evoke clinically significant symptoms. Recently, the

importance of determining whether the event is shocking to the individual or not, regardless of its form, has been emphasized in order to define it as traumatic, i.e. able to produce symptoms of traumatic stress (intrusion, numbing and arousal) (Galea et al., 2005). In fact, increasing evidence documents the importance the so-called "low-magnitude" events, such as divorce, serious illness and financial reverses, in determining post-traumatic stress reactions (Breslau & Davis, 1987; Solomon & Canino, 1990, Moreau & Zisook, 2002).

In line with these studies, in devising the SCI-TALS we included low magnitude, subthreshold events besides Axis I traumas as those assessed in the SCID Criterion A for PTSD diagnosis (DSM-IV) and listed before, except for the losses that, as already mentioned, are listed in Domain I.

Domain IV: Reaction to Losses or Upsetting Events (Items -59-76)

This domain includes the spectrum of the peritraumatic symptomatological response that the subject may experience during exposure. In accordance to DSM-IV-TR (Criterion A2), the person's response to the trauma must involve intense fear, helplessness, or horror in order to be able to determine a post-traumatic stress disorder. Nevertheless, only a small percentage of subjects exposed to a same stressor (almost 1 out of 10) develop PTSD, confirming the resilience of the human psyche. Risk factors that may increase the propensity to develop PTSD after exposure, have been long investigated but authors agree on confirming only few of them, such as: gender

(Breslau et al., 1991; Kessler et al., 1995; Fullerton et al., 1999; Bryant et al., 2003), certain characteristics of the trauma and the magnitude of and proximity to the stressor (Breslau et al., 1999; Prigerson et al., 2000), the occurrence of physical injury (Norris et al., 2000), and the immediate post-exposure response including, in particular, the occurrence of peritraumatic dissociation (Fullerton et al., 2001; Punamaki et al., 2005), with this latest representing one of the most relevant.

The way people respond during acute exposure to trauma is crucial in explaining whether they recover or develop mental health symptoms. It is generally agreed that showing dissociation, i.e., losing sense of time, behaving mechanically ("like a machine"), or feeling like a bystander watching events occur is a risk for PTSD. Shalev and his team (Shalev et al., 1997; Shalev et al., 1998; Freedman et al., 1999) confirmed, in their prospective studies, that peritraumatic dissociation predicts PTSD among accident victims. Positive associations between peritraumatic dissociation and PTSD have also been found in retrospective study settings among war veterans (Bremner et al., 1993; Marmar et al., 1994; O'Toole et al., 1999; Tichenor et al., 1996), disaster and accident survivors (Holen et al., 1993; Koopman et al., 1994; Ursano et al., 1999), and emergency workers (Weiss et al., 1995).

Moreover, recent studies highlighted that in more than 90% of the cases, patients also experience symptoms of anxiety and increased arousal at the time of exposure (Dunner, 2001) that can be experienced in higher or lesser degree, such as pounding heart, sweating, trembling, or shaking sensations of

shortness of breath or choking, chest discomfort or pain, nausea or abdominal distress, feeling dizzy, unsteady, light-headed, or faint. Shalev and collaborators (1998) reported early signs of neurophysyological activation as predictors of PTSD: heart rate in the per-traumatic phase, i.e. in the emergency room after traffic accidents, etc., was also positively correlated to the development of PTSD. In an extension of the study, again peritraumatic dissociation and heart rate predicted the development of PTSD and were associated with more intrusive symptoms and with exaggerated startle (Shalev et al., 1998).

In the actual nosography (DSM-IV-TR, 2000), whether a defined cluster of symptoms appear in the immediate aftermath of the trauma or it develops and lasts within a month form it, a diagnosis of Acute Stress Disorder (ASD) can be formulated. This disorder, which development typically occurs within a month after exposure to an extreme traumatic stressor (DSM-IV-TR, 2000), is denoted by the presence of characteristic anxiety and prominent dissociative symptoms (e.g. derealization, numbing) that can develop since the immediate aftermath of the trauma experience (DSM-IV-TR, 2000). Studies show that when acute stress disorder occurs after trauma, it identifies a subset of individuals who are at several fold increased risk for the subsequent development of PTSD (and major depression).

Nevertheless, new perspectives in the view of DSM-V definition highlight the artificial temporal delimitation that delineates ASD from PTSD suggesting its elimination.

In line with these recent concepts, while developing the SCI-TALS no domain for ASD assessment was developed. Domain IV includes a broaden spectrum of peritraumatic/acute reactions to the trauma that encompass from the symptoms of intense fear, helplessness, or horror defined in DSM-IV-TR Criterion A2 to the symptoms of increased anxiety and dissociative symptoms that characterize PTSD. Moreover, this Domain includes those symptoms that DSM-IV-TR describes as possible associated descriptive features of ASD. These are represented by symptoms of despair and hopelessness, besides feelings of guilt that the patient may experience if the trauma led to another's death or to serious injury. Survivors in fact, may feel guilty about having remained intact or about not providing enough help to others (DSM-IV-TR, 2000)

Domain V: Re-experiencing (Items 77-85)

The SCI-TALS is aimed at bringing to light not only the spectrum of the acute reactions (Domain IV) to potentially traumatic events, but also the persistent symptoms that may ensue from either type of life event (Domain V, VI, VIII).

The diagnosis of PTSD requires development of symptoms in 3 domains, re-experiencing, avoidance and hyperarousal, that persist for at least a month (DSM-IV-TR, 2000). Nevertheless, several studies on post-traumatic conditions, recently reported significant functional impairment and seek for treatment in a large number of victims who, even if exposed to a DSM-IV-

qualified trauma, did not fulfil the other criteria (B,C, and D) for PTSD (Stein et al.,1997; Marshall et al., 2001; Hepp et al., 2005). Other authors (Weiss et al., 1992; Carlier & Gersons, 1995; Stein et al.,1997) have introduced the concepts of partial, subthreshold or subsyndromal PTSD in order to better investigate the clinical relevance of these forms. Results from a latent class analysis of two large epidemiological samples suggest the existence of a three-class structure separating trauma exposed persons with pervasive disturbance from those with intermediate or no disturbance (Breslau et al., 2005).

The traumatic event can be reexperienced in various ways. Commonly the person has recurrent intrusive recollections of the event, including images, thoughts or perceptions (DSM-IV-TR Criterion B1, 2000) or recurrent distressing dreams during which the event is replayed (Criterion B2). In rare instances the person experiences dissociative states that last from a few seconds to several hours, or even days, during which components of the event are relieved and the person behaves as though experiencing the event at that moment (Criterion B3), this may include a sense of relieving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated. Intense psychological distress (Criterion B4) or physiological reactivity (Criterion B5) often occurs when the person is exposed to triggering events that resemble or symbolize an aspect of the traumatic event (e.g. anniversaries of the traumatic event; cold, snowy weather or uniformed guards for survivors of death camps in cold climates;

hot, humid weather for combat veterans of the South Pacific; entering any elevator for a woman who was raped in an elevator).

The whole list of "typical" symptoms reported in DSM-IV-TR criteria for PTSD has been reported in the SCI-TALS, making it possible to assess the full blown symptomatology of reexperiencing. Nevertheless, the clinical evidence that patients presenting with post traumatic symptoms characterized by fewer than the symptoms required from DSM-IV-TR may show a substantial impairment, similar to that of full PTSD (Stein et al.,1997; Marshall et al., 2001), prompted us to focus on detecting such phenomena systematically. Moreover, clinical evidence suggests that subthreshold and "atypical" symptoms are common in PTSD patients. These subclinical but distressing symptoms may sometime represent the only clinical manifestation of PTSD (Galea et al., 2005). It is not clear weather they are self limited or prodromal to a future occurrence or residual symptoms of full-blown PTSD. Although not listed among DSM-IV-TR criteria for PTSD, such symptoms may be experienced as a deep feelings of guilt, shame or blame, whose severity is comparable to that of a full-fledged PTSD; or sometimes they must be related to different behaviours that close friends or relatives tend to have in order to avoid patients sufferance (such as avoiding to talk about the event or the loss in order to avoid the patient to get upset). To a large extent, they tend to worsen and/or prolong reexperiencing, augmented arousal and avoidant symptomatology, opening the way to permanent, chronic changes in the emotional life and behaviour of the patients. DSM-IV-TR considers among the

associated descriptive features the possibility that patients with PTSD may describe painful guilt feelings about surviving, or feelings of ineffectiveness, shame and despair.

In the long run these often neglected subthreshold and atypical symptoms may become the major determinants of changes in personality, leading to a deceptive diagnosis of a personality disorder.

For these reasons "atypical" symptoms were included as a section of either the reexperiencing, avoidance and numbing and arousal domains, along with the "typical" ones reported in DSM-IV-TR.

Domain VI: Avoidance and numbing (Items 86-97)

As already mentioned, symptoms of avoidance and numbing represent one of the three symptoms clusters that constitute PTSD (DSM-IV-TR, 2000). Stimuli associated with the trauma are, in fact, persistently avoided. The person commonly makes deliberate efforts to avoid thoughts, feeling or conversations about the traumatic event (DSM-IV-TR Criterion C1, 2000) and to avoid activities, situations, or people who arouse recollections of it (Criterion C2). This avoidance of reminders may include amnesia for an important aspect of the traumatic event (Criterion C3). Diminished responsiveness to the external world, referred to as a "psychic numbing" or "emotional anaesthesia", usually begins soon after the traumatic event. The individual may complain of having markedly diminished interest or participation in previously enjoyed activities (Criterion C4), of feeling detached or estranged from other people (Criterion

C5), or of having markedly reduced ability to feel emotions (especially those associated with intimacy, tenderness, and sexuality) (Criterion C6). The individual may have a sense of a foreshortened future (e.g. not expecting to have a career, marriage, children, or a normal life span) (Criterion C7)

The whole list of "typical" symptoms reported in DSM-IV-TR criteria for PTSD has been reported in the SCI-TALS, making it possible to assess the full blown symptomatology of avoidance and numbing. Nevertheless, in line with the concepts applied for reexperiencing, while creating the spectrum of avoidance and numbing symptomatology subthreshold and "atypical" symptoms were taken into account. Symptoms such as those reported in the DSM-IV-TR associated features of PTSD were enlisted as "atypical" features, such as: feeling permanently damaged (Item 96. Did you ever feel as if your life was changed forever and things would never be the same?); impaired relationships with others (Item 94. Did you ever have difficulty trusting people, either strangers, people in your family, or your friends?); or a change from the individual's previous personality characteristics (Item 97. Did you ever feel as if your personality changed?).

Domain VIII: Arousal (Items 108-110)

As already mentioned, increased arousal represent one of the three symptoms clusters that constitute PTSD (DSM-IV-TR, 2000). Individuals experience persistent feeling of anxiety or increased arousal that were not present before the trauma. These symptoms may include difficulty falling or

staying asleep that may be due to recurrent nightmares during which the traumatic event is relieved (DSM-IV-TR Criterion D1, 2000), hypervigilance (Criterion D4), and exaggerated startle response (Criterion D5). Some individuals report irritability or outbursts of anger (Criterion D2) or difficulty concentrating or completing tasks (Criterion D3).

All "typical" symptoms reported in DSM-IV-TR criteria for PTSD has been reported in the SCI-TALS, besides adding subthreshold specifiers to each items that assess even milder responses of increased arousal.

Domain VII: Maladaptive Copying (Items 98-105)

PTSD can often be associated to the following constellation of symptoms that may occur and are more commonly seen in association with an interpersonal stressors (childhood sexual or physical abuse, domestic battering, being taken in hostage, incarceration as a prisoner of war or in a concentration camp, torture), as reported in DSM-IV-TR associated features to PTSD (2000): self destructive and impulsive behaviour; somatic complaints, feeling hopelessness and permanently damaged. All these features can often represent one of the major manifestations of the disorder that, if accurately investigated, can often even hide the presence of a post-traumatic symptomatology that the patients try not to express for the strong avoidance attitude of recalling.

Moreover, literature on PTSD has enhanced the high risk for suicide, suicidal ideations or behaviours in patients with PTSD. This Domain is aimed at exploring the spectrum of maladaptive behaviours that the patient can

develop as consequence of the trauma and its impact on his psychological balance. The items of this Domain encompass the spectrum of these behaviours including the atypical ones also listed in the associated features of DSM-IV-TR, in the light of a spectrum approach to self harming-suicidal behaviours (Did you ever…Item 98. stop taking care of yourself, for example, not getting enough rest or not eating right? …Item 99. stop taking prescribed medications or fail to follow-up with medical recommendations, such as appointments, diagnostic tests, or a diet? ….Item 104. intentionally scratch, cut, burn or hurt yourself…Item 105. attempt suicide?), and impulsive behaviours (Item 101...engage in risk-taking behaviours, such as driving fast, promiscuous sex, hanging out in dangerous neighbourhoods?).

Moreover, often patients develop substance or alcohol abuse as self medication of post-traumatic symptomatology. This is in fact the main reason for the relevant comorbidity between PTSD and substance and alcohol abuse disorders (Breslau et al., 2003). The SCI-TALS includes in this Domain the assessment of the presence of such behaviours (Item 100. Did you ever use alcohol or drugs or over-the-counter medications to calm yourself or to relieve emotional or physical pain?).

Either of these latest complications have been recently reported as possible consequence of a traumatic experience, increasing the debate on the possible implications, or cause effective correlations, of a concomitant mood liability.

Domain IX: Personal Characteristics/Risk factors (Items 111-116)

As already reported, individuals with PTSD may show associated constellations of symptoms that may occur and are more commonly seen in association with interpersonal stressor, such as feelings of hostility and change from individual's previous personality characteristics (Pat-Horenczyk et al., 2007). On the other hand, authors have tried to identify personality characteristics that may represent risk factors for the development of PTSD after trauma exposure (Heinrichs et al., 2005).

The SCI-TALS is a lifetime instrument and this may also allow to detect post-traumatic reactions happened long time before assessment. For this reason at the time of evaluation it can be often possible to detect personality characteristics that may derive from changes related to the impact of the event, or, conversely, represent stable personality traits that the patient present before the event or loss occurred and that may account as risk factors for the development of the spectrum symptomatology explored in the SCI-TALS.

In conclusions, the SCI-TALS is aimed at bringing to light an individual's exposure to a range of threatening experiences, as well as a variety of potentially significant losses, and at assessing the acute reactions and persistent symptoms that may ensue from either type of life event. We underline that, similarly to our other spectrum measures, the SCI-TALS explores the presence/absence of psychopathological manifestations associated with syndromes that might occur during the lifetime of an individual. This

instrument lists a range of life events and assesses lifetime exposure to these, as well as a range of lifetime symptoms in the aftermath of the worst event. Therefore, the duration, clustering and severity criterion symptoms needed to make a diagnosis according to DSM-IV or ICD-10 cannot be determined. The SCI-TALS cannot replace a diagnostic interview, such as the SCID. However this instrument provides information related to a range of subthreshold events that might have caused serious distress, as well as a broad array of clinical features associated with trauma and loss events.

4. SCI-TALS MULTICENTER NATIONAL VALIDATION STUDY

Aim of the study

Primary aim of the present thesis is to describe the SCI-TALS and document its acceptability, reliability and validity. This was done through a multicenter national validation study, involving 6 Italian University Departments of Psychiatry (Pisa, Cagliari, Milano, Napoli, Sassari and Siena), coordinated by the 2nd Psychiatric Clinic of the Azienda Ospedaliero-Universitaria Pisana, Pisa Italy, coordinated by Prof L. Dell'Osso and Dr. C. Carmassi. A consecutive group of 186 subjects was recruited, statistical analyses were performed on a subsample of 140 subjects who did not present any comorbidity between PTSD and CG.

We administered the instrument to study participants who met DSM-IV diagnostic criteria for PTSD and/or CG (Shear et al., 2005), and to a sample of healthy controls without any current or lifetime psychiatric disorder. We tested the reliability by analysing the correlations between domains of the SCI-TALS and the internal consistency of domains themselves. The test-retest and inter-rater reliability of the SCI-TALS were examined at Pisa site only. We examined the validity by testing whether the clinical samples showed from those of the comparison group.

Materials and Methods

The SCI-TALS was developed by the Italian-American team of researchers belonging to the "Spectrum" Project. Originally developed in English, the interview was then translated into Italian, back translated, and revised for inconsistencies between the two languages. In the present study we used the revised Italian version.

Sample

A consecutive group of 186 patients was recruited and analyses were performed on a subsample of 140 subjects who did not present any comorbidity between PTSD and CG. This latest sample included 92 out- and inpatients (48 patients with PTSD and 44 with CG), presenting for treatment at one of the 6 Italian University Departments of Psychiatry (Pisa, Cagliari, Milano, Napoli, Sassari and Siena), and 48 healthy Controls, collected at the same sites. Eligible patients were adult inviduals with a diagnosis of Post-Traumatic Stress Disorder (according to DSM-IV criteria, 1994) or complicated grief, determined by a score of at least 25 on the Inventory of Complicated Grief (Shear et al., 2005). Individuals with severe medical illness, neurological diseases, substance abuse or psychotic symptoms in the month preceding the index assessment, or inability to participate because of the severity of psychiatric symptoms were excluded. The final study sample included 48 patients with PTSD and 44 with CG. We also recruited a comparison group of 48 control subjects, without any Axis I psychiatric diagnoses. Controls were

individuals without any history of psychiatric disorders presenting at the Departments of Ophthalmology of the local Universities for a routine sight control, and their friends and relatives.

Data for the present report were collected between May 2004 and December 2005. The Ethics Committee of the Azienda Ospedaliera Universitaria of Pisa approved all recruitment and assessment procedures. Eligible subjects provided written informed consent, after receiving a complete description of the study and having the opportunity to ask questions. Subjects were not paid for their participation in accordance to the Italian laws for clinical studies.

Instruments and assessments

The diagnostic assessment was conducted on patients and controls using the Structured Clinical Interview for DSM-IV axis-I disorders (SCID-I/P, First et al., 1995) and the SCI-TALS. by psychiatrists trained and certified in the use of the study instruments at the Department of Psychiatry of the University of Pisa. The Inventory of Complicated Grief (ICG, Prigerson et al., 1995b) was administered to determine the presence of complicated grief, defined by a score of 25 or higher. The Impact of Event Scale (Horowitz et al., 1979) was administered to assess the symptomatology related to post-traumatic stress disorder.

The SCI-TALS includes 116 items exploring lifetime traumatic events or losses and lifetime symptoms, behaviours and personal characteristics that

might represent risk factors for the development of the disorder. The SCI-TALS description has been previously reported (see The SCI-TALS instrument chapter).

The acceptability of the SCI-TALS was determined using questions asking whether the interview was interesting, reassuring, distressing, and helpful for a better understanding of the disorder for either the patient or the physician. Items were rated on a 0-3 scale, where 0=not at all, 1= a little, 2= much, 3= very much.

Statistical analyses

The validity of the SCI-TALS was examined by comparing the mean scores of the domains among subjects with PTSD, CG and controls, by using one-way analysis of variance followed by post-hoc comparisons with Dunnett's C-test, that allows for heterogeneity of variance between groups. The alpha level was corrected for multiple comparisons (0.016=0.05/3). Analysis of covariance was performed to control for potential confounders such as age and gender. Comparisons of categorical variables across groups were conducted by using the 2x3 chi-square tests, followed by 2x2 chi-square tests. The reliability of the SCI-TALS was examined by analysing the correlations between domains and the internal consistency of domains. Kuder-Richardson coefficient, a variant of the alpha coefficient for dichotomous items (Nunnally & Bernstein, 1994), was used to determine the internal consistency. Test-retest and inter-rater reliability of the SCI-TALS was performed at Pisa site only, by having

different raters conduct a second SCI-TALS evaluation within 14 days of the initial assessment. We examined reliability using the intraclass correlation coefficient. Shrout criteria (Shrout, 1998) were used to define the range of reliability: 0-0.10 virtually none, 0.11-0.40 slight, 0.41-0.60 fair, 0.61-0.80 moderate, 0.81-1 substantial. Data analyses were carried out using SPSS 12.0.1.

Results

Subjects

Demographic and clinical characteristics of the study groups are provided in Table 1. Controls were younger than CG patients. The majority of patients with CG (84.1%) and of controls (64.6%) were females, while patients with PTSD were equally distributed by gender. Patients with CG were more likely to be widowed than the other groups, had a lower educational level and were less likely to be employed than controls,.

As expected, CG patients had a significantly higher ICG total score compared to PTSD and controls (Table 1).

Acceptability and validity of the SCI-TALS

The SCI-TALS was administered to patients and controls in one session of approximately 30 minutes. The acceptability of the interview was excellent: 96.9% of participants rated it as much or very much interesting, 49.6% rated it

as much or very much reassuring, 51.8% and 82.5% found that it was helpful to better understand the patients' own problems and to provide useful information to the physician, respectively. However, 32.8% of patients found the interview much or very much distressing. No one refused to participate and no participants failed to complete the interview. Mean SCI-TALS domain scores for each of the groups are provided in Table 2, together with the results of the one-way ANOVA and the post-hoc pairwise comparisons. The two patient groups did not differ on 6 out of 8 Domains (Table 2) and both scored significantly higher than controls. Interestingly, this was also true for number of loss events. PTSD and CG patients endorsed on average the same number of loss events. However, consistent with evidence that CG is different from PTSD (Langner & Maercker, 2005; Shear et al., 2005), CG patients scored significantly higher that those with PTSD on Domain II: Grief reactions. In contrast, those with CG endorsed a significantly lower number of potentially traumatic events, and did not differ from PTSD on re-experiencing, avoidance or hyper-arousal.

Analysis of covariance was performed on the SCI-TALS domains to determine whether the differences between groups depended on gender and age imbalance. No association was found between age and the SCI-TALS domains. Gender was associated with the domains 'grief reactions', 'maladaptive copying' and 'arousal', but this association did not affect the differences among diagnostic groups.

Reliability of the SCI-TALS

We examined the internal consistency of the domains and correlations of domains in the pooled sample of individuals with either PTSD or CG diagnosis (Table 3). All Kuder-Richardson coefficients exceeded the minimum standard of 0.50 suggested for group comparison by Helmstadter (1964). Additionally, all domains and 12 out of 16 sub-domains exceeded the 0.70 standard for individual comparisons suggested by Nunnally (1978). For domains I, III and IX the internal consistency was not determined because these were checklists of events or of personality characteristics rather than symptoms. As reported in Table 4, correlations between domains were all positive and significant, with Pearson's r ranging between 0.46 and 0.76 ($p<0.01$).

The test-retest and inter-rater reliability was excellent, with intraclass correlation coefficients values exceding .90 for each of the domains (Table 5).

Discussion

Results of this study provide evidence for the reliability and validity of a new spectrum instrument, the Structured Clinical Interview for Trauma and Loss Spectrum (SCI-TALS). We developed this instrument to characterize the range of life events, acute event reactions and persistent symptoms and behavioural tendencies that occur among patients with post-traumatic stress disorder and the persistent grief disorder often referred to as complicated grief.

We found excellent inter-rater reliability of this interview when administered by different raters a mean of 2 weeks apart. As expected, patients who met DSM-IV criteria for PTSD and ICG criteria for persistent grief disorder, scored significantly higher than a comparison control group. This supports the validity of this instrument as a measure of trauma-loss spectrum.

We believe that this interview, like the other spectrum instruments we have developed, has the advantage of helping patients understand themselves and feel understood by their clinician. Moreover, lifetime spectrum symptoms of a range of mood and anxiety disorders were found to contribute to impairment (Bazzichi et al., 2005; Fagiolini et al., 2005), to represent a risk factor for suicidality (Balestrieri et al., 2006), and to influence treatment outcome (Frank et al., 2000; Frank et al., 2002; Dell'Osso et al., 2007).

We believe the spectrum approach provides a more specific description of the clinical features of each patient with potentially important implications for treatment choice and research. We also think that a less restrictive approach to the definition of the potentially traumatic events, than that defined in DSM-IV, would particularly help clinicians to explore more accurately post-traumatic stress conditions. Moreover, the evidence of a different profile for those suffering the consequences of trauma versus loss suggests that the spectrum approach might help identify specific phenotypes to be used in clinical, neurobiological and genetic studies. Further studies are warranted to assess the potential utility of this approach in clinical practice.

5. LIFETIME SUBTHRESHOLD MANIA COMORBIDITY AND PERIPHERAL BENZODIAZEPINE RECEPTOR (PBR) IN PTSD

Introduction: Peripheral Benzodiazepine Receptor, Bipolar disorder and PTSD

Post-traumatic stress disorder (PTSD) is a severe, invalidating and often chronic psychiatric condition (Kessler et al., 1995) which characteristics have been progressively defined in the last years. From its first codification in the Diagnostic and Statistical Manual of Mental Disorders-IIIrd edition in 1980, up to the latest DSM-IV-TR, the characteristics of either the provoking trauma and of the symptomatology have been more accurately described. These progresses led to an increasing recognition of PTSD in civilians (such as victims of rape, physical assault, natural disasters, motor vehicle accidents or other traumatic events not combat related), even if the majority of early studies had been originally developed on male military or combat veteran populations because of historical precedents and subject availability (Keane & Wolfe, 1990). Clinical studies reported prevalence rates in the general population ranging between 9.5% and 11.2% (Helzer et al., 1987; Breslau et al., 1991; Kessler et al., 1995). These data support the relevance of detecting potential risk factors

for the development of such an invaliding condition. Nevertheless, agreement among authors has been reported for only few potential risk factors, such as gender, number of previous traumatic experiences and acute symptoms such as peritraumatic dissociation.

Recently, increasing attention has been given to the role of mood comorbidity, and particularly that of Bipolar Disorder (BD), as potential risk factor for PTSD onset. In psychiatric literature, consistent data have already shown the presence of high rates of comorbidity between the two disorders, suggesting higher vulnerability for the development of PTSD in patients with bipolar disorder (BD) (Otto et al., 2004).

In line with these studies, authors have started debating whether BD might represent a risk factor for PTSD (Pollack et al., 2006) or if this comorbidity might be due to the fact that patients with BD frequently present characteristics that have been identified as risk factors for PTSD, such as: trauma exposure (Darves-Bornoz et al., 1995; Mueser et al., 1998; Neria et al., 2002), depression and hypomania (Schnurr et al., 1993), comorbid anxiety disorders (Pollack et al., 2006).

Recently Pollock and collaborators (Pollack et al., 2006), examining PTSD onset following indirect exposure to the September 11, 2001, terrorist attacks, in a cohort of patients with BD (enrolled in the on-going longitudinal study Systematic Treatment Enhancement Program for Bipolar Disorder, STEP-BD), have reported, for the first time, that presence of manic state at the

time of exposure may represent the most critical risk factor for the onset of persistent PTSD.

Besides progresses in clinical assessments, biochemical studies have attempted to find reliable biological markers of post-traumatic stress conditions. Although the findings have been highly variable (de Kloet et al., 2006), a great number of data have suggested the presence of characteristic alterations in the function of hypothalamic-pituitary-adrenal (HPA) axis (Yehuda et al., 2000; Nemeroff et al., 2006), the network which coordinates steroid metabolism during the physiological responses.

The HPA axis, which consists in the hypothalamus, the pituitary gland and the adrenal gland, constitute the main stress response system. It receives information from the amygdala and the hippocampus, as well as from the autonomic nervous system (Holsboer, 2001), and in turn, it coordinates stress responses. Moreover, it can trigger hormonal cascade: the hypothalamus releases the corticotrophin releasing hormone (CRH), which stimulates the discharge of adrenocorticotropin releasing hormone (ACTH) from the pituitary gland. Then ACTH actives the steroid synthesis within the adrenal cortex from pregnenolone down to the glucocorticoid cortisol, which is subsequently secreted into the blood circulation. When the glucocorticoid blood concentration overpass a certain value, the cortisol provides negative feedback at the level of the hypothalamus, the pituitary and the hippocampus, blocking the stress response.

The HPA axis complexity is the result of the adaptive mechanisms needed to maintain body homeostasis also during strong stress conditions. Such hormonal and physical responses, organized by the HPA axis, have protective functions in acute stress states, but they can be harmful if deregulated. In fact, if stress hormones are overproduced for long periods of time without control, they can damage peripheral and central tissues, causing physical and mental diseases (McEwen, 2002). For example, excessively high corticoid levels induce cell atrophy by glutamate damage in the hippocampus, a brain area particularly important for memory and learning, which has a high density of glucocorticoid receptors (Lupien et al., 1998).

In patients with PTSD, highly variable alterations of the HPA axis have been reported, despite modifications of this system are actually certain in this disorder. Cortisol in fact, represents the principal steroid hormone in humans and the primary regulator of resting activity of the HPA axis. Some studies found high 24-h urinary cortisol levels in patients with PTSD (Lemieux & Coe, 1995; Pitman and Orr, 1990; Rasmusson et al., 2001), weather other reported low values (Yehuda et al., 2000), or also no differences versus controls (Baker et al., 1999; Kosten et al., 1990)

Recently, since a glucocorticoid levels elevation inhibits memory retrieval in animals and healthy human subjects, it has been suggested the administration of low-dose cortisol treatment (10 mg/day for 1 month) to obtained beneficial effects attenuating the incidence or intensity of traumatic memories, a cardinal symptom of PTSD (Aerni et al., 2004).

It's known that physical or emotional stress, besides cortisol level changes, can produce severe alterations in serum levels of other steroids (Charney, 2004). The dehydroepiandrosterone (DHEA) is an adrenal steroid secreted episodically and synchronously with cortisol. DHEA and its sulphate derivate (DHEAS), have been shown to determine a bimodal modulation effect on $GABA_A$ receptor: a positive allosteric modulation at nanomolar concentrations and a negative one at micromolar concentrations. Such modulating effects are mirrored in behavioural setting (Majewska, 1992). Elevated circulatory levels of DHEA and DHEAS have been detected in plasma of patients with combat-related PTSD (Spivak et al, 2000). On the other hand, decreased concentrations of both DHEA and DHEAS have been reported in stress characteristic paradigms as depression and chronic inflammation (Charalampopoulos et al, 2005).

The steroid biosynthesis occurs mainly in the adrenal gland, but also in the glial cells of the central nervous system, in which are synthesized the so-called neurosteroids. In both tissues, the pivotal limiting step in the synthesis is represented by the cholesterol transport within the mitochondria which is realized through a mitochondrial pore. Cholesterol is then converted in pregnenolone, catalyzed by the cytochrome P450 SCC present in the inner mitochondrial membrane, that then undergoes to metabolic transformations in the endoplasmic reticulum, giving rise to other steroids.

The mitochondrial translocator protein (Peripheral Benzodiazepine Receptor, PBR) has been demonstrated to be a component of such pore,

essential for the cholesterol crossing through the outer mitochondrial membrane, behaving either as a channel or as a chaperon (Culty et al., 1999; Lacapere & Papadopoulos, 2003). In fact, it has been suggested that PBR could form a channel allowing cholesterol to cross over the outer mitochondrial membrane (Culty et al., 1999), although the most accepted hypothesis is that PBR functions as chaperon which bind cholesterol with high affinity (Lacapere et al., 2003).

PBR density has been found altered in different pathological conditions, such as cancer and neurological illnesses, and in many psychiatric disorders (Papadopoulos et al., 2006) as well as in stress responses: up-regulation has been shown in acute stress conditions while down-regulation in repeated or chronic stress (Weizman et al., 1994; Gavish et al., 1996; Droogleever Fortuyn et al., 2004; Veenman & Gavish, 2006).

The binding of PBR ligands, inducing cholesterol transport into mitochondria and steroid formation by glial cells, leads to the formation of pregnane neurosteroids, such as allopregnanolone and pregnanolone, which positively modulate the functions of the GABAA receptor and have anxiolytic effects, as shown in animal models of anxiety (Papadopoulos, 2006).

In rats, acute stress has resulted in increase in PBR density in the brain, whereas repeated swim stress (Burgin et al., 1996), repeated foot shock (Drugan et al., 1988) and food deprivation stress (Weizman et al., 1990) led towards a reduction in PBR density, suggesting that such changes may be due to a receptor density compensatory shift to accommodate the demand of

steroids under stress conditions (Drugan, 1996; Drugan et al., 1993; Weizman & Gavish, 1993; Gavish et al., 1999).

In human subjects, lower levels of binding to the PBR have been reported in the platelets of patients with anxiety (Gavish, 1999, Marazziti et al., 1994). Moreover, these levels increased after subsequent treatment with diazepam (Weizman et al., 1987; Gavish, 1999), suggesting that PBR ligands could prevent psychiatric disorders that arise from a stress-induced imbalance of CNS function (Papadopoulos et al., 2006).

Only a few studies have investigated platelet PBR levels in patients with PTSD, reporting lower receptor levels, thus all have been conducted in veterans population samples during or after chronic war stress, (Weizman et al., 1994; Gavish et al., 1996, 1999).

Aim of the study

Since mitochondrial PBR is a key element in the steroidogenesis rate-limiting step, and alterations in the HPA axis seems to represent a characteristic finding of PTSD patients, secondary aim of the study reported in the present thesis was to explore lymphomonocyte mitochondrial PBR alterations in PTSD patients form the general population with not-combat related trauma. Since PBR is presented in whole cell membranes (plasmatic, nuclear and mitochondrial), we focused on the mitochondrial PBR density, in order to take account of the PBR amount mainly involved in steroid synthesis.

The study was conduced in a sample of Italian civilian patients affected by PTSD. All patients had been exposed to different type of traumas, all not-war related. The groups of subjects were also compared to a sample of healthy subjects, without any axis I current or lifetime psychiatric disorder, belonging to the same community background.

Further, aim of the present study was to detect, in the same group of subjects, the possible correlations between the PBR equilibrium binding kinetic parameters alterations and the presence of lifetime manic/hypomanic symptoms. In the last years increasing evidence supports the possible clinical relevance of detecting even mild manic-hypomanic symptoms in clinical populations, and in line with these studies new assessment instruments have been developed, such as the Mood-Spectrum Self Report (MOODS-SR) lifetime version (Dell'Osso et al., 2002; Cassano et al., 2004). This latest is an instrument that focuses on lifetime manic and depressive symptoms, characteristics, traits and lifestyles that characterize threshold and sub-threshold mood episodes related to Axis I mood disorders. Correlations between PBR changes and lifetime Mood Spectrum manic/hypomanic or depressive items in patients with PTSD diagnosis were investigated in order to corroborate the role of mood alterations as risk factors for adverse sequel following exposure to trauma.

Materials and Methods

Subjects

The data of the present report were collected at Department of Psychiatry, Neurobiology, Pharmacology and Biotechnology of the University of Pisa. The whole sample included 35 subjects: 22 with PTSD, and a comparison group of 13 control subjects, without any Axis I lifetime or current psychiatric diagnoses. Eligible subjects included new and continuing patients, over 18 years of age, with a diagnosis of PTSD (according to DSM-IV-TR criteria, 2000) and individuals without any history of psychiatric disorders (controls). Exclusion criteria for patients and controls were auto-immune, inflammatory or endocrine disorders, obesity, alcohol or drug abuse, on-going use of contraceptive drugs. Patients were asked to have discontinued any pharmacological treatment, including psychotropic medications, at least 4 weeks prior to entering the study. The study design was carried out in accordance with the latest version of the Declaration of Helsinki and it was reviewed and approved by the ethical committee of the Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy. After complete description of the study, a written informed consent of the participants was obtained.

Instruments and assessments

Patients were assessed by: the Structured Clinical Interview for DSM-IV axis-I disorders (SCID-I/P, 25); the Impact of Event Scale (IES, Horowitz et

al., 1979), in order to assess post traumatic on-going symptom severity; and the MOOD-SR (Dell'Osso et al., 2002) in order to assess the lifetime mood spectrum symptomatology, and in particular the manic/hypomanic and depressive spectrum symptoms. All assessments were conducted by psychiatrists or residents in psychiatry, who were trained and certified in the use of the study instruments at the Department of Psychiatry, Neurobiology, Pharmacology and Biotechnology of the University of Pisa.

Biological Sample Collecting

Blood samples (20 ml) were collected from both patients and controls, between 9 and 10.30 AM, after a overnight fast. Blood samples were drawn into test tubes containing Li-Heparin and than processed for PBMC purification, using differential centrifugations with Lymphoprep (Axis-Shield PoC AS, Oslo, Norway) according to the method of Boyum (Mueser et al., 1998). The final mononuclear cell pellet was stored at –80°C until analyses. The Ethics Committee of the Azienda Ospedaliera Universitaria of Pisa approved all recruitment and assessment procedures (N°00019916). Eligible subjects provided written informed consent, after receiving a complete description of the study and having the opportunity to ask questions.

Radio-ligand binding assays on lymphomonocyte mitochondria membranes

Mitochondria membranes from the mononuclear cells were prepared as previously described (Nemeroff et al., 2006) with minor modifications. In brief, the lymphomonocyte pellet was homogenized in an adequate ice-cold buffer, by using a Potter Elvehjem glass homogenizer, and centrifuged at 800 x g for 10 min at 4°C. After supernatant centrifugation (10,000 x g for 10 min at 4°C), the resulting mitochondria pellet was suspended in an adequate buffer and protein concentration was estimated by the method described by Lowry et al. (Neria et al. 2002) using bovine serum albumin as standard.

In radio-ligand binding assays, [3H]PK11195, a classical PBR ligand, was used for the determination of the PBR equilibrium binding parameters in lymphomonocyte mitochondria membranes (Scatchard Analyses).

In brief, [3H]PK11195 binding assays were conduced incubating membrane aliquots (30 μg of protein) with increasing [3H]PK11195 concentrations (0,5 nM-20 nM). Non specific binding was determined in the presence of 1 □M of unlabeled PK11195. Samples were incubated in duplicate for 90 min at 0°C.

After incubation time, samples were rapidly filtered under vacuum through GF/C glass fibre filters to separate the bound and the unbound ligand. After being washed three times with 4 ml of assay buffer, radioactivity trapped on the filter was measured in a liquid scintillation counter (TopCount; PerkinElmer Life and Analytical Sciences).

Data Analysis

Scatchard analysis of [3H]PK11195 saturation binding data were performed using Kell RadLig for Windows 6.0 (Copyright 1997-1999 Biosoft and G.A. McPherson).

Statistical analysis was executed using the Graph-Pad Prism 4 software (Graph-Pad Software Inc, San Diego, CA); analyses was performed by the unpaired Student's t test, in order to compare demographic, clinical (totals and subdomain scores of IES and MOODS-SR) and biochemical (PBR Kd and Bmax) characteristics between patients and controls. Linear regression analysis with Pearson test was performed in order to evaluate possible correlations between PBR Bmax and demographic and clinical (total and subdomain scores of IES and MOODS-SR) in patients with PTSD. All tests were two-tailed and a p value <0.05 was considered statistically significant. All data are presented as mean±SD.

Results

The study sample included 35 subjects: 22 patients with PTSD and a comparison group of 13 control subjects, without any Axis I current or lifetime psychiatric diagnosis. The demographic and clinical characteristics of the study groups are provided in Table 6. Patients and controls were mostly females (59,09% and 69.23% respectively), mean age was 44.77±14.10 (mean±SD) and

35.08±11.96 years, respectively, and a significantly lower proportion of PTSD patients than controls reported more than 8 years of education (63,64% versus 76,92% respectively, $p<0.05$).

All patients presented a diagnosis of chronic PTSD and mean duration of time since the triggering trauma was 82,86±125.9 months (mean±SD), moreover, 53.8% of patients reported to have experienced one single trauma, as defined in accordance to DSM-IV-TR criterion A for PTSD diagnosis, while 46.2% reported to have experienced more than one trauma in their lifetime. For what is concerned with the type of index trauma experienced by patients with PTSD: 8 (36.4%) had experienced an assaultive violence, 10 (45.4%) an injury or shock, while 4 (18.2%) the death of loved one. Among controls, only 5 subjects had experienced a traumatic event during their lifetime with: 1 (7.7%) patient having experienced an assaultive violence, 1 (7.7%) an injury or shock, and 3 (20%) the death of loved one.

As expected, patients presented significant higher scores than controls in the Impact of Event Scale total score (28.95±13.55 versus 17.38±3.885, $p<0.01$), and in the Intrusive (14.57±6.911 versus 8.462±2.504, $p<0.005$) and Avoidance (14.38±7.039 versus 8.923±1.553, $p<0.05$) subscales (Table 6).

Scatchard analysis of [3H]PK11195 saturation binding data performed in control and patient lymphomonocytes showed Kd value of 8.035±2.583 and 6.580±2.865 (mean±SD) nanomolar, respectively, and a Bmax value of 7991±1258 and 5707±1828 fmoli/mg of proteins, respectively. The Scatter grams of individual PBR Bmax values obtained from patients and controls are

illustrated in Figure 1. Unpaired t-test analysis demonstrated a highly significant decrease in Bmax values ($p<0,0005$) in patients with respect to control subjects, while the Kd values were not significantly different in the two groups.

The correlation analysis performed by using Pearson test, between PBR Bmax and demographic and clinical parameters (Table 7), showed significant inverse correlation between PBR Bmax and the Total Manic component of the Mood Spectrum ($p<0,05$), while a p value close to significance was also reported for the inverse correlation between the receptor density and the Cognition Manic domain.

Discussion

Along with the progressive delineation of PTSD diagnostic criteria, since its first appearance in DSM-III, an increasing number of studies have reported the incidence of this disorder in general population samples, rising the relevance of possible biological markers of the disorder that could support the diagnosis and maybe helping in delineating strategies for future research.

Biological markers have been investigated as supports for the clinical diagnosis, and among these the PBR was found altered in mental disorders, particularly stress related. Previous studies assayed PBR levels in blood cells of healthy controls during and following stressful situations, such as immediately

after an exam, showing that PBR density increased in students following academic examination (Droogleever Fortuyn et al., 2004; Karp et al., 1989; Nudmamud et a., 2000); on the contrary platelet PBR density appeared to be reduced after repeated parachute jumps during parachute training of soldiers (Dar et al., 1991). These findings have suggested that PBR density in blood cells can be increased in acute stress, but decreased under chronic stress conditions as occur with anxiety disorders (Veenman & Gavish, 2006). In general anxiety disorder, panic disorder and PTSD a lower platelet PBR levels have been detected (Veenman & Gavish, 2006). Thus, PBR alterations are not uniform among the anxiety disorder but restricted to those disorders presenting a persistent activation of the autonomic nervous system (Gavish et al., 1996).

Basic studies in rats have suggested that the PBR stress-changes may be due to a receptor density compensatory shift to accommodate the demand of steroids under stress conditions (Drugan, 1996; Drugan et al., 1993; Weizman & Gavish, 1993; Gavish et al., 1999).

Not surprisingly, PBR alterations have been investigated in subjects with PTSD, but the only study exploring alterations in platelet PBR of patients has been conduced in a special population, as all exposed to war stress (Weizman et al., 1994; Gavish et al., 1996). Weizman and colleagues (Weizman et al., 1994) have explored PBR alterations in soldiers before, during and immediately after exposure to repeated missile attacks during the Persian Gulf war, in conditions of acute and continued stress. In a later study, the same authors analysed a subgroup of the same sample, after two years from

the end of the war, evidencing a decrease in PBR density, but no correlation between the receptor and IES scores.

To our knowledge, this is the first study investigating PBR alterations in a group of civilian patients that reported a PTSD diagnosis not related to war traumas, comparing the receptor among subjects with chronic PTSD arisen after exposure to different types of traumas. Moreover, this is the first study in which PBR density determination was conduced only on mitochondrial membranes, assuring the PBR amount estimated is involved in the biosynthesis of steroids.

Our results showed a significant decrease in mitochondrial PBR density in the lymphomonocytes of civilian trauma victims with diagnosis of PTSD, according to data obtained in war-related PTSD patients. Further, in accordance to the findings reported by Weizman et colleagues (Weizman et al., 1994), we did not also evidenced any correlation between the receptor density and IES scores.

Since increasing data have reported the possibility of a relevant correlation between the presence of a manic or hypomanic state during exposure to traumatic events and the subsequent onset of PTSD (Otto et al., 2004), we investigated if the presence of lifetime manic/hypomanic spectrum symptoms, indicating the presence of mood vulnerability, could be correlated with PBR density decrease in civil patients with PTSD.

Since subjects affected by bipolar disorders are more sensible to psychophysical stress, we have chosen to assess possible correlations between

PBR and mood symptoms using a sharpened instrument: the Mood Spectrum-Self Report (Dell'Osso et al., 2002). We enhanced a significant correlation between PBR Bmax and total Mania values. In particular, patients with PTSD presenting the highest number of lifetime manic/hypomanic items showed the lowest PBR density.

In relation to mood disorders, no difference has been reported in platelet PBR density of subjects with major depression, with respect to controls. No studies are available about PBR in bipolar disorders, but in this psychiatric disease abnormalities of the HPA axis functions are well documented (Gavish et al., 1999; Watson et al., 2004).

It has been reported that high levels of circulating corticosteroids often induce psychiatric syndromes, conventionally known as steroid psychosis, and the first mood episode was often manic or hypomanic. Lewis and Smith (Lewis & Smith, 1983) reported seven manic, one depressive and two psychotic episodes from original series of steroid psychosis. Since PBR plays a important role in steroidogenesis, the chronic stress-induced decrease in PBR density could be the reflex of a neuroendocrine defence mechanism that affects the mitochondrial cholesterol transport and the stress-induced glucocorticoid production (Weizman & Gavish, 1993). The modifications in PBR kinetic parameters might account for the alterations in the levels of steroids observed in PTSD v and/or manic/hypomanic symptoms. Further studies are needed to better clarify this correlation.

6. CONCLUSIONS

Being exposed to life-threatening events represents an increasingly given human existence. Recent epidemiological studies confirm increasing rates of exposure in civil populations, but luckily, only a minority of the people exposed goes on to develop post-traumatic stress conditions. Nevertheless, an increasing prevalence of subclinical and subsyndromal forms in the general population is progressively emphasized as consequence of the burden of seek for treatment and impairment associated. This has led researcher to highlight these subsyndromal expressions of post-traumatic reaction showing and to investigate their clinical relevance.

Further, emerging literature documents the importance of the so-called "low-magnitude" or subthreshold events (e.g., divorce, serious illness and financial reverses) in determining post-traumatic stress reactions (Breslau and Davis, 1987; Solomon and Canino, 1990; Moreau & Zisook, 2002), increasing the never ending debate over the definition of the "nature" of an event in order to define it as traumatic. Higher relevance to the role of subjective vulnerability has been highlighted by these studies. This latest concept gives post-traumatic condition a particular importance for a better understanding of the continuum between genetically predetermined disorders and environmentally induced ones, in light with the actual debate on the research over new reliable models

for clinical phenotypes other that the misleading ones suggested by the rigid current nomenclature.

The results of the present thesis demonstrate the validity of a new assessment instrument, the Structured clinical interview for Trauma and Loss Spectrum, corroborating the relevance of a spectrum approach to post-traumatic stress conditions, including CG.

The SCI-TALS showed to be a valid and reliable instrument, able to provide a more specific description of patients' clinical features giving information on a broad spectrum of trauma, loss events and related symptoms beyond those covered by existing instruments. A less restrictive approach to the definition of the potentially traumatic events than that defined in DSM-IV, as reported by SCI-TALS, would particularly help clinicians to more accurately explore post-traumatic stress conditions. Moreover, the evidence of a different profile for those suffering the consequences of trauma versus loss suggests that the spectrum approach might help identify specific phenotypes to be used in clinical, neurobiological and genetic studies.

Further, in line with studies enhancing the need for neurobiological markers for a better understanding of either full blown and subsyndromal forms, the significant decrease in platelet PBR levels found in civilian patients with PTSD supports a role for this biochemical parameter in clinical assessments. Moreover, the correlation between this alteration and the presence of lifetime manic spectrum symptoms enhances the possible role of mood spectrum symptomatology on PTSD onset, and corroborates the relevance of

an accurate assessment of manic-hypomanic spectrum symptoms as risk factors for PTSD onset.

To our knowledge, this is the first study investigating PBR alterations in a group of civilian patients that reported a PTSD diagnosis not related to war traumas, comparing the receptor among subjects with chronic PTSD arisen after exposure to different types of traumas. This may help in characterizing the disorder independently for the provoking event, supporting the role of subjective vulnerability. Moreover, this is the first study in which PBR density determination was conduced only on mitochondrial membranes, assuring the PBR amount estimated is involved in the biosynthesis of steroids.

Further studies are warranted to assess the potential utility of this spectrum approach to PTSD and CG in clinical practice and to confirm the role of biological markers, such as PBR, in helping to increase the knowledge on the pathogenesis of these disorders and to allow more efficacious treatments.

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8. TABELS

Table 1. Demographic and clinical characteristics of the study samples.

	PTSD N=48	CG N=44	Controls N=48	Test ,significance (p)
	Mean± S.D.	Mean± S.D.	Mean± S.D.	
Age	44.8±14.3	49.3±14.5	41.2±12.2	F=4.0, p<0.05, CG>C
	N (%)	*N (%)*	*N (%)*	
Female	25 (51.2)	37 (84.1)	31 (64.6)	Chi-square=10.6, p<0.01, CG>PTSD
Marital status				Chi-square=27.8, p<0.001
Single	14 (29.2)	12 (27.3)	23 (47.9)	
Married/living with partner	32 (66.7)	18 (40.9)	24 (50.0)	
Widows-ers	1 (2.1)	12 (27.3)	1 (2.1)	
>8 y. of education	32 (66.7)	24 (54.5)	38 (79.2)	Chi-square=6.3, p<0.05, C>CG
Employed full/part time	30 (62.6)	21 (47.7)	53 (72.9)	Chi-square=6.2, p=0.05, C>CG
	Mean± S.D.	Mean± S.D.	Mean± S.D.	
IES Total score	26.1±17.2	30.3±15.0	12.0±11.8	F=19.7, p<0.001; CG, PTSD>C
Intrusive	13.4±8.9	16.0±8.5	6.6±6.6	F=16.8, p<0.001; CG, PTSD>C
Avoidance	12.8±9.4	14.4±8.5	5.4±5.7	F=16.8, p<0.001, CG,PTSD>C
ICG Total score	9.3±7.1	38.8±10.5	5.1±6.5	F=215.8, p<0.001, CG>PTSD, C

Table 2. Domain total scores of the SCI-TALS in the study sample

	PTSD N=48	CG N=44	Controls N=48	F	*p*	*Dunnett post Hoc comparison at p=0.016*
	Mean±S.D.	Mean±S.D.	Mean±S.D.			
I – Loss events	3.77±1.87	4.02±1.84	2.83±1.26	6.52	<.01	CG > controls
II – Grief reactions	6.42±5.13	12.00±3.80	3.23±3.21	52.63	<.001	CG> PTSD > controls
III – Potentially traumatic events	5.06±3.07	3.91±2.86	2.25±1.85	13.75	<.001	PTSD> CG > controls
IV – Reaction to losses or upsetting events	10.27±3.50	10.14±3.22	3.62±3.04	64.30	<.001	PTSD, CG > controls
V – Re-experiencing	5.10±2.35	5.14±2.19	1.17±1.36	60.91	<.001	PTSD, CG > controls
VI – Avoidance and numbing	5.89±2.88	5.70±2.72	0.92±1.35	64.97	<.001	PTSD, CG > controls
VII – Maladaptive coping	1.44±1.76	1.93±1.73	0.17±0.43	18.68	<.001	PTSD, CG > controls
VIII - Arousal	3.25±1.39	3.36±1.51	0.81±1.12	54.07	<.001	PTSD, CG > controls

Table 3. Internal consistency (Kuder-Richardson coefficient) of the SCI-TALS domains

	#ITEMS	***KR-20***
I – Loss events	10	/
II – Grief reactions	27	0.916
III – Potentially traumatic events	21	/
IV – Reaction to losses or upsetting events	18	0.863
V – Re-experiencing	9	0.809
VI – Avoidance and Numbing	11	0.858
VII – Maladaptive coping	8	0.773
VIII – Arousal	6	0.789
IX – Personal Characteristics-Risk Factors	7	/

Table 4. Pearson's correlations between SCI-TALS domains

Domains	IV Reaction to losses or upsetting events	V Re-experiencing	VI Avoidance and Numbing	VII Maladaptive coping	VIII Arousal
II - Grief reactions	0.549**	0.538**	0.545**	0.468**	0.521**
IV – Reaction to losses or upsetting events		0.709**	0.710**	0.535**	0.722**
V – Re-experiencing			0.762**	0.528**	0.706**
VI – Avoidance and Numbing				0.541**	0.676**
VII – Maladaptive coping					0.567**

** p<0.01

Table 5. Test-retest and inter-rater reliability.

	INTRACLASS CORRELATION COEFFICIENT
I – Loss events	.975
II – Grief reactions	.992
III – Potentially traumatic events	.974
IV – Reaction to losses or upsetting events	.981
V – Re-experiencing	.975
VI – Avoidance and Numbing	.995
VII – Maladaptive coping	.993
VIII – Arousal	.972
IX – Personal Characteristics-Risk Factors	.969

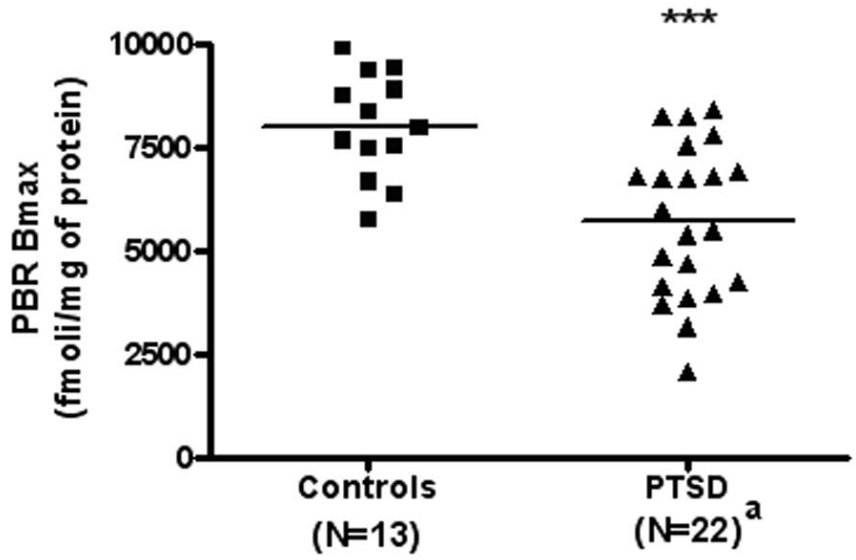
Table 6. Demographic, clinical and biochemical characteristics of the study samples.

	PTSD N=22	**Controls N=13**	
	%	**%**	
Female	59,09	69,23	p<0.005
Married/living with partner	59,09	30,77	p<0.005
>8 y. of education	63,64	76,92	p<0.05
Employed full/part time	86,36	76,92	p<0.05
Unemployed	9,09	7,69	Ns
Type of index trauma			
Assaultive violence	36,4 (N=8)	7,7 (N=1)	
Other injury/Shock	45,4 (N=10)	7,7 (N=1)	
Sudden death of a loved one	18,2 (N=4)	20 (N=3)	
	Mean±SD	**Mean±SD**	**p**
Age (years)	44,77±14,10	35,08±11,96	p<0,05
IES Total score	28,95±13,55	17,38±3,885	p<0,01
Intrusive subscale	14,57±6,911	8,462±2,504	p<0,005
Avoidance subscale	14,38±7,39	8,923±1,553	p<0,05
MOODS Total score	77,95±35,25	63,62±35,79	Ns
Mood Depressive	11,43±7,131	7,846±6,039	Ns
Mood Manic	12,86±7,378	8,000±6,245	p=0,057
Energy Depressive	5,810±3,881	3,923±3,278	p<0,05
Energy Manic	2,905±2,948	1,000±1,633	p<0,05
Cognition Depressive	21,62±5,053	26,07±2,530	Ns
Cognition Manic	12,43±6,384	7,462±6,995	p<0,05
Depressive Items Total	37,19±17,00	36,31±20,62	Ns
Manic Items Total	28,19±14,44	16,46±13,50	P<0,05
Rithmicity	12,57±7,194	10,85±7,198	Ns
PBR Bmax (fmol/protein mg)	5707±1828	7991±1258	<0.0005
PBR Kd (nM)	6.580±2,865	8.035±2,583	Ns

Table 7. Pearson test correlation between PBR Bmax and demographic and clinical (total and subdomain scores of IES and MOODS-SR) in patients with PTSD. A Pearson test p value <0.05 was considered statistically significant.

PTSD N=22			
Parameters		***Pearson r***	***P value (two-tailed)***
Age		0,04524	0,8415 Ns
Sex		0,1944	0,3984 Ns
N° of traumas		-0,3279	0,1363 Ns
Time from trauma		0,07020	0,7562 Ns
IES	Total score	-0,1274	0,5821 Ns
	Intrusive subscale	-0,2010	0,3822 Ns
	Avoidance subscale	-0,04793	0,8365 Ns
MOODS	Total score	-0,2688	0,2388 Ns
	Mood Depressive	-0,3263	0,1489 Ns
	Mood Manic	-0,3867	0,0833 Ns
	Energy Depressive	-0,06056	0,7943 Ns
	Energy Manic	-0,3613	0,1076 Ns
	Cognition Depressive	-0,07248	0,7549 Ns
	Cognition Manic	-0,4161	***0,0607***
	Total Depressive	-0,09401	0,6852 Ns
	Total Manic	-0,4552	***0,0381*** p<0,05
	Rithmicity	-0,1807	0,4330 Ns

Figure 1. [^{3}H]PK11195 Bmax values in lymphomonocyte mitochondrial membranes from patients with PTSD and controls. Each point represents an individual subject. The difference in Bmax values between controls and patients is statistically significant ($p<0.05$). [a]Significant difference ($t=3,972$ $df= 33$, $p=0,0004$)



9. APPENDIX: SCI-TALS

Structured Clinical Interview for Trauma and Loss Spectrum

INTRODUCTION:
Thank you for coming in to talk with me today. The interview we are going to do is focused on losses and upsetting events that you may or may not have experienced in your life and your reactions to them. We want to know whether you had these reactions at any time, even if it was a long time ago. There are eight sections of the interview and it should take us about half an hour to complete it. Do you have any questions before we start?

Interviewer: I am going to begin by asking you about some losses that you may have experienced.

DOMAIN I. LOSS EVENTS

Did any of the following things ever happen to you?

1.	…a change in homes, caregivers, schools, jobs, etc. that you didn't want or regretted?	Yes	No
2.	…separation from a close friend, romantic partner, or family member because of relocation, hospitalization, military service, or because of an argument or disagreement?	Yes	No
3.	…a painful break-up with a romantic partner or a close friend?	Yes	No
4.	…a divorce in your family?	Yes	No
5.	…the loss or death of a cherished pet?	Yes	No
6.	…being neglected or abandoned?	Yes	No
7.	…the death of a close friend or relative?	Yes	No
8.	…a miscarriage, stillbirth, or abortion? *Note to interviewer: can apply to male subjects as well as female.*	Yes	No

9.	Did you lose your sight, hearing, or have a serious disability?	Yes	No
10.	Did you have any other important losses, whether people, places or things that I haven't asked you about? What were they? *Record here:*	Yes	No

Note to interviewer: If the subject has not endorsed any losses up to this point, skip to Domain III (Traumatic Events).

DOMAIN II. GRIEF REACTIONS

Since you experienced these losses, have you ever had a period of time when…

11.	…you had a lot of trouble accepting the loss?	Yes	No
12.	…you constantly longed for the way things used to be?	Yes	No
13.	…you longed or searched for a loved one or a familiar place in a way that seemed excessive and/or uncontrollable?	Yes	No
14.	…you daydreamed a lot about the person or thing you lost?	Yes	No
15.	…you were bothered more than you expected by feelings of grief, or you had frequent intense pangs of grief?	Yes	No
16.	…you felt that your life had no purpose without the person or thing you lost?	Yes	No
17.	…grief interfered with your ability to function?	Yes	No
18.	…your family or friends told you that it was time to get over it?	Yes	No

Did you ever have a period of time when you…

19.	…had a great need to reminisce about the person, place or thing you lost?	Yes	No
20.	…spent a lot of time with objects that reminded you of the person, place or thing you lost, such as pictures, scrap books, mementos, etc.?	Yes	No
21.	…felt compelled to visit places that reminded you of the person, place or thing you lost?	Yes	No
22.	…had recurrent upsetting images of the person, place or thing you lost?	Yes	No
23.	…were extremely sad thinking about how special the person, place or thing was?	Yes	No
24.	…avoided going to the cemetery, going to the place where the person died, or any other place related to the death?	Yes	No
25.	…could not remember the things you loved, admired or enjoyed about the person you lost?	Yes	No
26.	…thought you saw, heard or talked with the person(s) you lost?	Yes	No
27.	…kept thinking you could have prevented the separation or death?	Yes	No
28.	…blamed yourself for doing something, or not doing something, that you think might have helped the person(s) you lost?	Yes	No
29.	…felt that if you stopped grieving you would lose the person(s) forever?	Yes	No
30.	…felt that it would be wrong if your grief were less intense, as though you were betraying the person(s) you lost?	Yes	No

Now I'm going to ask you some questions about how you are now.
Are you the type of person or have others told you that you…

31.	…enjoy or find satisfaction in taking care of people?	Yes	No
32.	…feel the need to <u>always</u> have someone to take care of (or feel lost or aimless if there isn't someone to take care of)?	Yes	No
33.	…find it difficult to ask for help?	Yes	No
34.	…tend to think that people you are close to will always be there?	Yes	No
35.	…form very close attachments to people and things?	Yes	No
36.	…have the feeling that you can't live without the people close to you?	Yes	No
37.	…get very upset when you lose things that you are attached to?	Yes	No

DOMAIN III. POTENTIALLY TRAUMATIC EVENTS

Now I'd like to ask you about some upsetting events that may have happened to you.
Note to interviewer: The point in asking these questions is simply to identify traumatic events, not to characterize them fully. [c indicates criterion symptoms].

Did any of the following things ever happen to you?

38.	…repeated failure in school or at work?	Yes	No
39.	…repeated severe arguments in your family?	Yes	No
40.	…being repeatedly teased or harassed?	Yes	No
41.	…being beaten up or physically threatened?	Yes	No
42.	…unwanted sexual advances?	Yes	No
43.	…physical or sexual abuse? [c]	Yes	No
44.	…rape? [c]	Yes	No
45.	…being the object of a lawsuit or disciplinary action?	Yes	No
46.	…being arrested or indicted for a crime?	Yes	No
47.	…an event that seriously threatened your well-being, employment, professional status, social standing or financial security?	Yes	No
48.	…a serious medical illness, surgery, or other distressing medical procedure? [c]	Yes	No
49.	…a serious accident or injury (for example, an automobile accident, or plane crash)? [c]	Yes	No
50.	…a disaster (for example, a hurricane, flood, fire, tornado, earthquake,	Yes	No

	or explosion)? [c]		
51.	…being threatened by criminals or terrorists? [c]	Yes	No
52.	…being a victim of a crime (for example, being robbed, assaulted, or mugged)? [c]	Yes	No
53.	…being in a war zone? [c]	Yes	No
54.	…being imprisoned, kidnapped, tortured, or held hostage? [c]	Yes	No

55.	Are there any other upsetting events that happened to you that I haven't asked you about? What were they? *Record here:*	Yes	No
56.	Did you ever witness any upsetting events, like the ones we've been talking about, that happened to someone else? [c]	Yes	No
57.	Did you ever hear about any upsetting events like these happening to someone else, so that you felt very affected by them?	Yes	No
58.	Are there periods of time in your life after the age of 5 about which you can remember absolutely nothing?	Yes	No

DOMAIN IV. REACTION TO LOSSES OR UPSETTING EVENTS

Note to interviewer: Before proceeding, make a note of the losses and events endorsed by the subject so you can refer to these during the rest of the interview. If the subject has not endorsed any losses or events up to this point, skip to Domain IX (Personal Characteristics).

Did this event or loss make you feel extremely…

59.	…afraid?	Yes	No
60.	…sad?	Yes	No
61.	…guilty or ashamed?	Yes	No
62.	…bitter or angry?	Yes	No
63.	…hopeless or helpless?	Yes	No
64.	…horrified or disgusted?	Yes	No
65.	…physically or emotionally numb or paralyzed?	Yes	No

At the time of the loss or event, did you have any of the following…

66.	…pounding heart, sweating, trembling, or shaking?	Yes	No
67.	…sensations of shortness of breath or choking?	Yes	No
68.	…chest discomfort or pain?	Yes	No
69.	…nausea or abdominal distress?	Yes	No
70.	…feeling dizzy, unsteady, light-headed, or faint?	Yes	No

At the time of the loss or event, did you feel…

71.	...like the event wasn't real, or as if you were in a dream or like you were a spectator?	Yes	No
72.	...you were doing things automatically, without thinking about them?	Yes	No
73.	...your sense of time changed, for example, things seemed to be happening in slow motion?	Yes	No
74.	...confused or uncertain about where you were or what time it was?	Yes	No
75.	...that colors, sounds and smells were unusually vivid or unbearable?	Yes	No
76.	...exceptionally alert or clear-headed?	Yes	No

DOMAIN V. RE-EXPERIENCING

Since the loss or event, have you ever…

77.	…had recurrent bad dreams or nightmares about the loss or event, or awakened terrified?	Yes	No
78.	…suddenly gotten bad feelings when you were around certain places, odours, sounds or people?	Yes	No
79.	…felt or acted as if the events were happening again?	Yes	No
80.	…had distressing thoughts, feelings, or images related to the loss or event?	Yes	No
81.	…become more distressed at the time of year when the loss or event occurred?	Yes	No

82.	Did you notice that other people avoided talking about the loss or event because you got so upset?	Yes	No

When <u>thinking</u> about the loss or event, did you ever…

83.	...feel upset or have waves of emotion or a sinking feeling in the pit of your stomach?	Yes	No
84.	...have other physical sensations, such as pain, palpitations, sweating, headache, etc.?	Yes	No
85.	…feel guilt or shame or blame yourself for what happened?	Yes	No

DOMAIN VI. AVOIDANCE & NUMBING

Did you ever <u>avoid</u>…

86.	...thinking or talking about the loss or event?	Yes	No
87.	...specific places, people, or social situations that reminded you of the loss or event?	Yes	No
88.	…reading the newspaper or watching certain TV programs or movies because they reminded you of the loss or event?	Yes	No
89.	…activities or things that evoked feelings of loneliness, crying or other distressing emotions related to the loss or event?	Yes	No

Since the loss or event, did you ever…

90.	…find that you were unable to remember things connected to the loss or event?	Yes	No
91.	…find that certain activities or things became pointless, meaningless or insignificant?	Yes	No
92.	…feel that you no longer had emotions you used to have, or that your feelings were dulled?	Yes	No
93.	...feel cut-off or detached, or like you were different from other people?	Yes	No
94.	…have difficulty trusting people, either strangers, people in your family, or your friends?	Yes	No
95.	…feel that you wouldn't live a long or satisfying life?	Yes	No
96.	…feel as if your life was changed forever and things would never be the same?	Yes	No
97.	…feel as if your personality changed?	Yes	No

DOMAIN VII. MALADAPTIVE COPING

Since the loss or event, did you ever…

98.	…stop taking care of yourself, for example, not getting enough rest or not eating right?	Yes	No
99.	…stop taking prescribed medications or fail to follow-up with medical recommendations, such as appointments, diagnostic tests, or a diet?	Yes	No
100.	… use alcohol or drugs or over-the-counter medications to calm yourself or to relieve emotional or physical pain?	Yes	No
101.	...engage in risk-taking behaviours, such as driving fast, promiscuous sex, hanging out in dangerous neighbourhoods?	Yes	No
102.	…wish you hadn't survived?	Yes	No
103.	…think about ending your life?	Yes	No
104.	...intentionally scratch, cut, burn or hurt yourself?	Yes	No
105.	…attempt suicide?	Yes	No

DOMAIN VIII. AROUSAL

Since the loss or event, did you ever…

106.	…have trouble concentrating or paying attention, for example, following the story line of a TV program or book or remembering what you had read?	Yes	No
107.	…feel like you just couldn't relax or let your guard down?	Yes	No
108.	…startle easily at the sound of sudden noises, or when someone touched you, spoke to you, or approached you unexpectedly?	Yes	No
109.	…feel more irritable, have outbursts of anger or rage, or lose your temper over minor things?	Yes	No
110.	…have more difficulty falling asleep or staying asleep than before or need a light on to go to sleep?	Yes	No

DOMAIN IX. Personal Characteristics/Risk Factors

Now I'm going to ask you some questions about how you are now.
Are you the type of person or have others told you that you…

111.	…are extremely sensitive to stress or loss?	Yes	No
112.	…are provocative?	Yes	No
113.	…like being the centre of attention?	Yes	No
114.	…often follow your instinct without really thinking about what you are doing?	Yes	No
115.	…usually find exciting what others would find frightening?	Yes	No
116.	…often engage in reckless or dangerous activities?	Yes	No