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Biological and psychological predictors of posttraumatic stress disorder onset and chronicity. A one-year prospective study

C. Gandubert [a, b, 1], J. Scali [a, b, 1, 2], M-L. Ancelin [a, b, 1, 2], I. Carrière [a, b], A-M. Dupuy [a, c], G. Bagnolini [a, b], K. Ritchie [a, b, d], M. Sebanne [b, e], L. Martrille [b, f, 3], E. Baccino [b, f], A. Hermès [b, g], J. Attal [a, b, g, 1], I. Chaudieu [a, b, *, 1]

[a] Inserm, U1061, Montpellier, F-34093, France
[b] Université Montpellier, Montpellier, F-34000, France
[c] CHU Montpellier, Department of Biochemistry A, F-34000, France
[d] Neuroepidemiology, Imperial College, London, United Kingdom
[e] CHU Montpellier, Department of Emergency, F-34000, France
[f] CHU Montpellier, Department of Forensic Medicine, F-34000, France
[g] CHU Montpellier, Department of Adult Psychiatry, F-34000, France

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ABSTRACT

Background: Few studies have prospectively examined risk factors for posttraumatic stress disorder (PTSD) in the aftermath of a traumatic exposure. The aim of this study is to identify the concurrent influence of psychological and biological diatheses on PTSD onset and maintenance, taking into account socio-demographic factors and psychiatric antecedents.

Methods: A total of 123 civilians (61.8% of women) recruited in emergency units, were assessed using validated instruments during the first week and then at 1, 4, and 12 months post-trauma. Baseline assessment included evaluation of the psychological diathesis (i.e. psychiatric history and peritraumatic distress and dissociation), and the biological diathesis [i.e. cortisol, norepinephrine, epinephrine, c-reactive protein, total cholesterol, HDL cholesterol, glycosylated haemoglobin, waist-to-hip ratio (WHR), body mass index, diastolic and systolic blood pressure (SBP), and heart rate].

Results: Multivariate logistic regression analyses demonstrated both psychological and biological diatheses to be independent risk factors for PTSD. Peritraumatic distress and dissociation predicted onset (1-month) and mid-term PTSD (4-months), respectively. PTSD risk was associated positively with SBP and negatively with WHR, throughout the follow-up. In addition, a higher level of 12 h-overnight urinary norepinephrine independently predicted mid-term PTSD (4-months).

Conclusions: This prospective study shows that peritraumatic psychological and biological markers are independent predictors of PTSD onset with specificities according to the stage of PTSD development; the psychological diathesis, i.e. peritraumatic distress and dissociation, being a better predictor of short-term dysfunction whereas biological diathesis was also predictive of development and maintenance of PTSD.

1. Introduction

Posttraumatic stress disorder (PTSD) occurs in people who have experienced, witnessed, or been confronted with an event involving actual or threatened danger. This event is followed by specific symptoms which have been recently reclassified in four diagnostic clusters in the DSM-5: re-experiencing, avoidance, negative cognitions and mood, and arousal symptoms (American Psychiatric Association, 2013). The majority of people exposed to trauma however do not develop PTSD, most victims maintaining, or rapidly returning to a normal functioning. The stressor initiates traumatic memories, and the onset of PTSD symptoms actually

* Corresponding author. Inserm U1061, Hopital La Colombiere, pav 42, 39, Avenue Charles Flahault, BP 34493, 34093 Montpellier Cedex 5, France.
E-mail addresses: catherine.gandubert@inserm.fr (C. Gandubert), jacqueline.scali@inserm.fr (J. Scali), marie-laure.ancelin@inserm.fr (M.-L. Ancelin), isabelle.carriere@inserm.fr (I. Carrière), am-dupuy@chu-montpellier.fr (A.-M. Dupuy), Guillaume.Bagnolini@etud.univ-montp2.fr (G. Bagnolini), karen.ritchie@inserm.fr (K. Ritchie), m-sebbane@chu-montpellier.fr (M. Sebanne), l-martrille@chu-nancy.fr (L. Martrille), e-baccino@chu-montpellier.fr (E. Baccino), a-hermes@chu-montpellier.fr (A. Hermès), j-attal@chu-montpellier.fr (J. Attal), isabelle.chaudieu@inserm.fr (I. Chaudieu).
[1] "ABC des psychotraumas" network, http://www.abcpsychotraumas.fr.
[2] These two authors have equally contributed to the article.
[3] Present address: Brabois Hospital, Vandoeuvre-les-Nancy, Department of Forensic Medicine, F-54511, France.

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depends on the ability of the individual to modify the associated hyperarousal and neurobiological cascade (McFarlane, 2000). This transition phase is likely to be the period when risk and protective factors are of greatest significance (McFarlane, 2000) and consequently an important window for intervention strategies, thus stressing the importance of developing risk models at this stage.

PTSD is a heterogeneous disorder with variable expressions of clinical distress immediately after exposure to a traumatic event and thus variable clinical presentations. Two principal clinical subtypes of PTSD have been described, primarily characterized either by the expression of hyperarousal symptoms or by symptoms of dissociation, numbness and physiological unresponsiveness (Lanius et al., 2010a; Weston, 2014). These two sets of symptoms are associated with different aspects of emotion dysregulation and distinct patterns of physiological and brain activation upon exposure to reminders of traumatic events (Lanius et al., 2010b). The etiological factors of PTSD thus encompass both psychological and biological aspects of the individual.

Of the theoretical diathesis-stress models proposed to identify vulnerability factors or predictors of PTSD development, the most recent models proposes that pre-trauma individual risk factors (diatheses) contribute to a constitutional vulnerability to a situational stressor (trauma) (Bomyea et al., 2012; Elwood et al., 2009; McKeever and Hiff, 2003). This stressor must be sufficiently severe to activate the diathesis and promote the development of PTSD. It is hypothesized that the less favorable the individual's diathesis, the less severe will be the trauma susceptible to initiate PTSD. According to Elwood et al. (2009) a comprehensive diathesis-stress model of PTSD should take into account not only pre-, but also peri- and post-trauma factors, as well as different types of vulnerability (e.g. biological, psychological and cognitive) (Elwood et al., 2009).

Predictors of psychological vulnerability were classified based on the weighted effect sizes and temporal proximity with the traumatic event. Peritraumatic distress (high level of emotion) and peritraumatic dissociation (dissociative experiences) during or in the immediate aftermath of the traumatic event are the most proximal to the traumatic event. They were recognized as the most robust predictors of PTSD symptoms (see for meta-analyses (Brewin et al., 2000; Ozer et al., 2003)), more than other pre-trauma factors (e.g. prior history of trauma, education, sex and age) and a lynchpin in the development of PTSD symptoms (Bremner et al., 1992; Marmar et al., 2006).

Regarding biological vulnerability, increased sympathetic nervous system (SNS) and decreased hypothalamic-pituitary-adrenal (HPA) functioning, within one month after trauma, have been reported to contribute to PTSD onset and maintenance through the formation of over-consolidated memories (Pitman, 1989). However none of these factors has individually demonstrated the ability to be a marker of PTSD development (Morris and Rao, 2013; Ostrowski and Delahanty, 2014; Pitman et al., 2012). Another approach considered the cost to the individual of adapting to cumulative stress across a range of physiological systems (McEwen and Stellar, 1993). This cost or allostatic load (AL) refers to the cumulative physiological wear and tear that results from repeated efforts of the organism to adapt to stressors over time (McEwen and Stellar, 1993). AL is evaluated by assessing biomarkers of multiple systems including primary mediators of stress systems (e.g. cortisol, epinephrine and norepinephrine) as well as biomarkers known to exhibit change in response to interaction with a primary mediator of stress (e.g. C-reactive protein (CRP)) or to represent secondary outcomes of these mediating processes, namely systolic and diastolic blood pressure (SBP and DBP, respectively), glycosylated haemoglobin (HbA1c) and visceral fat depositing. Although high AL was hypothesized to be a major contributor to the development of PTSD (Charney, 2004; McEwen, 2002), this has not been demonstrated. The validity of this concept is also questioned notably in the field of stress related disorders in which insufficient glucocorticoid signaling may play a significant role in the etiology (Fries et al., 2005; Heim et al., 2000; Raison and Miller, 2003).

Actually, it is becoming evident that simple biological models could not account for the complex etiology of PTSD which should consider together psychological and biological aspects and their relative weight in the onset and maintenance of PTSD overtime. However, to our knowledge, no study on PTSD etiology has studied both aspects concurrently. Our prospective study aimed to examine the effect of both psychological (psychiatric history and peritraumatic reaction) and a large range of potential markers of biological diatheses on PTSD onset (after 1-month) and maintenance (4- and 12-months), in people who have recently experienced a traumatic event of the civilian life, while taking into account sociodemographic pre-trauma factors.

2. Methods

2.1. Study population

People having experienced an event satisfying criterion A1 and A2 for trauma exposure (DSM-IV) (American Psychiatric Association, 1994) within the previous 7 days, were consecutively recruited in the emergency and forensic medicine departments of the Montpellier University Hospital (France) between 2006 and 2011 (the Phoenix study). The exclusion criteria were: 1) having experienced significant head injury defined as an external injury to the brain leading to a loss of consciousness for 10 min or more, 2) previously suffering from a psychotic illness or mental retardation, 3) being homeless, 4) use of corticosteroid medications which could interfere with cortisol measurement. A fifth exclusion criterion concerned domestic violence which is mostly woman specific, frequently chronic and associated with high prevalence of current PTSD which may introduce a methodological bias regarding causality. The study protocol was approved by the South-Mediterranean Ethics Committee and written informed consent was obtained from each participant.

Participants were administered standardized questionnaires by a single Master level research nurse at baseline and after 1, 4 and 12 month of follow-up. The first interview was within 2–7 days after trauma exposure [median (IQR) = 5 (4–6) days]. Venous blood samples were collected during the interview and 12 h-overnight urine during the subsequent night. Of the 123 individuals recruited, 89 completed the 1-month follow-up [median (IQR) = 39 (30–49) days], 85 the 4-month follow-up [median (IQR) = 136 (123–152) days], and 57 the 12-month follow-up [median (IQR) = 387 (361–413) days]. The subjects lost to follow-up more frequently reported lifetime psychiatric disorder ($p < 0.05$). Those lost specifically to the last follow-up after 12 months were also younger ($p = 0.04$) and with a higher peri-traumatic distress score ($p = 0.01$). No other significant differences were found between the participants included in analyses and those lost to follow-up.

2.2. Interview

2.2.1. Inclusion examination

The standardized interview included questionnaires on sociodemographic characteristics as well as clinical and biological evaluation and information relating to prescription drug and psychotherapy use over the last two years. Peritraumatic reaction and psychiatric history were also investigated as part of this baseline psychiatric evaluation. Peritraumatic distress was assessed using the validated French version of the Peritraumatic Distress Inventory

(PDI) (Brunet et al., 2001; Jehel et al., 2005) which evaluates emotional response during and immediately after traumatic exposure, using a 13 item on a 5-point Likert scale. Item scores were summed to calculate the total score.

The validated French version of the Peritraumatic Dissociative Experience Questionnaire (PDEQ) (Birmes et al., 2005), developed by Marmar et al. (1997), evaluated dissociation at the time of the trauma and immediately after. This self-reported questionnaire includes perceptions of depersonalization, derealization, corporal change, and altered notion of time. The subjects rate the 10 items on a 5-point Likert scale and item scores were summed to calculate the total score.

Lifetime and current DSM-IV diagnoses of Axis I disorders were evaluated using a standardized psychiatric interview, the Mini International Neuropsychiatric Interview (MINI, French version 5.00) previously validated within the general population setting (Lecrubier et al., 1997).

2.2.2. Follow-up visits

The Watson's PTSD Interview (PTSD-I) (Watson et al., 1991) was used to diagnose current (during the month preceding the examination) PTSD using the validated French self-report version at each follow-up (Brunet, 1995; Jehel et al., 1999). The traumatic event was explored through 17 items corresponding to PTSD specific symptoms. Answers to each question were given on a 7-point Likert scale ranging from "1-(never)" to "7-(extremely)". PTSD-I can provide a continuous measure of the severity of the disorder (a score of "4-(commonly)") is considered to be sufficient to meet the relevant DSM symptom criterion.

2.3. Biological and clinical markers

The current study is based on 12 biomarkers identified to represent different contributing factors to allostatic load. **Neuroendocrine 12-h overnight urinary excretion of markers**, i.e. cortisol, norepinephrine and epinephrine were normalized using 12-h urinary excretion of creatinine to adjust for variability in body size and renal function. Cortisol concentration was determined by radioimmunoassay kits (DSL 2100, Diagnostic Systems Laboratories, Inc, Webster, Texas, USA), and both norepinephrine and epinephrine were assessed by high pressure liquid chromatography on preliminary acidified urine. **Blood metabolic parameters** included HbA1c, assessed by high pressure liquid chromatography, and high density lipoprotein-cholesterol (HDL-cholesterol) and total cholesterol assessed by routine enzymatic methods. **Morphologic measures**: Hip and waist circumferences and height were measured by a tape-measure and weight using electronic scales. Waist circumference was measured at the narrowest point between the ribs and the iliac crest, and hip circumference was measured at the maximal site around the buttocks. Body mass index (BMI) and waist-to-hip ratio (WHR) were calculated. **Cardiovascular factors** included resting heart rate as well as resting SBP and DBP, calculated as the average of two seated recordings taken by a nurse at least 30 min after the beginning of the interview. **CRP was used as a marker of systemic inflammation**. High-sensitivity CRP was measured by means of particle enhanced immunonephelometry assay. Participants with CRP levels >10 mg/L were excluded from the analyses ($n = 6$), as this high level of CRP was considered to be owing to acute-phase response. All assays were conducted by the department of Biochemistry, Lapeyronie Hospital, Montpellier, France.

2.4. Statistical analysis

Classic statistically methods in epidemiology were used. Chi-square tests compared the characteristics of participants included in the analyses with those excluded. Associations between baseline participant characteristics (measured during the first week after the trauma) and acute (1-month), chronic mid-term (4-months) and long-term PTSD (12-months) were first assessed using logistic regression models adjusted for sex and age. In a second step, multivariate models included age, sex, and the baseline covariates associated with PTSD in previous logistic regression models with a p-value < 0.20. The linearity of the covariates was controlled using the likelihood ratio test. Multivariate models were reduced using a backward selection procedure. The models providing the best goodness of fit to the current dataset, as assessed using the Akaike Information Criterion (AIC), were selected. The model ability to properly classify the subjects was evaluated using an index of predictive discrimination, the concordance (c), that is identical to the area under the curve. As in the case of an exploratory study, we have not applied correction for multiple comparisons following the recommendations of several authors (Bender and Lange, 2001; Rothman, 1990; Savitz and Olshan, 1998), corrections possibly increasing the risk of type II errors. The analyses were undertaken with the subjects having no missing data on any covariates included in the most complete model. Analyses were performed using SAS statistical software (version 9.4; SAS Inc, Cary, North Carolina, USA).

3. Results

3.1. Baseline characteristics

The median age (Q25-Q75) was 36.5 years (26.8–47.1) with 61.8% of women (Table 1). Around 69% of subjects had experienced an interpersonal trauma (physical and sexual assault) and 71.5% reported at least one lifetime psychiatric disorder which was current for 57.7%. Table 2 describes baseline biological characteristics of the sample during the first week following the traumatic event.

3.2. Risk factors for acute and chronic PTSD over 12-month follow-up

Acute PTSD was diagnosed in 28.1% of the participants, 1-month after the traumatic event, and chronic PTSD after 4- and 12-months in 21.2% and 17.5% of the participants, respectively.

Regarding psychological characteristics in logistic regression models adjusted for age and sex, both peritraumatic distress and dissociation scores were associated with a 10% increased odds of PTSD (for 1 unit score increase), at each wave of the follow-up (Table 3). No significant association was found with lifetime psychiatric history ($p > 0.51$).

Examining biological and clinical markers individually, having higher SBP, DBP, HbA1c and BMI were significantly associated with the odds of developing acute PTSD after 1 month (Table 3). Mid-term chronic PTSD at 4 months was associated with higher SBP and norepinephrine, and lower cortisol. A higher HbA1c also predicted chronic PTSD at 4 and 12 months whereas a higher WHR was associated with a decreased odd of developing long-term chronic PTSD at 12 months. No significant associations were found with heart rate, epinephrine, CRP, HDL- and total cholesterol.

3.3. Multivariate models

Multivariate analyses included age, sex and psychological variables (PDI and PDEQ) as well as cortisol, norepinephrine, HbA1c, SBP, DBP, WHR and BMI which were found associated with PTSD in minimally adjusted models. SBP was positively, and WHR negatively associated with PTSD, consistently throughout the follow-up (Table 4). It should be noted that in our study, all the variables are

Table 1
Baseline socio-demographic, trauma, and psychological characteristics of the cohort (n = 123).

Characteristics	
Median age (Q25–Q75; years)	36.47 (26.84–47.05)
Female gender (%)	61.79
Education level >12 years (%)	47.15
Living alone (%)	21.95
Traumatic event type (%)	
Physical assault	58.54
Sexual assault	10.57
Serious accident	13.01
Other	17.89
Peritraumatic reaction scores:	
Median PDEQ (Q25-Q75)	24 (17–32)
Mean PDI (SD)	24.04 (10.20)
Psychiatric history (%):	
Lifetime psychiatric history	71.54
Lifetime PTSD	8.13
Psychotropic use during the 2 last years	25.20

Abbreviations: PDEQ, Peritraumatic Dissociative Experience Questionnaire; PDI, Peritraumatic Distress Inventory; PTSD, Posttraumatic Stress Disorder.

Table 2
Physiological characteristics of the cohort at baseline (n = 123).

Biomarker (Unit)	Median (Q25–Q75)
Urine:	
Cortisol (μg/g creatinine)	38.93 (28.01–55.45)
Epinephrine (μg/g creatinine)	1.43 (0.70–3.37)
Norepinephrine (μg/g creatinine)	22.18 (16.31–32.79)
Blood:	
Glycosylated haemoglobin (%)	5.30 (4.90–5.60)
C-reactive protein (mg/l)	1.30 (0.50–3.10)
Total Cholesterol (g/l)	1.90 (1.68–2.22)
HDL cholesterol (g/l)	0.61 (0.49–0.75)
Cardiovascular measures:	
Systolic blood pressure (mm Hg)	120 (110–130)
Diastolic blood pressure (mm Hg)	70 (70–80)
Heart rate (bpm)	76 (67–80)
Morphometric measures:	
WHR	0.92 (0.87–0.98)
BMI (kg/m^2)	22.96 (20.31–25.70)

Abbreviations: BMI, body mass index; WHR, waist-to-hip ratio.

continuous variables and unless specified otherwise the OR corresponded to 1 unit increase. For example in Table 4: SBP and PTSD diagnosis at 12-months post-trauma; OR = 1.11 [1.02–1.21], means that the risk increased by 11% for an increase of SBP of only 1 mmHg. A significant increased odd of chronic PTSD was also observed with higher norepinephrine after 4 months. These associations were independent of the peritraumatic reaction which was also significantly associated with PTSD; a higher baseline distress score being predictive of acute PTSD after 1 month whereas a higher dissociation score was predictive of mid-term chronic PTSD after 4 months. The model concordance coefficient which reflects the ability to properly classify the subjects, was very good at each follow-up including after 12 months (c = 0.96).

4. Discussion

This prospective study showed that peritraumatic psychological and biological markers are independent predictors of PTSD onset with specificities according to the stage of PTSD development; psychological markers were predictive of short- or mid-term PTSD whereas biological markers were also predictive of long-term PTSD.

Among psychological markers, peritraumatic distress was predictive of acute PTSD, one month after the traumatic event, whereas peritraumatic dissociation predicted mid-term PTSD at 4 months. Several studies have reported a significant association between peritraumatic distress or dissociation and PTSD symptom severity or current diagnosis but very few studies have investigated the dynamics of PTSD incidence over 1 year by examining the acute, mid-term, and long-term chronic stages (Lensvelt-Mulders et al., 2008; Ozer et al., 2003; Thomas et al., 2012; van der Hart et al., 2008; van der Velden and Wittmann, 2008). Our findings on peritraumatic factors are in agreement with prospective studies showing that PDI scores could predict acute PTSD symptoms 4–6 weeks post-trauma (Berna et al., 2012; Brunet et al., 2013; Bui et al., 2010a) as well as with a recent meta-analysis suggesting a systematic decrease over time, in the correlation between PDI scores and PTSD symptoms (Thomas et al., 2012). However, our data contrast with one recent longitudinal study in 39 elderly people suggesting that distress but not dissociation scores were predictive of acute and chronic PTSD (Brunet et al., 2013). This study was however limited by low statistical power and differs in cohort characteristics, e.g. age, sex, as well as type and/or severity of the traumatic events which may result in a lower dissociation score in that study (Olff et al., 2007; Wittmann et al., 2006).

Overall, our study showed that peritraumatic distress and dissociation are risk factors for PTSD development but not long-term maintenance. These two markers could predict PTSD symptoms before the time of “crystallization” or chronicity of symptoms (Bui et al., 2010b), in contrast with other factors including persistent dissociation (Briere et al., 2005; Halligan et al., 2003; Murray et al., 2002; O'Donnell et al., 2007), initial PTSD symptom severity (Marshall and Schell, 2002), and social support (Ozer et al., 2003) which have been reported to be better predictors of long-term adjustment (Ozer et al., 2003).

Regarding biological diathesis, our multivariate analyses identified two types of independent biomarkers, those consistently associated with PTSD onset and maintenance throughout the follow-up, e.g. SBP and WHR, and one transient marker, e.g. norepinephrine which was associated with 4-months PTSD diagnosis. These three biomarkers are individual components of AL but they differently predicted specific phases of PTSD development.

A longitudinal study in 125 civilian victims failed to show a significant association between 4-h diurnal urinary cortisol and norepinephrine levels collected immediately after trauma and PTSD at 5 months (Shalev et al., 2008; Videlock et al., 2008). In the other hand attenuated cortisol response during the early post-traumatic period has been reported in minimally adjusted studies, though not consistently (Bonne et al., 2003) to contribute to mid-term SNS disruption in exposed individuals (Delahanty and Nugent, 2006; Ehring et al., 2008; McFarlane et al., 2011; Mouthaan et al., 2014; Yehuda, 2002). We also observed a negative association between cortisol and PTSD after 4 months which was significant in minimally adjusted model but which failed to be significant in multivariate model. Besides, the positive association of norepinephrine with mid-term PTSD at 4 months remained significant independently of the other covariates. The inconsistencies between the studies could reflect differences in methodology (McFarlane et al., 2011); in most of the previous studies biomarkers were collected in emergency room whereas in our study they were collected 5 days post-trauma (IQR = 4–6). One explanation could also be that there is a delayed time window for the measurement of cortisol and catecholamine responses where the effect of cortisol may be early and transient within a narrow window immediately following the trauma (McFarlane et al., 2011).

In our study SBP, but not heart rate was an independent predictor of PTSD consistently throughout the follow-up. In theoretical fear-conditioning models of PTSD, cardiovascular arousal in response to the trauma has been linked to over-consolidation of traumatic memories and subsequent PTSD (Charney et al., 1993). Reports of an association between elevated heart rate or blood

Table 3
Logistic regression analyses[a] of biological and psychological markers associated with PTSD diagnosis during follow-up.

Variable (Unit)	1 month (n = 89)		4 months (n = 85)		12 months (n = 57)	
	OR [95% CI]	p-value	OR [95% CI]	p-value	OR [95% CI]	p-value
Education >12 years	0.64 [0.24–1.71]	0.378	0.48 [0.15–1.51]	0.210	0.48 [0.09–2.47]	0.382
Lifetime psychiatric history	0.93 [0.33–2.64]	0.895	1.50 [0.45–5.02]	0.514	0.68 [0.14–3.25]	0.626
Psychological reaction						
Peritraumatic distress (score)	1.11 [1.04–1.18]	**0.001**	1.09 [1.02–1.16]	**0.014**	1.09 [0.99–1.20]	0.086
Peritraumatic dissociation (score)	1.08 [1.02–1.13]	**0.004**	1.13 [1.06–1.21]	**<0.001**	1.09 [1.00–1.20]	0.055
12-h Urine						
Cortisol (μg/g creatinine)	0.98 [0.96–1.01]	0.129	0.95 [0.91–0.99]	**0.006**	0.97 [0.93–1.01]	0.125
Norepinephrine (μg/g creatinine)	1.02 [0.99–1.06]	0.261	1.05 [1.01–1.09]	**0.038**	1.03 [0.96–1.09]	0.437
Epinephrine (μg/g creatinine)	1.03 [0.87–1.21]	0.751	1.05 [0.83–1.33]	0.708	0.95 [0.61–1.48]	0.823
Blood						
Glycosylated haemoglobin (%)	1.14 [1.01–1.28]#	**0.028**	1.18 [1.04–1.34]#	**0.010**	1.19 [1.00–1.42]#	0.053
C-reactive protein (mg/l)	1.00 [0.83–1.22]	0.963	0.98 [0.78–1.22]	0.827	1.23 [0.89–1.70]	0.220
Total Cholesterol.	0.44 [0.11–1.71]	0.236	1.44 [0.30–6.93]	0.649	1.09 [0.14–8.42]	0.936
HDL cholesterol (g/l)	0.91 [0.70–1.19]#	0.495	1.06 [0.78–1.43]#	0.728	0.78 [0.48–1.26]#	0.303
Cardiovascular measures						
Systolic BP (mm Hg)	1.05 [1.01–1.09]	**0.007**	1.07 [1.02–1.12]	**0.005**	1.05 [1.00–1.11]	0.070
Diastolic BP (mm Hg)	1.05 [1.01–1.10]	**0.025**	1.04 [1.00–1.09]	0.074	1.05 [0.98–1.12]	0.167
Heart rate (bpm)	1.01 [0.98–1.05]	0.507	1.00 [0.96–1.04]	0.986	1.00 [0.94–1.05]	0.868
Morphometric measures						
WHR	0.58 [0.25–1.33]#	0.199	0.61 [0.25–1.52]#	0.292	0.15 [0.03–0.70]#	**0.016**
BMI (kg/m^2)	1.13 [1.01–1.27]	**0.031**	1.08 [0.97–1.21]	0.172	1.15 [0.97–1.37]	0.110

All the variables are continuous variables and the OR corresponded to 1 unit increase except for # where OR corresponded to 0.1 unit increase.
Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; OR, odds ratio; WHR, waist-to-hip ratio.
Boldface type indicates significance at p-value ≤ 0.05.
[a] Adjusted for age and sex.

Table 4
Multiple logistic regression analyses of biological and psychological markers associated with PTSD onset during the follow-up.

	1 month post-trauma			4 months post-trauma			12 months post-trauma		
	OR [95% CI]	*p-value*	*c*	*OR [95% CI]*	*p-value*	*c*	*OR [95% CI]*	*p-value*	*c*
	n = 83 (24 cases)		*0.84*	n = 77 (17 cases)		*0.93*	n = 52 (9 cases)		*0.96*
Cortisol (μg/g creat.)	–	–		0.96 [0.91–1.01]	0.120		–	–	
NE (μg/g creat.)	–	–		1.07 [1.00–1.14]	**0.041**		–	–	
Systolic BP (mm Hg)	1.04 [1.01–1.07]	**0.016**		1.10 [1.00–1.20]	**0.047**		1.11 [1.02–1.21]	**0.019**	
Diastolic BP (mm Hg)	0.94 [0.87–1.02]	0.150		0.92 [0.83–1.03]	0.147		–	–	
WHR#	0.29 [0.12–0.69]	**0.005**		0.12 [0.03–0.52]	**0.005**		0.03 [0.003–0.34]	**0.004**	
BMI (kg/m^2)							1.29 [1.01–1.66]	**0.045**	
PDI score	1.09 [1.00–1.18]	**0.040**		–	–		–	–	
PDEQ score	1.06 [0.99–1.13]	0.104		1.21 [1.08–1.36]	**0.002**		–	–	

All the variables are continuous variables and the OR corresponded to 1 unit increase except for # where OR corresponded to 0.1 unit increase.
Abbreviations: BMI, Body Mass Index; BP, Blood Pressure; c, concordance value of the logistic model; creat., creatinine; NE, norepinephrine; PDEQ, Peritraumatic Dissociative Experience Questionnaire; PDI, Peritraumatic Distress Inventory; WHR, waist-to-hip ratio.
Boldface type indicates significance at p-value ≤ 0.05.

pressure following trauma and subsequent PTSD have been inconsistent (Bryant, 2006; Bryant et al., 2008; Yehuda et al., 1998). Our study differs from previous studies in several respects regarding trauma type (interpersonal traumas vs. motor vehicle accident in most previous studies), male/female ratio (approximately 1/2 vs. 2/1 in the others studies) and methodology (heart rate and BP assessed around 5 days post-trauma vs. within a few hours). Very few studies have examined cardiovascular parameters in the aftermath of an acute stress exposure in ecological settings. In a large population of patients with hypertension, September-11 attacks were associated with substantial and sustained increase in blood pressure for 2 months (Gerin et al., 2005). Cardiovascular reactions have also been reported among 185 military survival trainees after a test of mock captivity including residual elevations in SBP after 24 h of recovery especially in females (Taylor et al., 2014). Whether a higher SBP found in our study is a "trait" parameter, present prior to trauma or the result of prolonged physiological arousal and failure of vulnerable subjects to restore biological homeostasis remained to be determined. Individual differences in recovery at more extended periods after a stressor may actually have greater consequences than those observed shortly after the stressor and a clear relationship may only be evident after the non-pathological acute reaction has subsided.

In our study, a higher WHR was associated with a lower risk of PTSD development and maintenance throughout all the follow-up stages. Peters et al. recently showed that exposure to chronic stress can result in two different phenotypes depending on genetic background (Peters et al., 2013). The A-phenotype accumulates visceral fat (high WHR) and does not habituate to chronic stress, whereas the B-phenotype, once exposed to a stressful environment, habituates but needs to increase food intake in order to maintain brain energy metabolism, subsequently accumulating peripheral fat (high BMI). As habituation to stress reduces the damaging effects of chronic stress, the risk of developing cardiovascular, metabolic and certain psychiatric diseases (e.g. typical depression) in stressful environments associated with the B-phenotype, would be globally lower (Peters et al., 2013). On the other hand, the absence of habituation to stress in the A-phenotype has been linked to higher cortisol secretion during exposure to uncontrollable psychological stressors, notably in lean women

(Epel et al., 2000). This suggests that a higher secretion of cortisol during and/or immediately after the traumatic exposure, may contribute to control of fear reactivity and thus lower PTSD risk as also observed using exogenous corticosteroids (Amos et al., 2014; Schelling et al., 2004; Suris et al., 2010). Establishing the significance of WHR in PTSD onset will require further investigation, notably in relation with the time-dependent effects of cortisol on the contextualization of emotional memories (Cornelisse et al., 2014).

Our study has several strengths, notably a prospective design with three follow-up waves over 12 months, and using standardized diagnostic procedures based on a structured clinical interview. This study has also for the first time taken into account simultaneously the biological status and the psychological vulnerability of the traumatized subjects. Participants experienced multiple traumatic events of civilian life in contrast with most previous studies mainly focusing on motor vehicle accident exposure in which the individual has not usually been specifically targeted (not interpersonal traumatic event).

The study however suffers from some limitations. Despite repeated attempts to convene all participants at each wave, 27.6% of the subjects initially included were missing at any subsequent follow-up. Of the 89 subjects with at least one follow-up, 85 (95.5%) were still in the study after 4 months. The main drop-out occurred at the last interview, with 64% of participants being followed-up after 1 year. This attrition rate was similar to that of most other studies in traumatized civilians. The subjects lost after 1 year only differed by higher rate of lifetime psychiatric disorder at baseline and having a higher peritraumatic distress score which may led to an underestimation of the strength of the associations. Despite this limitation, the concordance coefficients were very good even after 1 year follow-up. We cannot exclude the possibility that other factors not assessed in our study may also contribute to the development of PTSD such as childhood events and acute stress disorder, although peritraumatic dissociation, a distinctive feature of acute stress disorder diagnosis, was considered. Finally, since multiple analyses have been performed, we cannot exclude that some associations were due to chance. However our results are also supported by a strong physiopathological rationale.

5. Conclusion

This study suggests that the neurobiological mechanisms underlying the development of PTSD are heterogeneous differing in particular in relation to those initiating as opposed to those promoting the maintenance of the psychopathology. Our findings support the independent influence of both the psychological and the biological diatheses in PTSD installation; the psychological diathesis, i.e. peritraumatic distress and dissociation, being a better predictor of short-term dysfunction whereas biological diathesis appears rather to predict development and/or maintenance of PTSD. An important translational aspect of our study lies in the fact that most of the risk factors identified may be prevented by clinical intervention, thus suggesting potential intervention windows for prevention.

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