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ORIGINAL ARTICLE

Childhood traumata, Dexamethasone Suppression Test and psychiatric symptoms: a trans-diagnostic approach

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Background. Childhood traumatic events and functional abnormalities of the hypothalamus–pituitary–adrenal (HPA) axis have been widely reported in psychiatric patients, although neither is specific for any diagnosis. Among the limited number of studies that have evaluated these topics, none has adopted a trans-diagnostic approach. The aim of the present research is to explore the relationship between childhood stressors, HPA axis function and psychiatric symptoms, independent of the diagnosis.

Method. A total of 93 moderate to severely ill psychiatric out-patients of Florence and Pisa University Psychiatric Units and 33 healthy control subjects were recruited. The assessment consisted of salivary cortisol pre- and post-low dose (0.5 mg) Dexamethasone, early and recent life events, 121 psychiatric symptoms independent of diagnosis, SCID, BPRS.

Results. In total, 33.5% of patients were Dexamethasone Suppression Test (DST) non-suppressors, compared with 6.1% of controls ($p = 0.001$). Among patients, non-suppression was associated with particular symptoms (i.e. depressive and psychotic), but not to any specific diagnosis. Early stressful life events were significantly associated with higher salivary cortisol levels, with DST non-suppression and with approximately the same subset of symptoms. A recent stressful event seemed to be associated to the HPA response only in those subjects who were exposed to early traumata.

Conclusions. Our report suggests a relationship between life stress, HPA axis and psychopathology. A cluster of specific psychiatric symptoms seems to be stress related. Moreover, it seems that an abnormal HPA response is possibly triggered by an excessive pressure in vulnerable individuals.

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Key words: HPA axis, life event, psychopathology, transdiagnostic, vulnerability.

Introduction

An excess of stressful events during childhood has been reported in depressive disorders (Lloyd, 1980; Paykel, 1982; Faravelli *et al*. 1986; Heim *et al*. 2008*b*), anxiety disorders (Faravelli *et al*. 1985; Tweed *et al*. 1989; Bandelow *et al*. 2002), post-traumatic stress disorder (PTSD) (Copeland *et al*. 2007; Zlotnick *et al*. 2008), schizophrenia (Janssen *et al*. 2004; Read *et al*. 2005; Ucok & Bikmaz, 2007), eating disorders (de Groot & Rodin, 1999; Wonderlich *et al*. 2001; Thompson & Wonderlich, 2004), substance abuse (Simpson & Miller, 2002; Dube *et al*. 2003; Reed *et al*. 2007; Back *et al*. 2008) and personality disorders (Bierer *et al*. 2003; Chard, 2003; Goodman *et al*. 2004; Johnson *et al*. 2006). The effect of childhood traumata for psychopathology during adulthood is believed to be mediated by the hypothalamus–pituitary–adrenal (HPA) axis, that, once over-activated during the developmental processes, would remain permanently unstable, overdriven, vulnerable or dysfunctional (Nemeroff, 2004; Joëls *et al*. 2008; Tyrka *et al*. 2008), possibly due to transcriptional/epigenomic mechanisms (Meaney & Szyf, 2005; Weaver *et al*. 2006).

Functional abnormalities of the HPA axis have in fact been widely reported in psychiatric disorders, including depression (Carroll, 1977; Heim *et al*. 2008*a*), bipolar disorder (Daban *et al*. 2005), anxiety disorders (Risbrough & Stein, 2006; MacKenzie *et al*. 2007), eating disorders (Lo Sauro *et al*. 2008), schizophrenia (Walker *et al*. 2008), substance abuse (Gerra *et al*. 2008), dissociative symptoms (Bob *et al*. 2008), dementia (Magri *et al*. 2006), and PTSD (Atmaca *et al*. 2002; Yehuda *et al*. 2004*c*; Griffin *et al*. 2005; Delahanty

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& Nugent, 2006). In particular, an abnormal response to the Dexamethasone (Dex) Suppression Test (DST) has been repeatedly documented (Schreiber *et al*. 1996; Nestler *et al*. 2002; Simpson & Miller, 2002; Ceskovà *et al*. 2006; Back *et al*. 2008). Whereas non-suppression is the commonest abnormal response, hyper-suppression has been reported in PTSD patients and in patients with a history of child abuse when low dose Dex has been used (Yehuda *et al*. 1995*a*, *b*, 2002, 2004*a*, *b*; Goenjian *et al*. 1996; Newport *et al*. 2004; Rohleder *et al*. 2004).

Neither the abnormalities of the HPA axis, nor the excess of traumatic stressful events during childhood seem to be specific to any diagnostic group and a limited number of studies have evaluated both the early stress and the HPA axis in adult patients suffering from mental disorders (Bremner *et al*. 2007; Bradley *et al*. 2008; Gerra *et al*. 2008; Heim *et al*. 2008*a*). None has adopted a trans-diagnostic approach.

The present paper is aimed at evaluating the hypothesis that early events and DST non-suppression are related to a particular subset of symptoms occurring across several diagnostic entities rather than to specific diagnostic groups. Childhood stressors, DST and psychiatric symptoms have been evaluated in a group of moderately to severely ill psychiatric outpatients, selected independently of the diagnosis.

Method

The study was carried out at two University Psychiatric Units, one in Florence and the other in Pisa. Both provide intensive (i.e. on a daily basis) outpatient treatments, especially directed at severe mood, anxiety and eating disorders. These clinics were selected because of the need for having sufficiently severe cases non-hospitalized, since it is reported that staying in hospital may influence the cortisol response (Copolov *et al*. 1989).

Subjects who met the following criteria were included in the study: (1) aged between 18 and 65 years; (2) any Axis I diagnosis as assessed by the Structured Clinical Interview for DSM-IV – Patient Version 2.0 (SCID-P; First *et al*. 1995); (3) acute phase of the illness, i.e. the onset of the episode had to occur within a couple of months of the intake and the severity had to be sufficient to warrant intensive treatment; patients in whom the severity of illness was apparently declining were not included. The exclusion criteria were substance abuse or dependence, organic mental disorder, physical illnesses altering HPA axis function such as Cushing disease, obesity (body mass index >30 kg/m^2), thyroid dysfunctions, chronic infections, pregnancy or breast-feeding, epilepsy, concomitant treatment with oral contraceptives, L-dopa, β-blockers, metirapone, ketoconazole, lithium, anticonvulsants, including those used as mood stabilizers, as it is known that anticonvulsants may induce false positive DST results (Putignano *et al*. 1998), contraindications to Dex administration, such as congestive heart failure, K^+ depletion, hypertension, peptic ulcer, erosive oesophagitis, coagulation impairments, diabetes mellitus, ocular hypertension, glaucoma, severe osteoporosis, hypersensitivity to Dex.

A total of 93 consecutive patients were enrolled in the study, 49 from Florence University and 44 from Pisa University. Since the medical staff of the two institutions were overlapped, the two samples were combined. There were no age, gender and diagnoses differences between the two centres.

The patients were evaluated before the commencement of their treatment (within the first 2 days of intake) and were drug free whenever possible (in a minority of cases the already ongoing treatment was not stopped). After the enrolment in the study, saliva samples were taken at 08:00 hours and 20:00 hours on the first day and participants were given a 0.5 mg dose of Dex to take at home the same evening at 23:00 hours; a third saliva sample was taken the next morning at 08:00 hours. Saliva was collected into a device using a cotton swab that was chewed by the patients for 2 min and then inserted in a double-chamber plastic tube. The saliva samples were refrigerated at 4 °C (for a maximum of 10 h) and were eventually stored at -20 °C. Salivary cortisol levels were analysed by using a Roche (Switzerland) immunoassay (Elecsys), a competitive polyclonal antibody assay that uses a magnetic separation step, followed by electroluminescence (Chiu *et al*. 2003). All assays were conducted blind to diagnostic status or group and all the laboratory preliminary tests to evaluate recovery rate, sensitivity and reproducibility were amply satisfactory (intra-assay reliability 4.4%; inter-assay 9.5%).

Apart from the absolute values of saliva cortisol in the three samples, and their percent and absolute daily variations (cortisol at 08:00 hours minus cortisol at 20:00 hours), the ratio between cortisol levels after Dex administration and cortisol levels before Dex administration at the same hour (08:00 hours) was calculated and called Suppression Index (SI), (Newport *et al*. 2004).

In total, 33 healthy subjects, drawn from the hospital personnel, with no history of chronic physical diseases, allergies or current infections and not taking regular medication, were recruited as controls. They were matched with the patients for age (40.1 ± 14.0 and 43.6 ± 15.4, respectively) and gender (48.5% and 50.2% of females, respectively) and underwent the same assessment procedures as the patients. The study was

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approved by the Local Ethics Committee and informed written consent was obtained by all patients.

Clinical assessment

In order to have a comprehensive evaluation of psychiatric symptoms not influenced by a previous diagnostic selection, patients were given a series of rating scales combined in a single instrument. This derives from an earlier study, where a large number of patients were evaluated by means of several rating scales (Faravelli *et al*. 1996). The items derived from different scales that proved to be redundant and clearly explored the same aspect, with comparable definitions and with reciprocal correlations (r) greater than 0.85, were excluded. The definitions of items contained in the original instruments were left unchanged. When needed, quantification within a single item was modified to give each item the same weight. Each symptom is scored on a 5-point severity scale (0 = absent, 1 = dubious, 2 = mild, 3 = moderate and 4 = severe). A score of at least 2 was considered for a symptom to be present.

There were 121 symptoms, including almost all the symptoms in both the DSM-IV and ICD-10.

These items were inserted into one single instrument, the Florence Psychiatric Interview (Faravelli *et al*. 2001), which has been fully validated. The SCID-P and the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) were also administered.

The events occurring during the first 15 years of life were also studied. Loss events were evaluated by the method described by Faravelli *et al*. (1986); death of parents, prolonged separation from parents, divorce/*de facto* separation of parents, death of cohabiting relatives, severe illnesses of the child were taken into account. Childhood physical and sexual abuse was investigated using the questions provided by the Childhood Experience of Care and Abuse Questionnaire (Bifulco *et al*. 1994). All the interviews for early life events were made before the assessment of saliva cortisol.

The events occurred during the year prior to the onset of the index episode were also collected and evaluated according to the method described elsewhere (Faravelli *et al*. 2007) (semi-structured interview and independent assessment).

Statistical analyses

Student's t test for the comparison of continuous variables and χ^2 for the discontinuous variables were used. The binary logistic regressions were made using the Enter method as provided by the Statistical Package for Social Sciences (SPSS 15; SPSS Inc., USA).

Results

Saliva cortisol pre- and post-Dex: comparison of patients and healthy controls

Basal cortisol levels (08:00 hours and 20:00 hours) and their absolute and percent diurnal variation did not differ between patients and healthy control subjects, while significantly higher cortisol concentrations were found in the patient group after Dex administration. The post:pre-Dex ratio (SI) was also notably higher in patients as compared with healthy control subjects (Table 1, Fig. 1).

Considering different cut-off points for dividing suppressors from non-suppressors, both the SI and the absolute post-Dex saliva levels were able to separate patients from controls. As we aimed at the greatest specificity, a post-Dex saliva cortisol level >8 nmol/l was selected to define the condition of non-suppression on the basis of a ROC analysis.

No statistically significant differences were found between suppressor and non-suppressor patients for age or gender. As stated before, among patients the saliva cortisol was measured before the commencement of treatment so that the majority of cases were drug free. In a few ($n=9$) cases, however, the already ongoing treatment was maintained. Non-suppression, however, was not influenced by the treatment.

DST, diagnoses and symptoms

A total of 39 patients (41.1%) met more than one current diagnosis, including co-morbidities (i.e. more diagnoses than cases). There were at least 10 cases in the following categories: major depression (MDD); bipolar disorder; panic disorder; any mood disorder; any anxiety disorder; any eating disorder. For each of these, the proportion of DST escapers was significantly higher than that of the control subjects. On the other hand, the comparisons between the diagnostic groups in no case approached significance. Using one diagnosis per case (the one more meaningful on clinical grounds), the results were repeated. The association between cortisol suppression and co-morbidity was also evaluated, although non-suppressor patients showed higher rates of co-morbidity than suppressor patients (51.1% *v*. 35.5%), such a comparison was not significant ($\chi^2=2.287$, $p=0.188$). There were no differences between suppressor and non-suppressor patients in the BPRS total scores (35.63 ± 9.83 and 36.00 ± 9.66 respectively, $t=-0.177$, $p=0.860$).

Of the 121 symptoms initially taken into account, only 31 were present with frequencies that allowed statistical comparisons. Non-suppressors showed a significant higher incidence of specific symptoms, such as nightmares, suicidal ideation, loss of concentration,

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Table 1. *Basal and post-dexamethasone (Dex) saliva cortisol in psychiatric patients and healthy controls*

	Psychiatric patients ($n=93$)	Controls ($n=33$)	
Saliva cortisol, 08:00 hours (day 1, pre-Dex) (nmol/l)	16.74 (S.D. = 8.102)	15.82 (S.D. = 7.056)	$t=0.581$, N.S.
Saliva cortisol, 20:00 hours (day 1, pre-Dex) (nmol/l)	5.629 (S.D. = 3.498)	4.639 (S.D. = 4.1738)	$t=1.326$, N.S.
Saliva cortisol, 08:00 hours (day 2, post-Dex) (nmol/l)	7.54 (S.D. = 6.351)	3.77 (S.D. = 2.453)	$t=3.313$, $p=0.001$
SI (cortisol post-Dex/pre-Dex, 08:00 hours)	0.4618 (S.D. = 0.299)	0.2577 (S.D. = 0.143)	$t=3.759$, $p<0.001$
Daily variation (cortisol 08:00 hours – cortisol 20:00 hours)	11.113 (S.D. = 7.306)	11.180 (S.D. = 6.807)	$t=0.46$, N.S.
Percent daily variation	61.76 (S.D. = 23.55)	69.2579 (S.D. = 20.76)	$t=1.618$, N.S.
Number of DST non-suppressors by different cut-offs			
SI >1 S.D. of controls	46 (49.5%)	4 (12.1%)	$\chi^2=14.19$, $p<0.001$
SI >2 S.D. of controls	30 (32.3%)	2 (6.1%)	$\chi^2=8.82$, $p=0.003$
Post-Dex 08:00 hours >7 nmol/l	37 (39.8%)	4 (12.1%)	$\chi^2=8.49$, $p=0.004$
Post-Dex 08:00 hours >8 nmol/l	33 (35.5%)	2 (6.1%)	$\chi^2=10.51$, $p=0.001$

SI, Suppression Index; DST, Dexamethasone Suppression Test.

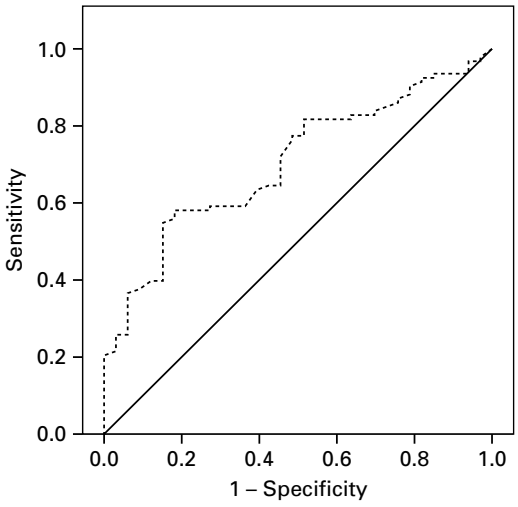

Fig. 1. ROC curve: sensitivity and specificity of post-dexamethasone saliva cortisol. Psychiatric cases *versus* healthy controls.

indecision, apathy, numbing, abulia, sexual impairment and psychotic symptoms (Table 2).

Childhood traumata and DST

Of the 93 patients interviewed, four (all females) reported early experiences of sexual or physical abuse. All the four abused patients were non-suppressors, compared with 14 (23%) of those who did not report serious traumata during childhood ($p=0.005$, Fisher's exact test). Of the 29 cases who reported loss events (such as death of or prolonged separation from parents, severe physical illness, etc.), 16 (55.2%) were non-suppressors ($\chi^2=7.14$, $p=0.008$ *v.* those with no traumatic events). As all the cortisol values of the cases with childhood abuse were in the same ranges of those with loss events, those two groups were combined. A history of an early trauma was significantly associated with higher saliva cortisol at 20:00 hours pre-Dex and at 08:00 hours post-Dex and with a lower percent daily variation of saliva cortisol.

The number of DST non-suppressors was also significantly higher among those with early trauma (Table 3). Given that there were only two non-suppressors among healthy controls, the relationship of early trauma with DST in healthy subjects cannot be explored. It is, however, of interest that both non-suppressors reported a history of childhood abuse.

Childhood traumata, diagnoses and symptoms

The occurrence of loss and abuse events (combined) during childhood was cross-tabulated against the current diagnoses. When compared with each other, no diagnostic category was significantly associated with a past history of loss/abuse. Childhood events, however, were significantly associated with some symptoms, especially those of the depressive series (Table 4).

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Table 2. *Current symptoms in suppressor (n = 60) and non-suppressor (n = 33) patients (only symptoms occurring in at least 15% of patients considered)*

Symptom	Non-suppressors *n* (%)	Suppressors *n* (%)	χ^2	*p*
Insomnia, initial	10 (30.3)	19 (31.7)	0.18	N.S.
Insomnia, late	11 (33.3)	22 (36.7)	0.10	N.S.
Hypersomnia, sleepiness	5 (15.2)	8 (13.3)	0.59*	N.S.
Nightmares	11 (33.3)	8 (13.3)	5.24	0.022
Binge eating	10 (10–3)	23 (38.3)	0.60	N.S.
Weight gain >5%	7 (21.2)	18 (30.0)	0.84	N.S.
Hyporexia	9 (27.3)	11 (18.3)	1.01	N.S.
Weight loss >5%	9 (27.3)	13 (21.7)	0.37	N.S.
Depressed mood	30 (90.9)	51 (85.0)	0.66	N.S.
Anhedonia	25 (75.8)	41 (68.3)	0.57	N.S.
Suicidal ideation	16 (48.5)	17 (28.3)	3.78	0.052
Self-esteem	25 (75.8)	35 (58.3)	2.82	N.S.
Feeling of guilt	20 (60.6)	34 (56.7)	0.13	N.S.
Psychic agitation	17 (51.5)	23 (38.3)	1.51	N.S.
Psychic retardation	14 (42.9)	23 (38.3)	0.15	N.S.
Loss of concentration	24 (72.7)	28 (46.7)	5.87	0.015
Motor retardation, bodily heaviness	15 (45.5)	18 (30.0)	2.22	N.S.
Fatigue, asthenia	24 (72.7)	33 (55.0)	2.82	N.S.
Indecision	25 (75.8)	34 (56.7)	3.35	0.067
Worse in the morning	17 (51.5)	25 (41.7)	0.83	N.S.
Lack of mood reactivity	17 (51.5)	31 (51.7)	0	N.S.
Apathy	20 (60.6)	25 (41.7)	3.06	0.080
Numbing	17 (51.5)	11 (18.3)	11.14	0.001
Abulia	18 (54.5)	19 (31.7)	4.65	0.031
Agoraphobia	8 (24.20)	12 (20.0)	0.22	N.S.
Panic attacks	17 (51.5)	20 (35.5)	2.94	N.S.
Autonomic symptoms	16 (50.0)	22 (36.7)	1.53	N.S.
Generalized anxiety	13 (39.4)	25 (41.7)	0.46	N.S.
Obsessions	10 (30.3)	17 (28.3)	0.40	N.S.
Sexual impairment	1 (3.1)	12 (19.7)	3.50	0.029
Delusion/hallucinations	11 (33.3)	5 (8.3)	9.34	0.002

Table 3. *Basal and post-dexamethasone (Dex) saliva cortisol by experience of traumatic events during childhood*

	With childhood traumata (*n* = 32)	Without childhood traumata (*n* = 61)	
Saliva cortisol, 08:00 hours (day 1, pre-Dex) (nmol/l)	17.07 (S.D. = 9.88)	16.57 (S.D. = 7.73)	*t* = 0.281, N.S.
Saliva cortisol, 20:00 hours (day 1, pre-Dex) (nmol/l)	6.82 (S.D. = 4.15)	5.01 (S.D. = 2.95)	*t* = 2.43, *p* = 0.017
Saliva cortisol, 08:00 hours (day 2, post-Dex) (nmol/l)	9.91 (S.D. = 6.34)	6.29 (S.D. = 5.99)	*t* = 2.697, *p* = 0.008
Suppression Index (cortisol 08:00 hours post-Dex/cortisol 08:00 hours pre-Dex)	0.60 (S.D. = 0.28)	0.39 (S.D. = 0.28)	*t* = 3.453, *p* = 0.001
Daily variation	10.25 (S.D. = 7.67)	11.56 (S.D. = 7.08)	*t* = 0.821, N.S.
% daily variation	52.96 (S.D. = 25.99)	66.37 (S.D. = 20.94)	*t* = 2.697, *p* = 0.008
Number of DST non-suppressors	19 (59.4%)	14 (23.0%)	χ^2 = 12.16, *p* < 0.0001

DST, Dexamethasone Suppression Test.

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Table 4. *Frequency of present symptoms by childhood traumata* (*only symptoms occurring in at least 15% of patients considered*)

Symptom	With early traumata ($n=32$) n (%)	Without early traumata ($n=61$) n (%)	χ^2	p
Insomnia, initial	12 (37.5)	17 (27.9)	0.91	N.S.
Insomnia, late	14 (43.8)	19 (31.1)	1.46	N.S.
Hypersomnia	8 (25.0)	5 (8.2)	3.63	0.057
Nightmares	9 (28.1)	10 (16.4)	1.78	N.S.
Binge eating	11 (34.4)	22 (36.1)	0.03	N.S.
Weight gain	10 (31.3)	15 (24.6)	0.47	N.S.
Decreased appetite	10 (31.3)	10 (16.4)	2.74	N.S.
Weight loss >5%	10 (31.3)	12 (19.7)	1.56	N.S.
Depressed mood	28 (87.5)	53 (86.9)	0.01	N.S.
Anhedonia	27 (84.4)	39 (63.9)	4.26	0.039
Suicidal ideation	16 (50.0)	17 (27.9)	4.49	0.034
Self-esteem	23 (71.9)	37 (50.7)	1.15	N.S.
Feeling of guilt	18 (56.3)	36 (59.0)	0.07	N.S.
Psychic agitation	15 (46.9)	25 (41.0)	0.30	N.S.
Psychic retardation	17 (53.1)	20 (32.8)	3.63	0.057
Loss of concentration	24 (75.0)	28 (45.9)	7.21	0.007
Motor retardation, bodily heaviness	18 (58.1)	15 (24.2)	10.36	0.002
Fatigue asthenia	28 (87.5)	29 (47.5)	14.13	<0.001
Indecision	25 (78.1)	34 (55.78)	4.54	0.033
Worse in the morning	16 (50.0)	26 (42.6)	0.78	N.S.
Lack of mood reactivity	21 (65.6)	27 (44.3)	3.83	0.050
Apathy	22 (68.8)	23 (37.7)	8.10	0.004
Numbing	14 (43.8)	14 (23.0)	4.31	0.038
Abulia	19 (54.9)	18 (29.5)	7.82	0.005
Agoraphobia	10 (31.3)	10 (16.4)	2.74	N.S.
Panic attacks	16 (50.0)	21 (34.4)	2.13	N.S.
Autonomic symptoms	15 (48.4)	23 (37.7)	0.97	N.S.
Generalized anxiety	17 (53.1)	21 (34.4)	3.04	N.S.
Obsessions	10 (31.3)	17 (27.9)	0.12	N.S.
Sexual impairment	4 (12.9)	11 (17.2)	0.28	N.S.
Delusion/hallucinations	6 (18.8)	10 (16.4)	0.08	N.S.

DST and recent stressful events

In total, 49 patients reported a severe stressful life event during the year preceding the onset of the current pathology. Overall, the presence of a recent event was not linked to the levels of saliva cortisol, either before or after Dex, neither was the rate of non-suppressors.

However, the suppression indices and the percent daily variation were significantly associated with the presence of a recent stressor in the patients with a history of childhood. (Table 5).

Characterizing patients with early trauma and patients with Dex non-suppression

The condition of DST suppression *versus* non-suppression was used as dependent variable in a binary logistic regression analysis, where age, gender, marital status, education, diagnoses, current symptoms (those occurring in at least 15% of cases), recent life events and childhood stressful events were the covariates. The only variables significantly and independently associated with DST non-suppression were childhood trauma ($B=3.34$, S.E. $=1.01$, $p=0.01$), delusions/hallucinations ($B=2.64$, S.E. $=1.15$, $p=0.021$), loss of concentration ($B=3.05$, S.E. $=1.53$, $p=0.046$) and loss of self-esteem ($B=3.53$, S.E. $=1.62$, $p=0.030$), with diagnoses and occurrence of a recent stressful event devoid of associations. This model, using the aforementioned four variables, could correctly identify 78.5% of the cases.

Discussion

Retrospective recall may bias the assessment of early events in several ways. The poor reliability of the memories relevant to childhood (Widom & Morris, 1997; Molnar *et al*. 2001; Copeland *et al*. 2007; Zlotnick

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Table 5. *Relationship between recent stressful events and saliva cortisol, with patients with and without a history of childhood traumata considered separately*

	Early trauma present			Early trauma absent		
	Presence of a recent stressful event ($n=19$)	Absence of a recent stressful event ($n=13$)		Presence of a recent stressful event ($n=30$)	Absence of a recent stressful event ($n=31$)	
Saliva cortisol, 08:00 hours (day 1, pre-Dex) (nmol/l)	15.33 (S.D. = 8.10)	19.62 (S.D. = 9.67)	$t=1.36$, N.S.	16.53 (S.D. = 6.97)	16.61 (S.D. = 8.0)	$t=0.43$, N.S.
Saliva cortisol, 20:00 hours (day 1, pre-Dex) (nmol/l)	7.12 (S.D. = 3.53)	6.36 (S.D. = 5.05)	$t=0.50$, N.S.	5.48 (S.D. = 3.70)	4.54 (S.D. = 1.93)	$t=1.25$, N.S.
Saliva cortisol, 08:00 hours (day 2, post-Dex) (nmol/l)	10.51 (S.D. = 6.70)	9.03 (S.D. = 6.18)	$t=0.64$, N.S.	6.55 (S.D. = 6.10)	6.04 (S.D. = 5.97)	$t=0.33$, N.S.
Suppression Index (cortisol 08:00 hours post-Dex/cortisol 08:00 hours pre-Dex)	0.72 (S.D. = 0.255)	0.43 (S.D. = 0.23)	$t=3.18$ $p=0.003$	0.39 (S.D. = 0.29)	0.38 (S.D. = 0.28)	$t=0.11$, N.S.
Daily variation (cortisol 08:00 hours – cortisol 20:00 hours)	8.20 (S.D. = 5.77)	13.25 (S.D. = 9.47)	$t=1.88$, N.S.	11.04 (S.D. = 6.26)	12.07 (S.D. = 0.86)	$t=0.56$, N.S.
Percent daily variation	45.4 (S.D. = 26.2)	63.9 (S.D. = 23.5)	$t=2.08$, $p=0.046$	65.7 (S.D. = 20.2)	67.1 (S.D. = 21.9)	$t=0.26$, N.S.
Number of DST non-suppressors	13 (68.4%)	6 (46.2%)	$\chi^2=1.59$, N.S.	6 (20%)	7 (22.6%)	$\chi^2=0.61$, N.S.

DST, Dexamethasone (Dex) Suppression Test.

et al. 2008), the 'search for meaning', by which the subjects tend to search the reasons for the present distress in their past experiences, the attitude of the interviewer, who may or may not encourage the patient, all affect the accurate retrieval of past events. We have tried, on the basis of previous experiences, to take into account events likely to be reliably recorded and verified, such as loss by death or separation of parents or divorce. For sexual abuse we decided to keep a high threshold for occurrence, only the cases where either another informant confirmed the event or there was a legal consequence were considered. This is the reason why the occurrence of childhood abuse is much lower than usually reported in psychiatric samples. We are aware that limiting the events in this way reduces the sensitivity of the method, as the finer psychological subjective reactions to the events are lost. Given that we have found a clear association between early events and clinical variables, sufficient sensitivity is retained, whereas selective recall of the past induced by the present pathology was minimized or excluded.

The procedure chosen for DST (saliva cortisol, 0.5 mg Dex, one single post-Dex cortisol measurement in the morning) may also be criticized. Admittedly, it is a rough indicator of the HPA axis function. Saliva cortisol, however, is a good and sensitive indicator of free (unbound) plasma cortisol (Umeda *et al*. 1981; Laudat *et al*. 1988; Raff, 2000; Cohen *et al*. 2004; Nishiyama *et al*. 2005), it is stable (Reid *et al*. 1992; Chiu *et al*. 2003; Tiefenbacher *et al*. 2003), sensitive to variations (Shinkai *et al*. 1993; Viardot *et al*. 2005) and its use for DST is well established (Hanada *et al*. 1985; Kahn *et al*. 1988; Copolov *et al*. 1989; McCracken & Poland, 1989; Castro *et al*. 1999, 2003; Gozansky *et al*. 2005). The use of low doses of Dex was initially proposed in order to explore increased suppression in patients affected by PTSD (Yehuda *et al*. 1993; Newport *et al*. 2004) and later used also in MDD (Sarai & Matsunaga, 1986; Heim & Nemeroff, 2001; Juruena *et al*. 2006), eating disorders (Díaz-Marsá *et al*. 2008) and burnout (Kudielka *et al*. 2006). It appears to be useful and sensitive (Costantin Faria *et al*. 2008), it is presently the first line diagnostic test for Cushing's syndrome (Pecori Giraldi, 2009) and is well correlated with the response to the usual dose of 1 mg (Huizenga *et al*. 1998; Matsunaga & Sarai, 2000). We did not measure afternoon post-Dex cortisol, in the exploratory study (unpublished observations), however, the number of 'late escapers' was too small to justify a further saliva sample. The levels of circulating Dex, which might be a potential confounder, were not measured. Evaluation of the precise neuroendocrine changes is in fact beyond the scope of this study.

Our results, with only 2/33 non-suppressors among healthy controls, confirmed that a reasonable specificity was attained. Clinically, non-suppression to DST is an abnormal functional state, related to the HPA axis, fairly common in psychiatric patients, inexpensive and easy to perform. The clinical characterization of these patients is in itself worthy of interest.

Finally, we have purposely avoided using diagnostic processes. This is somewhat unusual, though not new. The lack of diagnostic specificity seems to be common in psychiatry. Moreover, having one single diagnosis is unusual in psychiatry, where co-morbidity is the rule (Kessler *et al*. 2005). It would be more logical to reverse the course of the research process: first to clarify an abnormality among the broad spectrum of psychiatric disorders and then to explore the clinical aspects (including the diagnosis) that are related to such abnormality. Such a 'functionalization' of diagnoses, proposed initially by van Praag (1997, 2001*a*, *b*, 2004), may lead to the identification of specific endophenotypes, which may, in turn, help to resolve questions about etiological models of mental disorders (Gottesman & Gould, 2003).

The fact that DST, though distinguishing between psychiatric cases and healthy subjects, does not differ among psychiatric diagnoses was reported earlier (Arana *et al*. 1985; Copolov *et al*. 1989).

An increasing number of papers suggest that early events influence the HPA axis response during adulthood psychopathology (Bremner *et al*. 2003). Newport *et al*. (2004) found that depressed women with a history of child abuse showed hyper-suppression (i.e. lower cortisol) after low dose DST. Newport *et al*.'s sample was made up of survivors of child abuse with a large prevalence of PTSD and it has been reported that MDD patients co-morbid with PTSD have a different HPA response (Oquendo *et al*. 2003; de Kloet *et al*. 2008). The same group found that early traumata are associated to increased post-Dex cortisol production in male depressives (Heim *et al*. 2008*a*). The same result was found in women with Borderline Personality Disorder (Rinne *et al*. 2008).

To our knowledge, this is the first study dealing with this issue following a trans-diagnostic approach.

We found that:

(1) Low dose DST using saliva cortisol distinguishes the psychiatric patients from normal controls.
(2) An abnormal response to Dex does not distinguish between diagnoses, but is associated with a subset of symptoms, which occur transversally through several diagnostic groups.
(3) DST non-suppression is associated with early life events.
(4) A recent stressful event seems to affect the HPA response only in those subjects who have also been exposed to early traumata.
(5) A history of childhood traumata, HPA axis abnormalities and a few psychiatric symptoms seem to constitute a strict triad, which is independent of the diagnosis.

First, the possibility of a type II error is implicit in all the comparisons where we failed to detect differences (e.g. lack of differences in the rate of early events between patients and controls, comparisons among diagnostic groups). In almost none of the cases in which we did not find significant results, however, there were trends for differences. Second, as the measurement of saliva cortisol was temporarily close to the interview, individuals with a history of childhood trauma could have found the recall and discussion of their trauma experiences stressful. The observed effect of childhood trauma on HPA axis might therefore be linked to the differential effect of the interview procedure. Given that that non-suppression is also linked to the presence of symptoms clearly pre-existing the interview for early events, this interpretation seems less plausible.

Our results may be considered in different ways. On one hand, they give a further contribution to the position that considers early traumata as risk factor for adult psychopathology via the HPA axis. Having considered actual loss events rather than subjectively recalled memories gives further strength to our findings.

On the other hand, being early events and DST abnormal response associated with specific symptoms, rather than with specific diagnoses, some reflections on present classifications should be stimulated. The existence of a stress-related subset of symptoms ranging through different diagnostic groups could explain some inconsistencies, including the high rate of co-morbidity.

A final point is that as few of the control subjects showed a dysfunctional response to DST, in spite of having the same rate of childhood events as psychiatric patients, the early trauma, per se, is not sufficient to induce an abnormal response to Dex.

According to the authors, the considerations recently published by Pariante & Lightman (2008), regarding the HPA axis in MDD could be extended to all the psychiatric disorders where emotion/affectivity represents the core of symptomatology. The existence of a stress-related syndrome ranging aspecifically across psychiatric disorders is plausible. It would be at the same level as the general syndrome in internal medicine, with some symptoms (e.g. abulia, loss of concentration, numbing, sexual impairment,

anhedonia, fatigue) being the analogue of fever, pallor, asthenia, etc.

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Declaration of Interest

None.

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