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The impulsiveness level influences the salivary cortisol response and social stress sensitivity in suicidal patients

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ABSTRACT

Introduction: Suicide attempters (SA) are more vulnerable to social stress and show disturbed cortisol response in stressful conditions compared with psychiatric and healthy controls. Recent data suggest that this dysregulation might be related to impulsivity traits. However, little is known about the emotional consequences of social stress in SA exposed to stress.

Objectives: The aim of our study was to evaluate the cortisol and emotional responses to social stress in patients with depression with and without suicide attempt, by taking into account impulsivity traits and depression severity.

Methods: 67 adult women (41 SA and 26 affective controls (AC,i.e. without suicide attempt history)) with lifetime history of major depressive episode were included. Patients performed the Trier Social Stress Test (TSST), a well-validated social stress task. Patients provided seven saliva samples, to measure the cortisol response, and filled in questionnaires to assess psychological pain, positive and negative mood, and anxiety at different time points (from 10 min before to 120 min after the TSST). Moderated regression models were used including suicide attempt history, depression severity, and impulsivity as independent variables and their interactions.

Results: In patients with low depression and high impulsivity, salivary cortisol response during the TSST was higher in SA than in AC ($p < .001$). Psychological pain, negative mood, and anxiety were increased in all patients just after the TSST, followed by a decrease at 120 min. Positive mood recovery was slower in SA, and in patients with high impulsivity and low depression level ($p < .001$).

Conclusions: Impulsivity traits have an important role in suicidal vulnerability in stress conditions. Impulsivity traits might help to differentiate patients at risk of suicide who are highly sensitive to stress when depression level is low. Higher impulsiveness may increase the sensitivity to emotional distress that translates into inadequate physiological responses.

1. Introduction

Suicide is a major public health problem, and the second leading cause of death by injury worldwide (World Health Organization, 2017). According to the stress-diathesis model (Mann et al., 1999), only vulnerable patients will attempt or commit suicide upon exposure to environmental stressors. The brain centric model (Mann and Rizk, 2020) explains that hypothalamic-pituitary-adrenal (HPA) dysregulation is a part of the diathesis that makes people more vulnerable to suicide. In this model, genetic and epigenetic factors (like childhood and adult stressors and DNA methylation) are hypothesized to be the cause of suicide diathesis. When facing stressors, such as social rejection, suicidal patients show difficulties to interpret and to adapt the situation, partially due to HPA axis dysregulation (Courtet and Olié, 2020). Thus,

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dysregulation of the stress response, particularly at the level of HPA axis, might represent a vulnerability factor for suicide (Alacreu-Crespo et al., 2020b; O'Connor et al., 2020b), like in other stress-related disorders such as depression, anxiety, post-traumatic stress disorder (Zorn et al., 2017) or borderline personality disorder (Drews et al., 2019).

Upon activation, the HPA axis induces the secretion of the glucocorticoid cortisol that is considered a potential biomarker of suicide and suicide attempt (SA) risk (Sudol and Mann, 2017). A meta-analysis showed that baseline cortisol concentration was associated with suicidal behavior (O'Connor et al., 2016). However, the cortisol response during stressful events could be a better predictor of suicide risk (Van Heeringen and Mann, 2014). For instance, O'Connor et al. (2017) found that the cortisol response to the Maastricht Acute Stress Test (MAST) was blunted in euthymic women with history of SA compared with women with lifetime suicidal ideation and healthy women. Similarly, two studies reported that the cortisol response to the Trier Social Stress Test (TSST: Kirschbaum et al., 1993) was blunted in euthymic patients with history of SA compared with patients with history of suicidal ideation or with history of psychiatric disorders without suicidal ideation or SA, and also healthy controls (Eisenlohr-Moul et al., 2018; Melhem et al., 2016). Moreover, O'Connor et al. (2018) found in a sample of euthymic people with an history of SA or ideation, that those with high exposure to childhood trauma had the most blunted cortisol response to the MAST. Finally, another study found that the cortisol response to the TSST was not different in patients with current depression with and without history of SA, with the exception of the subgroup of suicide attempters with high impulsivity/aggression (Stanley et al., 2019). A meta-analysis reported lower cortisol reactivity to acute stress in women with current major depressive episode (MDE) than in controls (Zorn et al., 2017). Therefore, the physiological response to social stress may differ according to the suicide behavior phenotype (ideation or attempt) and the presence of current depression, past trauma and of impulsivity-aggressivity traits.

Due to the close relationship between stress response and emotional system, self-reported anxiety and mood response also are usually assessed in experimental stress procedures (Bali and Jaggi, 2015). However, previous studies on the acute stress response in suicidal patients focused on the cortisol response, but neglected the emotional response. Only Wilson et al. (2016) showed higher self-reported anger in patients with SA than in psychiatric controls using the TSST. Moreover, social stress may induce feelings of rejection and social exclusion, and consequently increases psychological pain (Gunn, 2017). Olié et al. reported that during an experimental task of social exclusion, the activity of left insula and supramarginal gyrus was decreased in euthymic women with past history of SA compared with the non-SA group (Olié et al., 2017). These brain regions are closely related to psychological pain (Eisenberger, 2012), which is at the core of the suicidal process (Ducasse et al., 2018; Olié et al., 2021) and predicts future SA (Alacreu-Crespo et al., 2020a).

Therefore, we aimed to evaluate the cortisol and emotional responses to the TSST in patients with lifetime history of MDE with and without SA by taking into account impulsivity traits and depression severity. We hypothesized that: (1) the salivary cortisol response would be blunted in the SA compared with the non-SA group, and also in patients with higher depression level. As few studied explored the following relationships, we explored two more tentative hypotheses: (2) the interaction between SA, depression severity, and impulsivity would predict the salivary cortisol response to TSST; and (3) this interaction would predict a greater emotional response (i.e. anxiety, negative mood and psychological pain) in patients with than without SA history.

2. Methods

2.1. Participants

In total, 67 adult women (mean age ± SD = 39.26 ± 1.54 years) were recruited at the Department of Psychiatric Emergency and Acute Care, Academic Hospital of Montpellier, France. All women had lifetime history of MDE, according to the DSM-IV criteria, among whom 41 reported lifetime history of SA (i.e. SA group) and 26 did not (i.e. affective controls, AC). SA was defined as a self-destructive act carried out with some intent to die, different from self-mutilation, use of substances, and non-compliance with medical treatment (Van Heeringen and Mann, 2014). Exclusion criteria were: pregnant or breastfeeding woman, treatment or medical condition known to interfere with salivary cortisol levels (e.g. Cushing's syndrome or corticosteroid intake), anti-inflammatory drug or antibiotic intake, lifetime history of schizoaffective disorder or schizophrenia, current (hypo)mania, current eating disorder, and drug/alcohol abuse or dependence within the last 12 months.

The study protocol was approved by the local research ethics committees (CPP Montpellier Sud-Méditerranée IV, CHU Montpellier) and was carried out according to the tenets of the Declaration of Helsinki. All participants signed a written informed consent and received 50 euros for their participation (two sessions: clinical assessment and social stressor procedure).

2.2. Clinical assessment

At inclusion, patients were interviewed by a trained psychiatrist to collect information on demographic characteristics, gynecological history, medication intake, and smoking history. Psychiatric disorders, according to the DSM-IV criteria, were assessed using the French version of the Mini International Neuropsychiatric Interview (MINI 5.0) (Sheehan et al., 1998). SA history was assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011). Depressive symptomatology was evaluated with the Inventory of Depressive Symptomatology, clinician-rated (IDS-C) (Rush et al., 1996).

Participants also completed self-report questionnaires: the Barratt impulsiveness scale, version 10 (BIS-10) (Patton et al., 1995) to assess trait impulsivity, the UCLA Loneliness Scale (Russell et al., 1980) to assess loneliness, the Rejection Sensitivity Questionnaire (RSQ) (Downey and Feldman, 1996) to measure social rejection sensitivity, and, the brief Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003) for childhood history of trauma and neglect.

Participants' height and weight were also measured.

The second visit, to perform the social stressor procedure (TSST), was scheduled between 0 and 7 days after the clinical assessment.

2.3. Social stress procedure

Before the stress procedure, patients were instructed to maintain their general habits, to sleep as long as usual, not to make heavy physical exercise, not to drink alcohol the day before, not to take stimulants (coffee, cola, tea or chocolate) 2 h before the session, and to avoid eating/drinking anything (but water), smoking and brushing their teeth at least 30 min before the session. The procedure was performed between 1.00 and 5.00 p.m. to take into account the circadian rhythms. When arrived to the hospital, participant was settled in the experimental room with the experimenter and was instructed to rest 10 min. During these 10 min, experimenter asked participant whether she followed the pre-protocol instructions. Then, 10 min before the stressor, participants provided the first saliva sample (−10 min) and completed a visual analog scale (VAS) on current psychological and physical pain (Olié et al., 2010), the positive and negative affect schedule (PANAS) (Watson et al., 1988), and items 1–20 of the state-trait anxiety inventory to measure state anxiety (STAI-S) (Spielberger, 1983).

Social stress was induced with the TSST (Kirschbaum et al., 1993). Participants were informed about the stress task (a 5-min speech followed by an arithmetic task in front of a committee). The speech task consisted in giving the personal and professional reasons to explain why they were the best candidates for a job. Participants had 5 min to prepare

the speech. Participants provided saliva samples just before (0 min) and at the end of the speech (+10 min). This was followed by an arithmetic task that lasted 5 min. Participants were informed that both tasks (i.e. speech and arithmetic) would be filmed and recorded with a video camera and microphone that were clearly visible. The committee included a man and a woman who interacted only with participants of the opposite sex.

After the TSST end, participants answered seven questions about the perceived effort, frustration, stress, performance, difficulty, importance, and outcome of the task (answers rated on a Likert scale from 1 = nothing/not at all, to 5 = very much). They also filled in a 4-item questionnaire to measure internal ("effort", "own capacity") and external ("luck", "task difficulty") attributions with answers rated using a 5-point Likert scale (1 = Not important at all, to 5 = Maximum importance) (Frieze and Weiner, 1971). Participants provided four more saliva samples (+20, +30, +60, +90 min) and completed again the VAS for psychological and physical pain, the PANAS and the STAI-S at + 20, +60, and +120 min.

2.4. Salivary cortisol quantification

Detailed written and verbal instructions for saliva sampling were given to all patients. Saliva samples, collected using Salivette® tubes (Sarstdet), were centrifuged (2 °C, 5000 rpm for 15 min) and stored at −20 °C until biochemical analysis.

Salivary cortisol was quantified by electrochemiluminescence with the Elecsys Cortisol II Kit from Cobas® at the Laboratory of clinical biochemistry, Montpellier University Hospital. All samples from the same patient were analyzed in the same run. The within- and inter-assay variation coefficients were all below 9.3%.

2.5. Data analysis

For salivary cortisol, the area under the curve with respect to increment (AUCi) (Pruessner et al., 2003), which represents the cortisol response to the stressor, was calculated. For the emotional response (psychological pain, anxiety, positive and negative mood), the ΔReactivity (difference between the −10 and the +20 scores: Task score - Baseline score), and the ΔRecovery (difference between the +20 and +60 scores: Recovery score - Task score) values were calculated. The absence of outliers was checked and confirmed using the ±3 standard deviation criterion. Then, preliminary analyses were performed using logistic regression models to identify the sociodemographic and clinical variables related to SA.

To analyze changes in the emotional scores and salivary cortisol response in the whole sample during the procedure, a growth model was used in which all variables measured several times (psychological pain, suicidal ideation, state anxiety, positive mood, negative mood and salivary cortisol) were considered as dependent variables. Time (−10, +20, +60, +120 for the clinical outcomes; −10, 0, +10, +20, +30, +60, +90 for salivary cortisol) was included as fixed effect, whereas participants, intercepts and slopes were included as random effects. Fixed effects, omnibus test, degrees of freedom were corrected using the Satterthwaite method.

Moderated regression analyses were used to assess whether group (SA vs. AC), depression (IDS-C scores) and impulsivity (BIS-10 total score) interacted to predict the salivary cortisol (baseline and AUCi) and emotional responses (baseline, ΔReactivity and ΔRecovery). In step 1, age, years of education, and body mass index (for salivary cortisol) were included as covariates. In step 2, group (0 = AC, 1 = SA), IDS-C and BIS-10 were introduced. In step 3, two-way interactions (Group × IDS-C, Group × BIS-10, and IDS-C × BIS-10) were included, followed by a three-way interaction (Group × IDS-C × BIS-10) in step 4. Moderated regression analyses were performed using mean-centered predictors to calculate the interaction term. Significant and trend interactions were decomposed using simple slopes analyses (Aiken and West, 1991).

As childhood trauma is a main theorical cause of HPA axis dysregulation, we performed the same regression models using CTQ total score to predict salivary cortisol. Thus, moderated regression analyses were used to assess whether group (SA vs. AC), depression (IDS-C scores) and childhood trauma (CTQ total score) interacted to predict the salivary cortisol (baseline and AUCi). In step 1, age, years of education, and body mass index (for salivary cortisol) were included as covariates. In step 2, group (0 = AC, 1 = SA), IDS-C and CTQ were introduced. In step 3, two-way interactions (Group × IDS-C, Group × CTQ, and IDS-C × CTQ) were included, followed by a three-way interaction (Group × IDS-C × CTQ) in step 4.

The alpha significance level was fixed at 0.05. All statistical analyses were performed with SPSS 26.0.

3. Results

3.1. Descriptive analysis and task interpretation

Compared with AC, SA were younger (odds ratio, OR [95% CI] = 0.94 [0.90, 0.99], $p < .010$) and less educated (OR [95% CI] = 0.79 [0.65, 0.96], $p < .019$). They also had higher suicidal ideation, according to the IDS-C suicidal item (OR [95%CI] = 2.76 [1.47, 5.19], $p < .002$), and higher total impulsivity (OR [95%CI] = 1.11 [1.04, 1.17], $p < .001$), motor impulsivity (OR [95%CI] = 1.15 [1.02, 1.30], $p < .019$), cognitive impulsiveness (OR [95%CI] = 1.21 [1.05, 1.39], $p < .009$) and non-planning impulsivity (OR[95%CI] = 1.23 [1.08, 1.39], $p < .002$). Moreover, compared with AC, SA thought that the TSST was more difficult (OR [95%CI] = 1.69 [1.00, 2.84], $p < .050$). Psychopathology, medication intake, and gynecological status were comparable between groups (all $p > .050$), as well as all the other sociodemographic and clinical variables and task interpretation ($p > .050$) (Table 1).

3.2. Salivary cortisol response

3.2.1. Salivary cortisol concentration changes during the TSST

Compared with baseline, salivary cortisol progressively decreased, with a significant fixed effect of time ($F_{6, 396} = 7.06$, $p < .001$). Although linear, quadratic and cubic terms were all significant, salivary cortisol levels seemed to follow a linear (β (SE) = - 1.28 (0.03), $p < .001$) rather than a quadratic (β (SE) = - 0.63 (0.03), $p < .017$) or cubic model (β (SE) = 0.80 (0.03), $p < .002$) (Fig. 1).

3.2.2. Influence of group, depression and impulsivity on salivary cortisol response

Higher depression level (IDS-C score) predicted lower baseline salivary cortisol concentration (β(SE) = - .006(0.003), $p < .017$). Conversely, group, impulsivity, and their interactions did not explain the baseline salivary cortisol concentration ($p > .050$) (Table 2).

Moderated regression analysis of the salivary cortisol AUCi showed a significant effect of depression severity (β(SE) = 0.003(0.001), $p < .037$). The group × BIS-10 interaction was significant (β(SE) = 0.008 (0.004), $p < .022$). Simple slopes analysis showed that for patients with high total impulsiveness score (+1SD), AUCi levels were significantly higher in the SA than AC group (b = 0.11, se = 0.05, $p < .045$) (Supplementary Fig. 3E). Conversely, no difference was observed ($p > .050$) for patients with low total impulsiveness score (-1SD) (Supplementary Fig. 1A). The IDS-C × BIS-10 interaction also was significant (β(SE) = 0.001(0.001), $p < .007$). Similarly, simple slopes analysis showed that for patients with high impulsiveness (+1SD), AUCi levels were significantly higher in patients with high depression than with low depression score (b = 0.01, se = 0.01, $p < .003$). No significant difference ($p > .050$) was observed for patients with the subgroup with low impulsiveness (-1SD) (Supplementary Fig. 1B). Finally, the group x IDS-C x BIS-10 interaction was significant (β(SE) = - 0.007(0.001), $p < .002$). Simple slopes analysis showed that for patients with low depression score (-1SD) and with high impulsiveness (+1SD), AUCi levels were higher in

Table 1
Sociodemographic, clinical variables and task interpretation.

	Suicide attempters	Affective control	*p* value	OR [95% CI]
N =	41	26		
Sociodemographic variables				
Age	**35.99 ± 1.98**	**44.43 ± 2.12**	***p* < .010**	**.94 [.90, .99]**
Years of education	**12.90 ± .41**	**14.54 ± .51**	***p* < .019**	**.79 [.65, .96]**
BMI	23.99 ± .67	25.88 ± 1.34	*p* < .173	.94 [.85, 1.03]
Div./Sep./Wid., n (%)	7 (17.1%)	3 (11.5%)	*p* < .538	1.58 [.37, 6.75]
Children, n (%)	22 (53.7%)	18 (69.2%)	*p* < .208	.52 [.18, 1.44]
Prof. Active, n (%)	19 (46.3%)	10 (38.5%)	*p* < .526	.72 [.27, 1.97]
Current smoker, n (%)	3 (7.3%)	3 (11.5%)	*p* < .559	.61 [.11, 3.25]
Medications				
Antidepressants, n (%)	29 (70.7%)	20 (76.9%)	*p* < .578	.73 [.23, 2.25]
Benzodiazepines, n (%)	25 (61.0%)	17 (65.4%)	*p* < .716	.83 [.29, 2.30]
Antiepileptics, n (%)	6 (14.6%)	7 (26.9%)	*p* < .221	.47 [.14, 1.58]
Antipsychotics, n (%)	15 (36.6%)	8 (30.8%)	*p* < .625	1.29 [.46, 3.70]
Lithium, n (%)	4 (9.8%)	6 (23.1%)	*p* < .146	.36 [.09, 1.45]
Medication load	3.49 ± .52	3.81 ± .75	*p* < .498	.91 [.70, 1.19]
Psychiatric status				
Lifetime bipolar, n (%)	13 (32.5%)	11 (42.3%)	*p* < .419	.66 [.24, 1.82]
Current anxiety, n (%)	30 (75.0%)	17 (68.0%)	*p* < .716	.83 [.29, 2.30]
Psychiatric hospit. (n)	2.95 ± .66	2.15 ± .82	*p* < .452	1.05 [.92, 1.20]
IDS-C	27.02 ± 2.09	27.62 ± 3.12	*p* < .858	.99 [.96, 1.03]
IDS-C suicidal item	**1.44 ± .19**	**.46 ± .11**	***p* < .002**	**2.76 [1.47, 5.19]**
Number of SA	3.06 ± .92	–		
Age of first SA	28.09 ± 1.92	–		
Violent SA, n (%)	6 (12.8%)	–		
Serious SA, n (%)	7 (14.9%)	–		
Current Psych. pain	3.87 ± .42	4.28 ± .59	*p* < .560	.95 [.79, 1.14]
Mean Psych. Pain	5.36 ± .47	5.44 ± .67	*p* < .918	.99 [.84, 1.17]
Max. Psych. Pain	7.05 ± .50	6.44 ± .65	*p* < .449	1.06 [.91, 1.25]
Current Physical Pain	2.10 ± .34	2.20 ± .49	*p* < .865	.98 [.78, 1.23]
Mean Physical Pain	2.95 ± .45	3.16 ± .66	*p* < .782	.99 [.83, 1.16]
Max Physical pain	3.97 ± .52	3.92 ± .75	*p* < .950	1.01 [.87, 1.17]
Gynecologic status				
Menopause, n (%)	7 (17.1%)	7 (26.9%)	*p* < .337	.56 [.17, 1.83]
Irregular menstr. cycle	5 (18.5%)	6 (42.9%)	*p* < .103	3.30 [.79, 13.88]
Contraceptives, n (%)	18 (52.9%)	10 (62.5%)	*p* < .526	.68 [.20, 2.28]
Loneliness/Social rejection				
Loneliness (UCLA)	43.33 ± 1.17	40.63 ± 1.83	*p* < .197	1.04 [.98, 1.11]
Rejection concern	77.69 ± 1.79	78.32 ± 2.21	*p* < .823	.99 [.95, 1.04]
Impulsivity				
BIS-10 Total	**44.39 ± 1.77**	**34.31 ± 1.79**	***p* < .001**	**1.11 [1.04, 1.17]**
BIS-10 Motor	**13.55 ± .75**	**10.62 ± .88**	***p* < .019**	**1.15 [1.02, 1.30]**
BIS-10 Cognitive	**16.13 ± .66**	**13.27 ± .72**	***p* < .009**	**1.21 [1.05, 1.39]**
BIS-10 Non Planning	**14.71 ± .78**	**10.42 ± .86**	***p* < .002**	**1.23 [1.08, 1.39]**
Childhood trauma (Low/Moderate/Severe)				
CTQ total	54.83 ± 3.09	47.08 ± 2.69	*p* < .089	1.03 [.99, 1.06]
Physical abuse, n (%)	12 (29.3%)	5 (19.2%)	*p* < .361	1.74 [.53, 5.68]
Physical neglect, n (%)	19 (46.3%)	10 (38.5%)	*p* < .526	1.38 [.51, 3.76]
Emot. abuse, n (%)	20 (48.8%)	11 (42.3%)	*p* < .605	1.29 [.48, 3.49]
Emot. neglect, n (%)	27 (65.9%)	13 (50.0%)	*p* < .200	1.93 [.71, 5.26]
Sexual abuse, n (%)	16 (39.0%)	10 (38.5%)	*p* < .963	1.02 [.37, 2.81]
Task interpretation				
Effort	4.24 ± .18	4.08 ± .24	*p* < .581	1.13 [.74, 1.72]
Frustration	4.19 ± .16	3.84 ± .21	*p* < .192	1.37 [.85, 2.20]
Performance	1.83 ± .91	2.12 ± .78	*p* < .195	.68 [.38, 1.22]
Stress	4.24 ± .96	3.96 ± 1.14	*p* < .282	1.30 [.81, 2.12]
Difficulty	**4.14 ± .94**	**3.64 ± 1.03**	***p* < .050**	**1.69 [1.00, 2.84]**
Importance	4.36 ± .89	4.16 ± .98	*p* < .380	1.27 [.74, 2.17]
Perceived Outcome	1.71 ± .87	2.16 ± 1.03	*p* < .068	.60 [.35, 1.04]
Internal Attribution	7.42 ± 2.07	7.08 ± 1.72	*p* < .494	1.09 [.84, 1.42]
External Attribution	5.58 ± 1.81	5.17 ± 2.01	*p* < .401	1.13 [.85, 1.49]

Note: BMI = Body Mass Index; Div./Sep./Wid. = Divorced/Separated/Widowed; Prof. = Professional; Hospit. = Hospitalization; IDS-C = Inventory of depressive symptomatology; SA = Suicide attempt; Psych. = Psychological; menstr. = menstrual; Max. = Maximum; BIS-10 = Barratt Impulsiveness Scale, version 10; CTQ = Childhood trauma questionnaire; Emot. = Emotional.

the SA than AC group (b = 0.52, se = 0.10, p < .001). There were no other significant slopes for the triple interaction ($p > .050$; Fig. 2). The results of the multiple regression analysis are summarized in Table 2.

3.2.3. Influence of group, depression and trauma on salivary cortisol response

No significant effects in the overall model (baseline cortisol $p = .317$; AUCi cortisol $p = .182$) and none in the single predictors or interactions were found (all $p > .050$; see supplementary material for a complete description).

3.3. Emotional response

3.3.1. Emotional changes during the TSST

For the whole sample, psychological pain, positive mood and state anxiety changes during the stress test followed a quadratic model (β (SE) = - 1.06 (0.19), $p < .001$; β (SE) = - 1.56 (0.40), $p < .001$; β (SE) = - 7.13 (0.78), $p < .001$, respectively; see supplementary material for a complete description), with an increase of psychological pain and state anxiety from −10 to +20 and a decrease from +20 to +120 min, and the opposite for positive mood (Fig. 1). Negative mood changes followed a

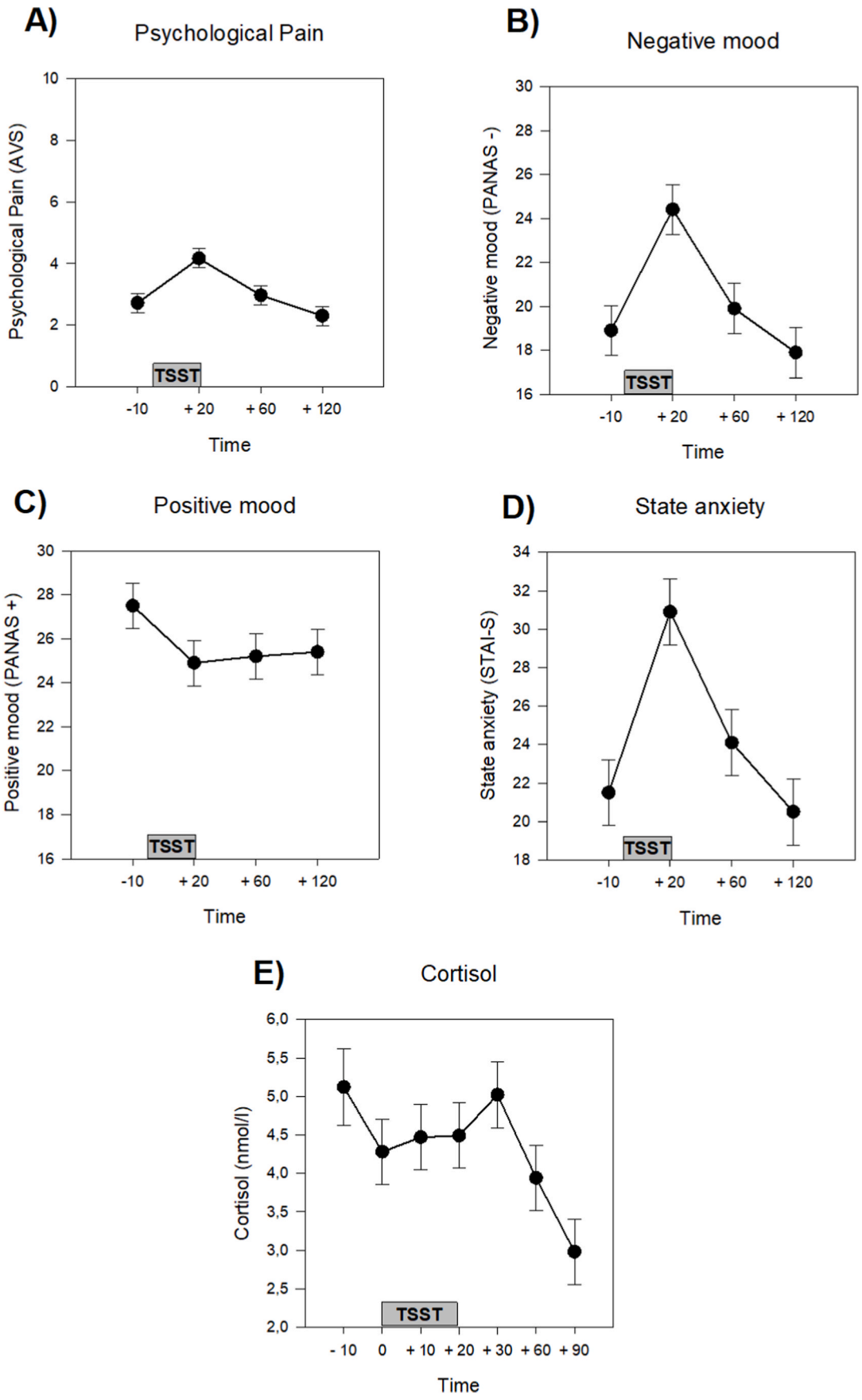

Fig. 1. Emotional and salivary cortisol responses at different time points during the stress procedure.

Table 2
Multiple regression analysis: suicide x depression × impulsiveness interaction predicting the cortisol response.

Baseline cortisol	β (SE)	p-value	Cortisol AUCi	β (SE)	p-value
Overall model: R^2 = .201		.249	Overall model: R^2 = .408		.001
Step 1			*Step 1*		
Age	.001 (.003)	.967	Age	.001 (.001)	.504
BMI	−.009 (.007)	.184	BMI	.004 (.003)	.246
Years of education	.014 (.013)	.310	Years of education	−.010 (.006)	.125
Step 2			*Step 2*		
Suicide attempt, Y = 1	−.104 (.082)	.208	Suicide attempt, Y = 1	.057 (.038)	.145
Depression (IDS-C)	**−.006 (.003)**	**.017**	**Depression (IDS-C)**	**.003 (.001)**	**.037**
Impulsiveness (BIS-T)	.001 (.004)	.858	Impulsiveness (BIS-T)	−.004 (.002)	.067
Step 3			*Step 3*		
SA*Depression	−.003 (.005)	.498	SA*Depression	−.001 (.002)	.584
SA*Impulsiveness	−.003 (.008)	.717	**SA*Impulsiveness**	**.008 (.004)**	**.022**
Depression*Impulsiveness	.001 (.001)	.133	**Depression*Impulsiveness**	**.001 (.001)**	**.007**
Step 4			*Step 4*		
SA*Depression*Impulsiveness	.001 (.001)	.389	**SA*Depression*Impulsiveness**	**−.001 (.001)**	**.017**

Note: BMI = Body mass index; Y = Yes; IDS-C = Inventory of Depressive Symptomatology-clinician rated; BIS-T = Barratt Impulsiveness Scale, total score; SA = Suicide attempt; AUCi = Area under the curve with respect to increment.

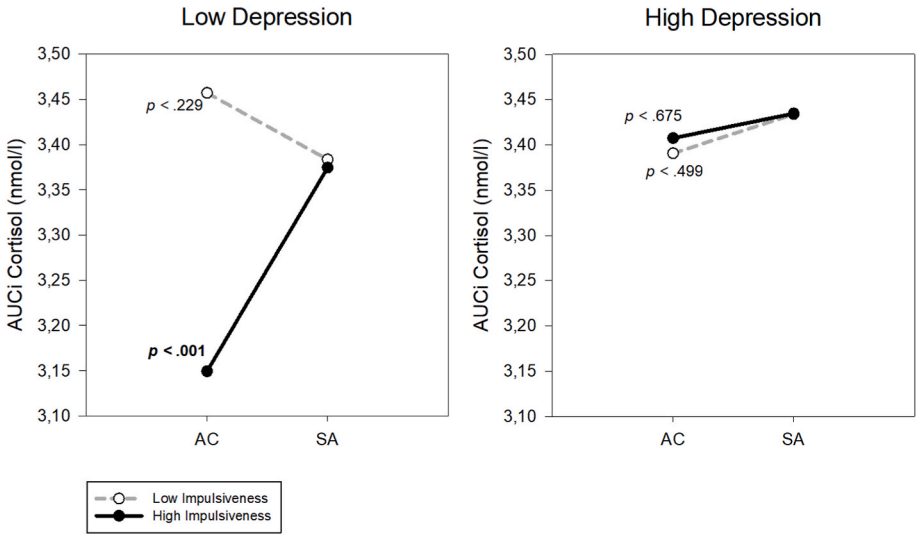

Fig. 2. Salivary cortisol AUCi in function of the impulsiveness score and suicide history (patients with suicide attempt, SA, vs affective controls, AC) in patients with low and high depression level (IDS-C score). Note: Plotted points represent conditional low and high impulsiveness scores (±1 SD).

cubic model (β (SE) = 0.09 (0.01), $p < .001$), with an increase from −10 to +20 min, a decrease from +20 to +60 min, and a stabilization from +60 to +120 min (Fig. 1).

3.3.2. *Influence of group, depression and impulsiveness on emotional response and recovery*

Higher depression severity predicted higher baseline psychological pain (β(SE) = .062(0.020), $p < .003$), negative mood (β(SE) = 0.005 (0.001), $p < .001$), and anxiety (β(SE) = 0.300(0.112), $p < .009$). Higher impulsiveness predicted higher baseline positive mood (β(SE) = 0.235(0.094), $p < .016$). The group × BIS-10 interaction was significant for baseline psychological pain (β(SE) = 0.186(0.063), $p < .005$). Simple slopes analysis showed that for patients with low impulsiveness (-1SD), baseline psychological pain was lower in the SA than AC group (b = −2.88, se = 0.85, p < .001). No difference ($p > .050$) was observed for patients with high impulsiveness (+1SD) (Supplementary Fig. 2A). Group and the other interactions did not explain the baseline emotional scores ($p > .050$) (Supplementary material).

Moreover, group, depression severity, impulsiveness and their interactions did not predict the emotional response (ΔReactivity) (all $p > .050$) (Supplementary material). Conversely, higher impulsiveness scores predicted slower positive mood ΔRecovery (β (SE) = −0.186 (0.071), $p < .011$). Moreover, the IDS-C × BIS-10 interaction was significant for positive mood ΔRecovery (β(SE) = −0.013(0.005), $p < .011$). Simple slopes analysis showed that for patients with high impulsiveness (+1SD), positive mood ΔRecovery was slower in patients with high than with low depression level (b = −1.85, se = 0.06, p < .001). No difference ($p > .050$) was detected for patients with low impulsiveness score (-1SD) (Supplementary Fig. 2B). The group x IDS-C x BIS-10 interaction also was significant for positive mood ΔRecovery (β(SE) = 0.021(0.010), $p < .038$). Simple slopes analysis showed that for patients with low depression level (-1SD) and high impulsiveness (+1SD), positive mood ΔRecovery was hindered in the SA compared with the AC group (b = −5.09, se = 2.39, p < .038) (Fig. 3). The other factors and interactions did not explain the anxiety, psychological pain and negative mood ΔRecovery ($p > .050$).

4. Discussion

Our analysis indicates that high impulsiveness could explain the differences in salivary cortisol and emotional response to social stress in patients in function of their depression level. Overall, patients showed a

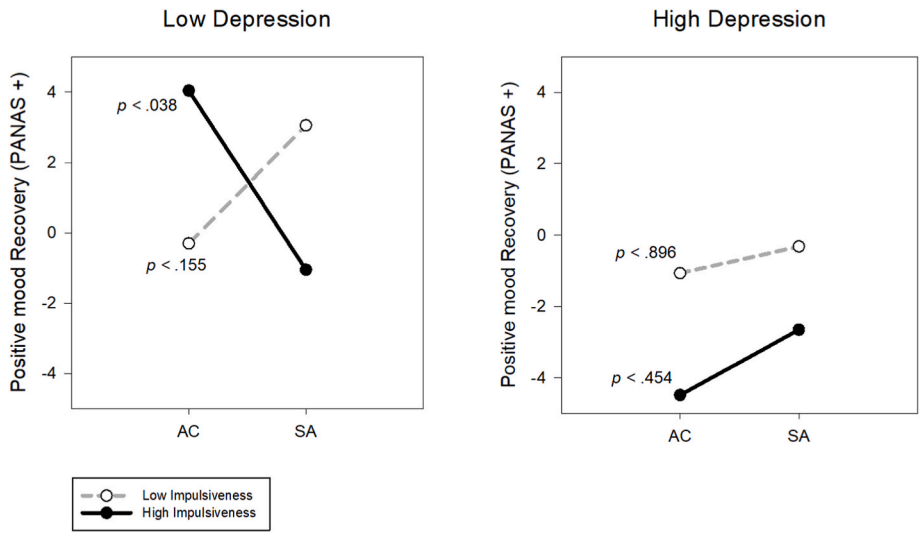

Fig. 3. Positive mood recovery in function of the impulsiveness score and suicide history (patients with suicide attempt, SA, vs affective controls, AC), in patients with low and with high depression level (IDS-C score). Note: Plotted points represent conditional low and high impulsiveness scores (±1 SD).

small increase in salivary cortisol concentration and a greater response of negative emotions (negative mood, anxiety and psychological pain) after the TSST, followed by a fast decrease of all these variables. Only in patients with high impulsiveness, salivary cortisol responses were different between groups, with higher salivary cortisol reactivity to stress in the SA than AC group. When taking into account the depression level, salivary cortisol response was higher in SA than in the AC group only for patients with low depression and high impulsiveness scores. Similarly, positive mood level after the TSST was lower in the SA than AC group in patients with low depression and high impulsiveness scores. However, the response to stress and recovery of negative emotions were similar between subgroups.

The relationship between suicide risk and HPA axis dysregulation has been confirmed, but with contradictory findings (O'Connor et al., 2020b). According with the Brain centric model (Mann and Rizk, 2020) HPA axis dysregulation is a trait that forms part from suicidal diathesis. HPA axis malfunction comes from genetic effects and epigenetic changes (i.e. methylation with childhood adversity) in glucocorticoid (GR) and mineralocorticoid (MR) receptors (McGowan et al., 2009; Steinberg and Mann, 2020; Yin et al., 2016). Several studies using the dexamethasone suppression test have shown the HPA axis dysregulation in suicidal patients (Alacreu-Crespo et al., 2020b; Coryell and Schlesser, 2001; Jokinen et al., 2008, 2009; Westrin and Niméus, 2003), showing a chronic alteration in the feedback loops were GR and MR receptors are involved. Previous studies using stress procedures, as we used in our study reported blunted cortisol response in suicide attempters compared with psychiatric controls or healthy participants (Eisenlohr-Moul et al., 2018; Melhem et al., 2016; O'Connor et al., 2017). All those studies using stress tasks recruited euthymic patients, concretely suicidal patients with lifetime history of suicide, showing that the cortisol response did not depend of the depressive or the suicidal status at the moment of evaluation.

Conversely, the study by Stanley et al. (2019) and our present analysis did not find any significant effect of suicidal history on the salivary cortisol response in patients with depression. These discrepancies may be related to the inclusion of patients with current depression, a population that already had a HPA axis dysregulation (Zorn et al., 2017). Indeed, our results show an effect of depression on the baseline salivary cortisol concentration and the salivary cortisol response to stress, highlighting the importance of the depressive status in the HPA axis dysregulation.

Regarding the salivary cortisol response to TSST, our results show a linear negative trend for cortisol showing a decrease of cortisol across the procedure. However, this result not means that our patients not had response to the stressor. First, our patients were currently depressed, meaning that we could expect an initial blunted cortisol response (Zorn et al., 2017). Second, as we measured cortisol in the afternoon, this linear decrease may be due to the natural circadian rhythm of cortisol. Third, although less significant, the quadratic term for cortisol was also significant. Fig. 1E shows a peak of cortisol at 30 min after the stressor, where cortisol peak should appear. However, probably because of the fast decrease at 60 and 90 min the linear term was more significant. Finally, all the measures of emotional distress showed a peak just after the TSST (see Fig. 1A, B and 1D) meaning a clear effect of stress in participants.

About trauma, childhood traumatic experiences did not have any effect in the cortisol response of our patients. Previous research has shown that childhood trauma predicted blunted cortisol awakening response (O'Connor et al., 2020a) and blunted cortisol reactivity to stress in suicidal patients (O'Connor et al., 2018). However, our procedure was different compared to those from O'Connor et al. (2018) in terms of the stressor (we used TSST instead of MAST) and the sample (we included current depressed patients). This could explain the differences in results despite the similar levels of childhood maltreatment.

Our results also confirmed that impulsivity traits influence the cortisol response to social stress in patients with depression and suicide history (Stanley et al., 2019). The suicide-impulsivity relationship has been widely studied (Giner et al., 2016), and impulsivity traits might be positively correlated with the lethality of future suicide attempts (Gvion, 2018). Using the dexamethasone suppression test, we previously found that post-dexamethasone cortisol levels are higher in violent and/or severe attempters that in non-violent and/or non-severe attempters (Alacreu-Crespo et al., 2020b). Post-dexamethasone cortisol level also predicted re-attempts with higher suicidal intent. Therefore, the HPA axis might respond differently to stress in patients with higher impulsiveness. This suggests a SA phenotype with a specific biological dysregulation of the stress response that might be found particularly in patients with low or moderate depression level. In agreement, some authors hypothesizde two types of suicidal individuals: responsive and non-responsive to stress (Bernanke et al., 2017; Rizk et al., 2018). The relationship between impulsivity and cortisol response may help to disentangle these two subgroups of patients.

Those results have also importance from a transdiagnostic perspective. Firstly, HPA axis dysregulation during stress response had been consistently reported for several stress-related disorders such as depression, anxiety disorders, post-traumatic stress disorders,

schizophrenia (Zorn et al., 2017) or borderline personality disorder (Drews et al., 2019). Secondly, impulsivity, another well-reported transdiagnostic marker in psychopathology (Liu et al., 2017; Pasion and Barbosa, 2019) appears as a moderator for the salivary cortisol response. Thus, it is possible that a combination of high impulsivity and a dysregulated stress response may be a marker of different sub-types in psychopathology. If that is true, patients responsive to stress may benefit from stress-focused therapies. Indeed, Oquendo et al. (2020) in an Ecological momentary assessment study across 2 years has found two groups of suicidal ideators, those with low suicidal ideation variability and those with high suicidal ideation variability. Curiously, the study showed that suicidal ideation variability was a trait. Patients with high suicidal ideation variability had higher impulsivity and higher increase in suicidal ideation after a stressor than those from the low variability, showing similarities with our results.

Our study suggests that the negative emotion response to the social stressor was similar in all patients. Indeed, as expected, all negative emotions increased just after the TSST with a return to basal levels after the initial emotional response. Unlike Wilson et al. (2016), we did not find any significant difference in the negative emotions in the two groups (SA and AC). However, Wilson et al. (2016) evaluated anger, whereas we measured anxiety, psychological pain and negative mood. Our results show differences in positive mood recovery according to the SA history. As observed for salivary cortisol, positive mood recovery was impaired in the SA group only in patients with high impulsiveness and low depression scores. This result strengthens the idea that in the stress response, the recovery is the most important part rather than the reactivity, because faster recovery to basal levels is associated with better health (Geurts and Sonnentag, 2006; McEwen, 2017). Moreover, some studies highlighted that positive emotions and well-being are correlated with better physiological recovery from stress, and better global health (Cavanagh and Larkin, 2018; DuPont et al., 2020).

Our study has some limitations. First, the lack of aggressive trait and anger evaluation limits the replication of previous results (Stanley et al., 2019; Wilson et al., 2016). Second, we included patients with unipolar disorder reducing the generalizability to other psychiatric disorders. Third, we did not evaluate the complete physiological stress response by including also autonomous nervous system measures. Fourth, although we asked for gynecological status (i.e. regularity, contraceptive intake and menopausal status), we did not control the menstrual cycle phase at inclusion in the stress protocol. Future studies should consider the whole stress response (autonomous nervous system, HPA, and inflammatory response). Finally, suicide attempt is a stressor itself that may alter HPA axis, as patients with lifetime suicide attempt were included, the closeness of attempt may impact our results, future studies should check the cortisol response to stress of patients with recent attempts.

In conclusion, our results highlight the importance of impulsiveness in the response to stress in suicidal patients. Future studies should test the hypothesis that patients with depression, impulsivity traits and greater sensitivity to social stress may be more prone to future suicidal behavior. Moreover, in this population, recovery of positive emotions might be hampered. Therefore, therapies to increase well-being, such as well-being therapy (Fava, 2016), and emotional intelligence (Lea et al., 2019) might be beneficial in these patients.

Author contributions

Adrián Alacreu-Crespo: Conceptualization, Data curation, Formal analysis, Visualization, Writing-original draft, Writing-review and editing. **Vanesa Hidalgo:** Methodology, Writing-review and editing. **Chloé Girod:** Investigation, Data curation, Validation, Writing-review and editing. **Emilie Olié:** Conceptualization, Resources, Project administration, Writing-review and editing. **Philippe Courtet:** Conceptualization, Methodology, Resources, Supervision, Funding acquisition, Writing-review and editing.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2022.10.008.

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