Neurobiology of Stress 18 (2022) 100454

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: www.elsevier.com/locate/ynstr

'Doctor, I am so stressed out!' A descriptive study of biological, psychological, and socioemotional markers of stress in individuals who self-identify as being 'very stressed out' or 'zen'

Sonia J. Lupien [b,c,d,1,*], Sarah Leclaire [a,b,c,1], Danie Majeur [a,b,c], Catherine Raymond [a,b,c], Francelyne Jean Baptiste [b], Charles-Edouard Giguère [b]

[a] Department of Neurosciences, University of Montreal, Canada
[b] Research Center of the University Institute in Mental Health of Montreal, Canada
[c] Centre for Studies on Human Stress, Canada
[d] Department of Psychiatry, University of Montreal, Canada

ARTICLE INFO

Keywords:
Stress
Glucocorticoids
Subjective stress
Stress biomarkers
Anxiety
Depression
Emotion regulation

ABSTRACT

Surveys report that about three-quarters of visits to general practitioners in America are for stress-related complaints. Animal and human studies have consistently demonstrated that exposure to acute and/or chronic stress leads to the activation of the autonomic nervous system (ANS) and/or hypothalamic-pituitary-adrenal (HPA) axis, and to the production of catecholamines and glucocorticoids. Yet, many studies performed in humans do not report significant associations between subjective feelings of stress and increases in these stress biomarkers. Consequently, it is not clear whether the stress-related complaints of individuals are associated with significant increases in these stress biomarkers. In the present study, we measured whether individuals who self-identify as being 'very stressed out' or 'zen' present differences in psychological (depression and anxiety symptoms), biological (basal and reactive levels of glucocorticoids and alpha-amylase) and socioemotional (emotion regulation, mind wandering, personality, resilience and positive mental health) factors associated with stress. Salivary levels of cortisol and alpha-amylase were obtained in the home environment and in reaction to the Trier Social Stress Test in 123 adults aged between 19 and 55 years. All participants completed questionnaires assessing the psychological and socioemotional factors described above. The results showed that groups significantly differed on almost all psychological and socioemotional factors, although we found no significant group differences on biological markers of stress (cortisol or alpha-amylase). These results suggest that when people complain of being *'very stressed out'*, what they may really be alluding to is an experience of *psychological distress* that is related to poor emotion regulation capacities. It is thus possible that the construct of stress used by people to discuss their internal state of 'stress' is quite different than the construct of stress measured in animal and human laboratories using biomarkers of 'stress'.

1. Introduction

For the field of human psychoneuroendocrinology, 1968 was a very important year. It was the year that Bruce McEwen and his colleagues found the presence of glucocorticoid receptors in the rodent brain (McEwen et al., 1968). Glucocorticoids (cortisol in humans, corticosterone in rodents) are the end-product of the HPA axis. In animals, as in humans, a significant increase in levels of glucocorticoids is generally observed when the organism is exposed to a physical or psychological stress (McEwen and Stellar 1993).

In humans, various studies have reported significant associations between dysregulated levels of glucocorticoids and the presence of mental health disorders. For example, a meta-analysis of 361 studies including 18,454 individuals led to the conclusion that higher levels of

* Corresponding author. Centre for Studies on Human Stress, Research Centre, Montreal Mental Health University Institute, 7401, Hochelaga Stress, Montréal, Quebec, Canada, H1N 3M5.
E-mail address: sonia.lupien@umontreal.ca (S.J. Lupien).
[1] These authors contributed equally to this manuscript and share first authorship. They can thus change the order of first authorship as a function of their respective curriculum vitae.

https://doi.org/10.1016/j.ynstr.2022.100454
Received 17 January 2022; Received in revised form 25 March 2022; Accepted 18 April 2022
Available online 21 April 2022

glucocorticoids are observed in depressed compared to non-depressed individuals (Stetler and Miller 2011). Other groups found that chronic production of glucocorticoids is associated with an increased risk for the development of emotional exhaustion (Pruessner et al., 1999) and that post-traumatic stress disorder is associated with changes in circulating levels of glucocorticoids (Yehuda et al., 2005). Altogether, these results led to the idea that glucocorticoids are biomarkers of stress that can provide important information as to how chronic stress can get 'under the skin and skull' and increase vulnerability to physical and/or mental disorders (McEwen 2000).

As one of the first authors of this paper (S. Lupien), I completed a post-doctoral fellowship in Dr. McEwen's lab. After having left Bruce's lab, we both met regularly at scientific meetings around the world. Each encounter was a unique opportunity for me to learn about new ideas that were developing in his fabulous mind. One day after a meeting, we were discussing the concept of 'stress' and how this construct is often over-utilized in the public eye. Bruce asked me whether I thought that the definition that scientists use to describe and study 'stress' is the same that individuals use when they state that they are 'stressed out' while visiting their doctor. In other words, Bruce was asking whether glucocorticoids are good markers of subjective stress in humans. I did not have the answer to this question. A few years later, we performed a study in collaboration with Sarah Leclaire, a graduate student at my lab, to provide data on this simple, yet very important question.

Bruce, this study is for you.

1.1. Are glucocorticoids good markers of subjective stress in humans?

Studies show that 75% of visits to primary care facilities are for stress-related complaints at a cost of approximately $50 billion per year (Tangri 2003). In 2019, results from the Stress in America survey revealed that nearly one third of Americans rated their average stress levels as 'extreme', and a significant number of individuals reported that stress had a negative impact on their mental and physical health (Association AP, 2019). The results of this large survey could serve as confirmation that the feeling of subjective stress experienced by individuals translates into significant increases in biomarkers of stress which then impact physical and mental health (for a review, see (Lupien et al., 2009). This assumption has been called the 'common cause hypothesis', which suggests that *'subjective and objective stress measures both reflect a common cause of stress-related psychophysiological changes within the individual'* (Weckesser et al., 2019).

However, human research is far from systematically reporting significant associations between subjective levels of stress and circulating levels of glucocorticoids. In 2004, a meta-analysis performed on the association between subjective feelings of stress in normal populations and glucocorticoid levels revealed that 8 out of 14 studies reported no association, 4 reported a positive association and 2 a negative one (Hjortskov et al., 2004). Another meta-analysis published in 2012 assessed whether glucocorticoid reactivity to the Trier Social Stress Test [TSST; a laboratory stressor (Kirschbaum et al., 1993)] correlated with subjective feelings of stress during the procedure (Campbell and Ehlert 2012). In short, the TSST involves a 10-min anticipation period followed by a 5-min speech and a 5-min mental arithmetic task in front of judges (Kirschbaum et al., 1993). The results of this meta-analysis showed that only 25% of articles reported a significant association between participants' subjective feelings of stress during the stress procedure and glucocorticoid secretion.

With no consensus reached by these correlational studies, Ali and colleagues (Ali et al., 2017) used an experimental approach in which they pharmacologically suppressed the neuroendocrine and autonomic stress responses with dexamethasone and propranolol before exposing participants to the TSST. They measured subjective feelings of stress during the TSST procedure. The results showed that even though the physiological stress response was completely shut down by the combined administration of dexamethasone and propranolol, all the participants reported increased feelings of stress during the procedure. This thoughtful study showed that physiological activation of the HPA axis is not necessary to confer the subjective feeling of acute stress in humans.

These and many other results led to heated debates between scholars in the field of stress (Kagan 2016a, 2016b; MacDougall-Shackleton et al., 2019; McEwen and McEwen 2016) to explain the lack of coherence between the different stress outcome systems. Here, various factors have been proposed to explain this lack of association.

First, it has been suggested that glucocorticoids may not be the only and/or best biomarker to correlate with subjective feelings of stress (Andrews et al., 2013; Chen et al., 2015). Exposure to stress in both animals and humans leads to the concomitant activation of the HPA and ANS systems, and both systems have been shown to contribute to the pathogenesis and maintenance of mental disorders (Chrousos 2009). One method to assess ANS functioning is through measurements of salivary alpha-amylase, an enzyme produced by the salivary glands and released in response to ANS activation (Nater and Rohleder 2009). Recent studies show that there is not always a concordance in the activation of the HPA and ANS system and that a lack of cortisol secretion can be accompanied by significant changes in markers of ANS function (Ali and Pruessner 2012; Booij et al., 2015). It is thus possible that subjective feelings of stress in humans may better correlate with changes in ANS activity than with changes in HPA activity.

Second, it has been suggested that the reliance on only one measure of subjective stress in most of the studies assessing the association between subjective feelings of stress and glucocorticoid levels, along with the use of different subjective stress scales across studies could explain the discrepancies of data (Weckesser et al., 2019). Moreover, questionnaires are known to be prone to different kinds of bias and this can compromise their predictive value (Coughlin 1990). Consequently, studies should use more than one measure of subjective feelings of stress when assessing the association between subjective feelings of stress and biomarkers of stress.

Third, some scientists have suggested that in many studies, the subjective levels of stress measured in participants may have varied within an intensity range that was too low, leading to effects of subjective stress that were too weak to be apparent on glucocorticoid levels [called the stress intensity hypothesis, see (Mauss et al., 2005; Weckesser et al., 2019)]. To prevent this, studies should try to recruit participants in such a way as to assess the two extreme tails (very low and very high) of the subjective stress distribution within the population similar to what has been done in various animal studies (Caldji et al., 2000; Champagne and Meaney 2001; Champagne et al., 2003).

The goal of this study was to assess the relationship between subjective feelings of stress and stress biomarkers in humans by controlling these factors. We recruited individuals self-selecting themselves as being 'very stressed out' and compared their biological (glucocorticoids and alpha-amylase levels) and psychological (depression and anxiety symptoms) markers of stress to that of a 'low stress' group (see methods section for the rationale used for the selection of this group). The second objective of the study was to compare the two groups on vulnerability (emotion regulation, personality and mind-wandering) and protective (resilience and positive mental health) factors (thereafter called socio-emotional factors) known to be associated with biomarkers of stress in humans. Given that this was a descriptive study, we did not have any apriori hypotheses. However, the results of this descriptive study would allow us to generate new hypotheses (Gaus et al., 2015) about the biological and/or psychological and/or socioemotional factor(s) that are associated and/or contribute to high levels of subjective feelings of stress in the general population.

2. Material and methods

2.1. Participants

One hundred and twenty-three healthy men (n = 54), and women (n = 69) between the ages of 19 and 55 (M = 32.13, SD = 9.26) took part in this study. Upon responding to our recruitment ads, each participant underwent a phone interview to collect demographic information and to control for exclusion criteria prior to their participation. The exclusion criteria included any endocrine, cardiovascular, psychiatric or other chronic diseases, as well as antidepressant, anxiolytic and other systemic medications that could affect diurnal and reactive cortisol levels. Furthermore, participants were asked to report any significant alcohol or substance use due to possible effects on cortisol secretion. Selected women did not use any type of hormonal contraceptives and were all tested in the late luteal phase of their menstrual cycle (Kirschbaum et al., 1999a). This study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of the Institut universitaire en santé mentale de Montréal. All participants provided written consent after receiving information regarding the study. They were compensated for their time and effort.

2.1.1. Self-selection recruitment procedure

We designed a procedure to intentionally recruit participants from the two extreme tails of the subjective stress distribution in the population ('very high' *versus* 'very low' subjective stress) (Mauss et al., 2005). We chose to allow participants to self-select themselves as being 'very stressed out' to prevent any a posteriori inclusion of participants in the group of 'high stress individuals' that would be based on questionnaires of perceived stress (Weckesser et al., 2019). We also considered that this self-selection method of recruitment would be a better representation of what happens when an individual visits his/her doctor with complaints of high stress.

We reasoned that recruiting participants self-selecting themselves as having 'low stress' could be problematic because the intensity of stress experienced by individuals can be highly variable and we would run the risk of recruiting participants in the middle of the distribution. For this reason, we used a label that is associated in the public eye with a state of very low stress, namely the notion of 'zen'. The notion of 'zen' as representing a person with high control over emotions and thus, low stress and anxiety was spread in the USA during the 50s and 60s (Kato 2005). For many historians, it is after the publication of a book by Robert Pirsig, whereby it was examined how humans live and how zen meditation can help to live a better life, that the notion of 'zen' became synonymous with being calm, practicing meditation and presenting low stress and anxiety (McWatt 2017). In the 1960s, scientists started to measure the effects of zen meditation on EEG. These studies contributed to the uptake of the construct of 'zen' as representing low stress and high coping capacity (Kato 2005). Given the mindset associated with the notion of 'zen' as representing people in full control of their stress, we decided to use this construct to recruit participants self-selecting themselves as having low stress.

We used an overt recruitment method based on a protocol described by Foroughi et al. (2016) which was also used in some of our previous studies with individuals exposed to early adversity (Raymond et al. 2021a, 2021b). More precisely, participants self-selected themselves into one of two groups ('very stressed out' *versus* 'zen' individuals) by answering one of two recruitment ads for 'very stressed out' (*'Are you very stressed out? Then participate in a study…'*) or 'zen' (*'Are you zen? Then participate in a study…'*) individuals. Ads were posted at different timepoints in a counterbalanced order until we had reached ±60 participants in each group. Participants who answered both advertisements were not recruited in the study. Within the 123 participants recruited, 66 self-selected themselves in the 'very stressed out' group (54.5% women) while 57 self-selected themselves in the 'zen' group (57.9% women).

2.2. Questionnaires and tasks

2.2.1. Measures of subjective stress

To ensure that our self-selecting recruitment method was successful in creating two different groups in terms of subjective stress levels, we used two methods to assess participants' subjective stress levels. First, participants were asked to complete the *Perceived Stress Scale* (Cohen et al., 1983). This 10-item questionnaire assesses how frequently individuals have experienced stressful situations in the past month. All responses are made in reference to a five-point Likert scale (0 = never to 4 = very often). The mean Cronbach alpha coefficient of this questionnaire is 0.85. Second, participants were asked to rate their daily life subjective stress level on a 10-point Likert scale (1 = lowest level of stress to 10 = highest level of stress). They were specified not to assess their stress level on a precise time frame, but rather on their general and diffused feeling of stress.

2.2.2. Psychological markers of stress

We assessed depressive symptomatology and state/trait anxiety as psychological markers of stress. We used the 21-item Beck Depression Inventory II [BDI II; (Beck et al., 1996)] to measure depressive symptoms. This questionnaire asks participants to evaluate the severity of various depressive symptoms on a four-point scale. The total score varies between 0 and 63. This questionnaire has a high reliability (Cronbach alpha coefficient: 0.92). As per ethical regulation of our research centre, if a participant had a score that reached the threshold for depression, we communicated with the participant and informed him/her of the free resources available to obtain an evaluation, diagnosis and/or help. Trait anxiety was assessed with the *State-Trait Anxiety Inventory for adults* [STAI-Y; Spielberger et al., 1983]. This questionnaire consists of 40 items and is divided into two subscales: Trait and State anxiety. Questions are answered on a scale ranging from 1 to 4 (1 = hardly ever and 4 = almost always), where a high score indicates a high level of anxiety in general. The Cronbach alpha coefficient of the State-Trait Anxiety Scale is 0.89 (Spielberger & al., 1983).

2.2.3. Physiological markers of stress

We assessed salivary cortisol and alpha-amylase levels obtained in the home environment (basal diurnal levels) and in reactivity to the TSST at the laboratory (reactive levels). For the assessment of diurnal levels, participants had to provide saliva samples at home at 5 time points (upon awakening, 30 min after awakening, 2pm, 4pm and before going to bed) on two nonconsecutive sampling days, one weekday and one weekend day (Kunz-Ebrecht et al., 2004). Participants were given a journal in which they were given clear written instructions and a section where they had to write down each sampling time. They were also provided with a Medication event monitoring system (MEMS) cap to ensure compliance (Stalder et al., 2016). For the assessment of reactive levels, participants were exposed to the TSST, a validated psychosocial stressor (Kirschbaum et al., 1993). Briefly, the TSST involves a 10-min anticipation period followed by a 5-min speech and a 5-min mental arithmetic task. Saliva samples for measurement of cortisol and alpha-amylase were obtained every 10 min, starting 30 min before the TSST and ending 40 min later. We also measured participants' subjective feeling of stress throughout the TSST procedure, on a 10-point Likert scale, at each salivary sampling time.

Saliva samples were collected through passive drool and stored at the Centre for Studies on Human Stress (http://humanstress.ca/saliva-lab/general-information/), at −20 °C until biochemical analysis. Frozen samples were brought to room temperature and centrifuged at 1500×*g* (3000 rpm) for 15 min. High-sensitivity enzyme immunoassays were used (Salimetrics®, No. 1–3102, sensitivity: 0.012–3 μg/dl). Inter-assay and intra-assay coefficients of variance for cortisol were 5.3%–12.4%. All assays were duplicated and averaged. For alpha-amylase, the assay uses a substrate containing 2-Chloro-p-nitrophenol (CNP), linked with maltotriose and data are converted into a U/ml result. Absolute range of

assay for alpha-amylase is 3.1–423.1U/ml. Samples were all run in duplicate and averaged.

2.2.4. Socioemotional markers of stress

We assessed modulatory factors known to affect biomarkers of stress (Lupien et al., 2018). Some of these factors are known to be associated with increased levels of subjective and physiological stress [emotion regulation, mind wandering and personality (Friedman and Booth-Kewley 1987; Raymond et al. 2019a, 2019b)] while others have been shown to have protective effects against stress [resilience and positive mental health (Curtis and Cicchetti 2003; Keyes 2002)].

Emotion regulation was measured by the *Emotion Control Questionnaire* [ECQ2 (Roger and Najarian, 1989)]. The ECQ2 is a 56-item scale (true or false) that measures 4 factors; i.e. rehearsal (the tendency to ruminate over stressful events), emotional inhibition (tendency to suppress negative emotions), aggression control (capacity to inhibit hostile behaviors) and benign control (capacity to control impulsivity). The ECQ2 demonstrates very good internal consistency, with alphas of .86 for rehearsal, 0.77 for emotional inhibition, 0.81 for aggression control and 0.79 for benign control. We measured mind wandering using the 5-items *Mind Wandering Questionnaire* [MWQ (Mrazek et al., 2013)]. The MWQ measures the frequency of deliberate and spontaneous mind-wandering and has a Cronbach's alpha of 0.850. Our research team used a double-blind translation technique to translate the questionnaire from English to French. Within our sample, we obtained a Cronbach's α of 0.87. We measured personality using the *Ten Items Personality Inventory* [TIPI (Gosling et al., 2003)]. This 10-item questionnaire asks participants to evaluate (on a scale from 1 = strongly disagree to 7 = strongly agree) the degree to which some statements fit their personality. This questionnaire has five subscales: Extraversion, Agreeableness, Conscientiousness, Emotional stability and Openness to experience. The Cronbach alphas for each subscale are 0.68, 0.40, 0.50, 0.73 and 0.45 respectively.

Resilience was measured using the *Brief Resilience Scale* [BRS (Smith et al., 2008)], a 6-item questionnaire with a mean internal consistency coefficient of 0.86. Finally, psychological well-being was measured using the short form of the *Mental Health Continuum* [MHC-SF (Keyes 2002)]. The MHC-SF has 14 items that measure three facets of well-being, i.e. emotional, psychological and social well-being. The short form of the MHC has shown excellent internal consistency >0.80).

2.3. Procedure

Fig. 1 presents a schematic representation of the protocol used in this study. The protocol was performed over two time periods. First, participants from the two groups were asked to come to the Center for Studies on Human Stress (CSHS) where they were exposed to the TSST. Participants were tested between 12:00 and 18:00 to minimize confounds due to diurnal patterns of cortisol. At the end of the 2-h session, participants received instructions to collect saliva samples at home and to answer questionnaires measuring the psychological and socioemotional stress markers online. All questionnaires were filled out via the Studies Web Automation Tool (SWAT), a secured web platform developed by the CSHS. To ensure confidentiality, participants were given individualized secure codes to log in and access the online questionnaires. At the end of those two weeks, we collected saliva samples from the participants' homes. The researchers who interacted with the participants were blind to the group to which the participants belonged to.

2.4. Statistical analysis

Outliers were defined as values outside of 3.29 standard deviations from the mean. Outlier data were winzorised for further analyses. For diurnal cortisol and alpha-amylase, we verified participant's compliance and eliminated samples that were taken within less than 20 min or 45 min after sampling time. Following the analysis of compliance, a total of three measurements were considered missing for further analyses. All analyses were conducted using *R* version 4.0.5. Package *nlme* (Pinheiro and Bates, 2000) and *emmeans* (Lenth 2021) have been used to conduct linear mixed-effect modelling and post-hoc contrasts respectively. When

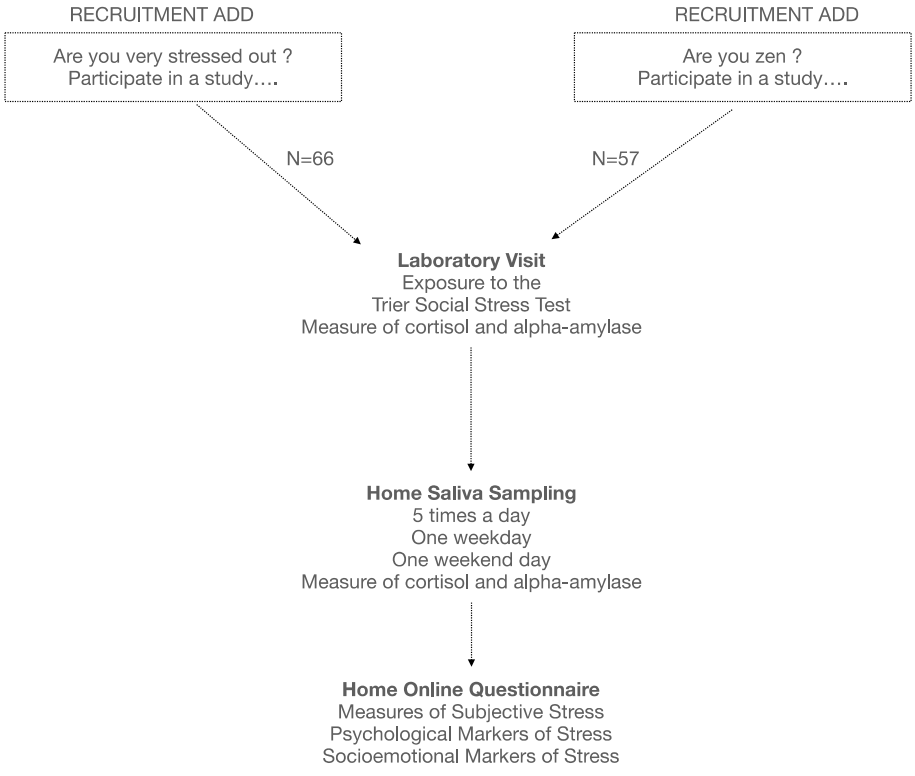

Fig. 1. Schematic representation of the protocol used in the study for recruitment and testing of participants in the 'very stressed out' and 'zen' groups.

a block of analyses was made on multiple similar outcomes, for example different markers of stress, Benjamini-Hochberg (BH) correction was used to protect against false-discovery (Hochberg 1988).

Preliminary analyses were first performed to investigate differences between the two groups ('very stressed out' *versus* 'zen') on demographic factors. The mean of continuous variables was compared using a Welch *t*-test and categorical variables on the percentage in each group using either a Chi-square test or a Fisher exact test if an expected cell count was lower than 5. Second, a confirmatory group analysis was performed on self-attribution in each group using mean comparison (Welch *t*-test) on the two subjective stress scales. Third, psychological markers of stress were compared using a Welch *t*-test. Evolution of the subjective stress scale during the Trier social stress test (TSST) was analyzed using a linear mixed-effect (lme) model where we included a time, group, and time by group interaction as fixed effect and a random effect on the intercept with heterogeneous residuals variance across time. Contrasts were made if an effect was found to be statistically significant. Fourth, diurnal secretion of cortisol and alpha-amylase were analyzed using the same lme model across the 5 samples from awakening to bedtime to test for differences in biological markers of stress. Weekday and weekend days were combined if no difference was found between the two periods. Cortisol and alpha-amylase were analyzed using a lme model across each stage of the TSST to assess differences in biological stress reactivity. Finally, secondary analyses were made to verify if the two groups differed on socioemotional factors related to stress using series of *t*-test with p-values corrected for false-discovery rate using the BH correction.

Our analysis plan was uploaded to the Open Science Framework (OSF) and is available at: https://osf.io/9tw5x/. The database of this study is available at https://osf.io/mtu5y/.

3. Results

3.1. Preliminary analyses

Preliminary analyses showed that the two groups were similar except for civil status where a larger proportion ($p = 0.004$) of 'zen' participants (43.9%) were in a relationship compared to the 'very stressed out' group (18.2%; see Table 1). Moreover, groups did not differ on years of education, or yearly salary (all $p > 0.1$). Age was entered as a covariate in all analyses and results did not change. Consequently, age was not considered further in subsequent analysis of result.

3.2. Confirmatory group analyses

The self-attribution of participants in the two groups was confirmed (all $p < 0.001$) by the Likert scale score and the perceived stress scale (see Table 2). No sex difference was observed on subjective stress markers showing that men and women did not differ on the level of subjective stress they reported within each group. Consequently, sex was collapsed across subsequent analyses to conserve statistical power.

3.3. Psychological markers of stress

Participants from the 'very stressed out' group scored higher on the Beck Depression Inventory ($p < 0.001$; see Fig. 2A), the trait anxiety ($p < 0.001$; see Fig. 2B) and state anxiety ($p < 0.001$; see Fig. 2C) when compared to the 'zen' group.

During the TSST, subjective stress scores were systematically higher in the 'very stressed out' group ($F(1,119) = 17.69$; $p < 0.001$; see Fig. 3), the stress response was however similar in the two groups ($F(7, 821) = 0.84$; $p = 0.56$). All participants had a statistically significant time effect ($F(7,821) = 33.61$; $p < 0.001$) which indicates that they had a subjective stress response to the TSST.

Table 1
Demographic information. The p-value corresponds to either a *t*-test or a Pearson Chi-square test for continuous and categorical variable respectively unless stated otherwise.

Mean (se)/n (%)	Zen (n = 57)	Stressed (n = 66)	p-value
Sex (Female)	33 (57.9%)	36 (54.5%)	0.85
Age	32.5 (1.2)	31.8 (1.1)	0.65
Years education	17.3 (0.3)	17.2 (0.4)	0.86
Body Mass Index	23.8 (0.4)	23.4 (0.5)	0.60
Ethnicity			
Arab	4 (7.0%)	4 (6.1%)	0.22*
Asian	4 (7.0%)	7 (10.6%)	
African	4 (7.0%)	2 (3.0%)	
Latin American	8 (14.0%)	3 (4.5%)	
White	32 (56.1%)	37 (56.1%)	
Other	5 (8.8%)	13 (19.7%)	
Civil Status			
Single	31 (54.4%)	50 (75.8%)	**0.004**[a]
Married/common law	25 (43.9%)	12 (18.2%)	
Separated/Divorced	1 (1.8%)	4 (6.1%)	
Work status			
Student	12 (21.1%)	20 (30.3%)	0.28
Unemployed	5 (8.8%)	8 (12.1%)	
Worker	30 (52.6%)	33 (50.0%)	
Student & Worker	10 (17.5%)	5 (7.6%)	
Tobacco use	3 (5.3%)	5 (7.6%)	0.72[a]
# cigarettes/month	0.2 (0.2)	0.6 (0.5)	0.47
Alcohol use	46 (83.6%)	49 (74.2%)	0.30
# Alcohol drinks/month	8.8 (1.6)	7.7 (1.3)	0.59
Drug use	4 (7.0%)	12 (18.2%)	0.12
# drug/month	0.05 (0.03)	0.12 (0.04)	0.17
History of physical health problem	23 (40.4%)	29 (43.9%)	0.83
Mental problem past	9 (15.8%)	17 (25.8%)	

[a] A Fisher exact test was used instead of a chi-square test because there was at least an expected cell count of less than five participants in one of the categories.

Table 2
Confirmatory analysis of grouping.

Mean (se)	Zen	Stressed	p-value
Likert Stress Scale	3.4 (0.3)	7.0 (0.2)	<0.001
Perceived Stress Scale	17.5 (1.0)	28.4 (0.9)	<0.001

3.4. Biological markers of stress

Biological markers did not differ between weekdays and weekend days neither for cortisol ($p = 0.47$) nor alpha-amylase ($p = 0.27$). Consequently, both set of measures were included in the analyses without distinction. For diurnal cortisol, we detected a time by group interaction ($F(4,977) = 3.46$; $p = 0.008$; see Fig. 4A). Post-hoc comparisons showed that the 'very stressed out' group had salivary cortisol levels significantly higher than the 'zen' group 30 min after awakening (Diff(stressed - Zen) = 0.077; $p = 0.029$). We did not observe differences in alpha-amylase between the two groups either as main effect ($F(1,109) = 1.27$; 0.26) or in interaction with time ($F(4,977) = 1.29$; $p = 0.27$; see Fig. 4B).

The cortisol response to the TSST was similar in the two groups, i.e. no main effects of Group ($F(1,118) = 0.59$; $p = 0.44$) nor group by time interaction ($F(7,821) = 1.43$; $p = 0.19$; see Fig. 5A). For alpha-amylase, no main effect of Group was observed ($F(1,118) = 1.75$; $p = 0.19$) nor group by time interaction ($F(7, 821) = 1.77$; $p = 0.09$); see Fig. 5B).

3.5. Socioemotional factors

Groups significantly differed on three ECQ subscales. Participants from the 'very stressed out' group scored significantly higher on rehearsal (tendency to ruminate over stressful events; $p < 0.001$), and scored significantly lower on aggression control (capacity to inhibit hostile behaviors; $p = 0.010$) and benign control (capacity to control

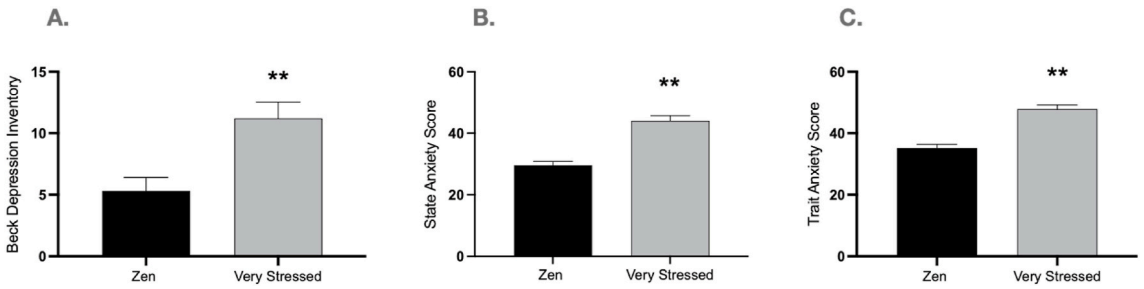

Fig. 2. Scores on the Beck Depression Inventory (**A**), State Anxiety (**B**) and Trait Anxiety Scale (**C**) in the 'very stressed out' and 'zen' groups.

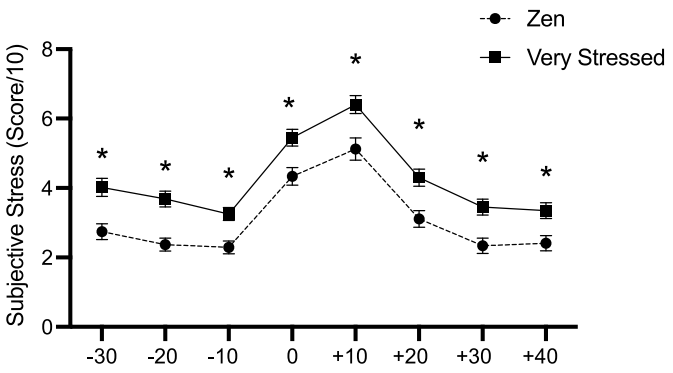

Fig. 3. Subjective stress scores in response to the TSST in the 'very stressed out' and 'zen' groups.

impulsivity; p = 0.012, see Table 3). Participants from the 'very stressed out' group also scored significantly higher on mind wandering (p = 0.019; see Table 3). In terms of personality, the 'very stressed out' group was lower on the agreeableness scale (p < 0.001) and on the emotional stability scale (p < 0.001) when compared to the 'zen' group (see Table 4).

In terms of protective factors, participants who identified as 'zen' scored higher on the resilience scale (p < 0.001) and had higher scores on the positive mental health scale on all dimensions (emotional p < 0.001; social p = 0.003; psychological p < 0.001; see Table 5) when compared to the 'very stressed out' group.

3.6. Evidential value of null results using Bayes factors

In this study, the analyses performed on biological markers of stress (basal and reactive alpha-amylase and reactive cortisol) yielded mostly non-significant results. As thoroughly discussed by Aczel and colleagues (Aczel et al., 2017, Aczel et al., 2018), null results can occur because the effect does not exist, or because the power was insufficient to detect the true effect. To further investigate this, recent reports propose to use Bayes factors to evaluate the strength of evidence for the null hypothesis (Dienes 2014, 2016). Unlike power analyses that require specifying the minimal effects expected to address a given theory as based on a priori

Table 3
Comparison of the two groups on emotion regulation and mind wandering scales. P-values are adjusted using Benjamin-Hochberg correction for false-discovery rate.

Mean(se)	Zen	Stressed	p-value
Emotion control/Rehearsal	4.07 (0.36)	6.93 (0.33)	<0.001
Emotion control/Inhibition	5.47 (0.38)	5.25 (0.38)	0.67
Emotion control/Aggression	9.33 (0.24)	8.03 (0.36)	0.010
Emotion control/Benign control	8.93 (0.35)	7.59 (0.34)	0.012
Mind Wandering	15.60 (0.64)	17.89 (0.67)	0.019

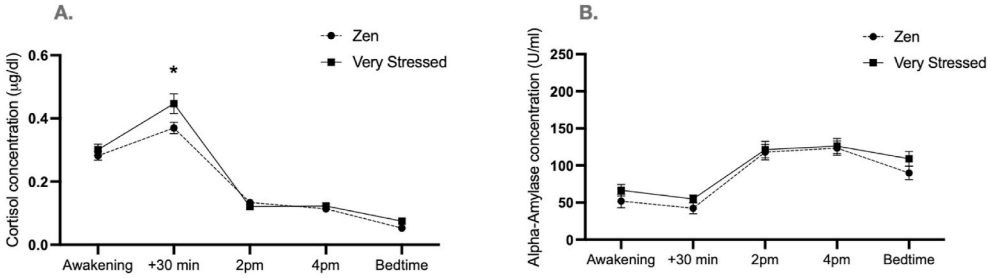

Fig. 4. Diurnal cortisol (A) and Alpha-Amylase (B) concentrations in the 'very stressed out' and 'zen' groups.

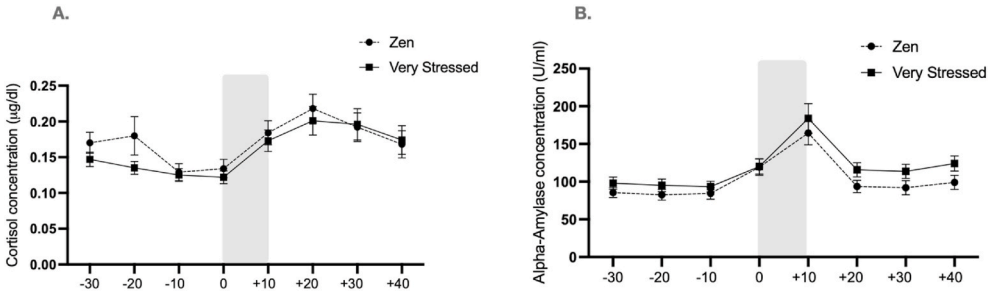

Fig. 5. Cortisol (A) and Alpha-Amylase (B) concentrations in reactivity to the TSST in the 'very stressed out' and 'zen' groups.

Table 4
Comparison of the two groups on the personality scale. P-values are adjusted using Benjamin-Hochberg correction for false-discovery rate.

Mean (se)	Zen	Stressed	p-value
Extraversion	3.82 (0.20)	3.89 (0.21)	0.79
Agreeableness	5.59 (0.13)	4.88 (0.15)	0.001
Conscientiousness	5.40 (0.17)	5.32 (0.16)	0.79
Emotional stability	5.52 (0.19)	3.68 (0.18)	<0.001
Openness	5.78 (0.16)	5.34 (0.16)	0.07

Table 5
Comparison of the two groups on protective factors. P-values are adjusted using Benjamin-Hochberg correction for false-discovery rate.

Mean (se)	Zen	Stressed	p-value
Brief resilience scale	3.66 (0.10)	3.08 (0.11)	<0.001
Emotional well being	11.76 (0.37)	9.23 (0.39)	<0.001
Social well being	13.96 (0.80)	10.56 (0.75)	0.003
Psychological well being	21.87 (0.74)	17.62 (0.82)	<0.001

knowledge and data, Bayes factors use the data of the current study to determine their sensitivity in distinguishing theories (Dienes 2014, 2016). Bayes factors calculate evidential support for the null results (H_0) and Bayes factors greater than 1 usually indicate relative evidence for the null hypothesis. In contrast, Bayes factors smaller than 1 indicate relative evidence for the alternative hypothesis (H_1 = significant difference).

We calculated Bayes factors (BF_{01} - evidence in favour of the null or alternative hypothesis) with a medium-scale ($r = \sqrt{2}/2$) Cauchy under the alternative hypothesis (see Table 6). The 6 tests yielded 3 strong and 3 very strong evidence in favour of H_0. These results show that the absence of a significant difference between groups for alpha-amylase (basal and reactive) and cortisol (reactive) has a low probability of being explained by insufficient power to detect the true effect.

4. Discussion

The goal of this study was to recruit adults who self-identify as being 'very stressed out' or 'zen' and to compare them on psychological, biological and socioemotional factors associated with stress. The results showed that groups mostly differed on psychological and socioemotional factors of stress, although they were highly similar on biomarkers of stress. When compared to the 'zen' group, participants from the 'very stressed out' group presented more depressive and anxiety symptoms, they reported significantly higher levels of subjective stress when exposed to the TSST and they presented lower capacity for emotional regulation and more mind wandering. In contrast, participants from the 'zen' group were more agreeable and presented greater emotional stability. They also scored significantly higher on scales of resilience and positive mental health when compared to the 'very stressed out' group. When we compared groups on diurnal and reactive cortisol and alpha-amylase levels, we found that the only difference between groups was greater concentrations of cortisol 30 min after awakening in participants from the 'very stressed out' group.

Table 6
Bayes factors for A) basal alpha-amylase, B) reactive alpha-amylase and C) reactive cortisol.

A) Basal alpha-amylase		
Description	BF_{01}	Interpretation
Time + Group	16	Strong evidence in favour of H_0
Time + Group + Time × Group	>100	Very strong evidence in favour of H_0
B) Reactive alpha-amylase		
Time + Group	12.24	Strong evidence in favour of H_0
Time + Group + Time × Group	>100	Very strong evidence in favour of H_0
C) Reactive cortisol		
Time + Group	22	Strong evidence in favour of H_0
Time + Group + Time × Group	>100	Very strong evidence in favour of H_0

The results obtained in the 'very stressed out' group suggest that when people complain of being very stressed out, what they may really be alluding to is an experience of *psychological distress* that is related to poor emotion regulation capacities. Our results show that this state of psychological distress is not a sufficient condition to elicit a significant increase in biological markers of stress. As suggested by Dickerson and Kemeny in their review of the stress literature in 2004 (Dickerson and Kemeny 2004), and in the heated debates around the concept(s) of stress that emerged in recent years (Kagan 2016a, 2016b; MacDougall--Shackleton et al., 2019; McEwen and McEwen 2016), stress is not a one-dimensional construct that can be related to significant increases in biological stress markers. In their review of the literature, Dickerson and Kemeny (2004) showed that situations that are novel, unpredictable and constituting a threat to the ego are potent activators of the HPA system. Yet, the diffuse feeling of distress that people may feel when they state that they are 'very stressed out' may relate more strongly to deficits in emotion regulation than to a physiological stress response per se. This result goes along with a study showing that neither high negative nor low positive affect in response to minor daily stressors predicts worse long-term mental and physical health (Piazza et al., 2013). These results suggest that the way people emotionally respond to daily stressors in their lives could be a better predictor of subjective reports of stress than biomarkers of stress.

This conclusion does not preclude the fact that glucocorticoids and alpha-amylase *are* appropriate biomarkers of stress. Indeed, it is important to remember that these biomarkers are highly reactive to physical and/or psychological stressors in both animals and humans and in the present study, both cortisol and alpha-amylase concentrations significantly increased in response to the TSST. Consequently, a wealth of data show that when an animal or a human is exposed to a threat/stressor, there *is* a significant increase in these biomarkers of stress. Moreover, many studies have assessed the effects of glucocorticoids on cognitive function and mental health and showed that these hormones have potent effects on the brain [for a review see (Lupien et al., 2009)] and other longitudinal data suggest that these hormones are significantly involved in the pathogenesis of mental health disorders (Halligan et al., 2007). What the results of our study suggest is that when people state that they are 'very stressed out', this feeling is more strongly related to poor emotion regulation capacities than to activation of the ANS and/or HPA systems.

It is also important to note that many studies comparing individuals with stress-related mental health disorders (e.g. depression) to normal populations *do* report significant changes in these biomarkers (Stetler and Miller 2011). It can thus be suggested that dysregulation of the ANS and/or HPA systems may only occur when a state of 'psychological distress' evolves into a mental health disorder. When people report being 'very stressed out' without showing a full-blown mental disorder, this feeling of distress might be more significantly related to an incapacity to regulate emotions than to a dysregulation of physiological stress systems. However, in the long run, these difficulties in regulating negative emotions may evolve into a physiological stress state, at which point a dysregulation will occur in one or more of the stress physiological systems and lead to the development of a mental disorder (Miller et al., 2007). Longitudinal studies measuring emotion regulation capacities over time and development of stress-related mental health disorders could provide very important data on this hypothesis.

The only difference in stress biomarkers observed between the two groups was that the 'very stressed out' group secreted significantly more cortisol 30 min after awakening than the 'zen' group. Greater secretion of cortisol within a period of 60 min post-awakening is part of the 'Cortisol Awakening Response' [CAR (Stalder et al., 2016)]. Although the CAR has been debated as stemming from a biological or a psychological origin (Stalder et al., 2016), it has been suggested that stressed

individuals may wake up with a feeling of mental overload that may create a negative appraisal of the upcoming day, which could then impact cortisol secretion (Kunz-Ebrecht et al., 2004). The finding that groups mainly differed in emotion regulation capacities and mind wandering, and the fact that only the +30 min after awakening sample was increased in the 'very stressed out' group goes along with this suggestion.

It is important to remind ourselves that when we are measuring levels of glucocorticoids in saliva, we are measuring the free portion of the hormone that has not crossed the blood-brain barrier to act on brain receptors located in the hippocampus, amygdala, frontal cortex and other regions of the brain (Lupien et al., 2009). It is thus possible that individuals who report being 'very stressed out' produce significantly more glucocorticoids than 'zen' individuals, but that a significant proportion of these hormones is acting on the brain on a chronic basis, leading to the feeling of subjective stress reported by these individuals. A study comparing salivary and blood cortisol levels in these two groups of participants could provide very important information on this issue [for an example of such an approach, see (Kirschbaum et al., 1999b)].

Another possibility to explain the absence of differences in biomarkers of stress between the 'very stressed out' and 'zen' group is that the relation between subjective and physiological markers of stress is not linear. An inverted-U shape function between circulating levels of glucocorticoids and cognitive performance has been repeatedly reported in animals and humans [for a review, see (Lupien and McEwen 1997)] and recent studies suggest the presence of a similar U-shape function between exposure to early adversity and biomarkers of stress (Cantave et al., 2021; Ouellet-Morin et al., 2021). It is thus possible that there exists an inverted-U shape function between subjective feelings of stress and circulating levels of stress biomarkers so that both ends of the distribution present similar levels of stress biomarkers. The presence of such an inverted-U shape function between subjective levels of stress and biomarkers of stress could also explain why many authors have failed to find significant (linear) associations between these two variables in previous years (Campbell and Ehlert 2012, Hjortskov et al., 2004).

Finally, there is still a possibility that the groups may have differed on biomarkers of chronic stress such as hair cortisol and/or allostatic load. As discussed in many papers by Bruce McEwen over the years, the various physiological stress systems adjust to resting and active states of the body to ensure adaptation [called allostasis (Sterling and Eyer 1988)]. Allostatic load refers to the cost the body pays for this adaptation when this adaptation needs to be maintained for long periods of time. From the standpoint of survival and health of the individual, the most important feature of the primary stress mediators associated with allostasis is that they have protective effects in the short run. However, they can have damaging effects in the longer time intervals if there are many adverse life events or if the secretion of hormones is dysregulated due to sustained stress responses. When this happens, it leads to allostatic load. It is possible that we did not find any significant difference in the stress biomarkers (cortisol and alpha-amylase) tested in this study because the 'very stressed out' group was still in an allostatic phase or the presence of an allostatic load in this group was related to dysregulation of one or more of the *other* biomarkers of stress. Future studies assessing multiple biomarkers of acute and chronic stress should provide valuable information on this issue.

Although the results of this study are very interesting, there are limitations to our experimental protocol that are important to take into consideration for the development of future studies on this topic. First, we did not measure exposure to early adversity in our study participants. Given previous studies showing that exposure to early adversity can modify the developmental trajectory of the brain (Lupien et al., 2009), it could be possible that what best distinguishes 'very stressed out' versus 'zen' participants is stress experienced early in life. Future studies should thus assess this important factor in order to better delineate the effects of early versus actual stress on the obtained results. Second, it is important to note that the human stress response can also be assessed with other physiological measures such as blood pressure and heart rate variability and that concordance between these peripheral measures of the stress response and circulating levels of glucocorticoids is not always reported (Andrews et al., 2013). It is thus possible that we may have found group differences on these measures. Future studies should thus try to incorporate a large set of physiological markers of stress in order to better understand the nature and extent of associations between subjective markers of stress and stress biomarkers in humans.

In summary, the results of this study show that people who complain of being 'very stressed out' present greater difficulties in regulating their emotions and are more prone to mind wandering than people who state that they are 'zen'. Recent studies suggest that mind wandering could represent a risk factor for depression in healthy adults (Smallwood et al., 2007) because the constant attention allocated to threatening information, paired with difficulties in regulating the negative emotions that emerge from this processing could lead to cognitive vulnerability to depression (Beevers 2005; Smallwood et al., 2007, Smallwood et al., 2007). This suggests that it might be a good strategy to teach emotion regulation strategies to children and/or help parents teach these cognitive coping strategies to their offspring (England-Mason and Gonzalez 2020).

Although teaching emotion regulation strategies could help individuals decrease their subjective feelings of stress, we would still be facing what some scientists have called the *'stress test'* (Raio et al., 2013). The stress test is based on an interesting paradox: studies over the years have consistently shown that glucocorticoid elevations due to acute stress negatively impact cognitive functions (Lupien et al., 2009). Consequently, in stressful situations where people might benefit the most from what they learned about emotion regulation strategies, recall of what they learned may be impaired by the acute physiological stress response that they are experiencing. In other words, because of the effects of stress hormones on the brain, interventions created to teach people how to regulate their emotions may not pass the 'stress test'. This hypothesis is consistent with a study showing that after exposure to an acute stress, individuals were unable to retrieve techniques taught previously to regulate their emotions (Raio et al., 2013). These results help understand why strategies taught in the classrooms or other environments may not always have a significant impact in the real world, where stress can sometimes be omnipresent.

By better understanding the biological basis of the various psychological constructs related to stress (anxiety, emotion regulation, stress, adversity, hassles, distress, negative emotions, etc.), it will be possible, in future studies, to measure the unique and shared influence of each of these constructs on physical and/or mental health. This will allow us to pursue the work of Bruce McEwen and to better understand how 'stress' can get under the skin and under the skull.

CRediT authorship contribution statement

Sonia J. Lupien: Conceptualization, Methodology, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Sarah Leclaire:** Investigation, Methodology, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Danie Majeur:** Investigation, Data curation. **Catherine Raymond:** Investigation, Methodology, Supervision, Writing – review & editing. **Francelyne Jean Baptiste:** Data curation. **Charles-Edouard Giguère:** Formal analysis, Writing – review & editing.

Declaration of competing interest

We declare no conflict of interest.

Data availability

Data is available on Open Science Framework and DOI provided in the paper.

Acknowledgements

This study was funded by a Foundation Grant from the Canadian Institutes of Health Research. The work of SJL is supported by a Canada's Research Chair on Human Stress.

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