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ORIGINAL ARTICLE

Acute stress response to a cognitive task in patients with major depressive disorder: potential metabolic and proinflammatory biomarkers

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Abstract

Responses of the hypothalamic-pituitary-adrenal axis (HPAA), immune system and metabolic pathways are involved in adaptation to stress, while alterations in these responses have been implicated in the development of major depressive disorder (MDD). Multiple laboratory indices are known to react in response to the acute stress, however, no valid biomarkers have been reported, which can differentiate stress response in depressed individuals. The aim of this study was to assess changes in a set of laboratory parameters in patients with MDD in response to a moderate mental stress and to find potential markers of altered stress reactivity associated with depression. A group of 33 MDD patients and 43 control subjects underwent clinical evaluation to assess depression and anxiety symptoms, as well as heart rate variability (HRV) analysis. Participants were asked to perform a time constrained cognitive task, and selected hormones (cortisol, ACTH), cytokines (IL-6, IL-1β, TNF-α), neurotrophic factors (BDNF, CNTF) and metabolic parameters (glucose, cholesterol, triglycerides) were measured before and 60 min after the task performance. HRV analysis showed increased sympathetic input in MDD patients. The MDD group manifested an elevated HPAA activity as well as IL-6 and CNTF levels at baseline. A specific stress-induced increase in glucose and TNF-α was revealed in the MDD group, which was absent in control subjects. The data confirm the impairments of stress response in MDD and suggest that the reaction of simple metabolic and pro-inflammatory indices to a mild stressogenic challenge may be indicative of a depressive state.

Keywords Stress · Major depression · HPAA, inflammation · Metabolism · Autonomic regulation

Introduction

The role of both chronic and acute stress in the pathogenesis of major depression disorder (MDD) is widely discussed, changes in hypothalamic-pituitary-adrenal axis (HPAA) activity, activation of a proinflammatory response and cytokine production, as well as changes in neuroplasticity and autonomic regulation being considered as the major links (Miller et al. 2009; McEwen 2017). Experimental models show that the HPAA stress response is mediated by input from limbic structures including the medial prefrontal cortex, lateral septum and amygdala, both activating and inhibitory pathways interacting with hypothalamic and brainstem nuclei (Myers et al. 2016). The resulting autonomic and psychological reactions are further modulated by glucocorticoid feedback mechanisms (Ghosal et al. 2014).

HPAA-mediated stress response stimulates increased cytokine production through sympathetic catecholamine release (Bierhaus et al. 2003; Slota et al. 2015). Proinflamatory cytokines, including IL-6 and TNF-α, in turn, promote several signaling cascades and transcription of genes, ultimately altering production and reuptake of neurotransmitters, including serotonin (5-HT), which is believed to be closely involved in

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the mechanisms of MDD development and treatment resistance (Fabbri et al. 2017; O'Brien et al. 2007). MDD is associated with chronic increase in cytokine levels as well as more prominent proinflammatory response to acute stress (Pace et al. 2006). This is related to the shift in autonomic regulation towards increased sympathetic input typical for MDD patients as well as healthy individuals subjected to an acute stressor (Lee et al. 2012; Sgoifo et al. 2015). The accumulation of these changes over a lifetime, particularly in early life, affects the development of neural circuits involved in stress response and adaptation, altering the ability of the brain to "process" future stress experiences, with depression and other mental illness as possible outcomes of excessive allostatic burden (McEwen 2013).

In human subjects, evaluating markers of "allostatic overload" can be quite accessible in clinical settings, with the majority of measured variables routinely available in most clinical laboratories. Yet, absence of a comorbid somatic disorder, relatively normal laboratory parameters and individual variability makes it a challenge to develop a single sample diagnostic marker(s); hence measuring the reaction to a stressor seems to be an optimal way of assessing changes in stress/adaptation mechanisms.

The aim of this study was to assess a set of hormonal, inflammatory and metabolic parameters in patients with MDD and to test their alterations in response to a challenge (mild acute mental stress), in order to identify potential clinical markers associated with underlying neuroendocrine and immune alterations.

Methods

Study subjects and design

We recruited 33 in-patients with MDD at the Moscow Research and Clinical Center for Neuropsychiatry. All patients fulfilled inclusion criteria: age between 18 and 45 years; diagnosis of MDD; signed an informed consent for participation in the study. The exclusion criteria were: a present diagnosis or history of psychotic disorders, alcohol or drug abuse, serious neurologic disorders (stroke, dementia, severe traumatic brain injury, epilepsy, neurodegenerative conditions, etc.); endocrine disorders (diabetes, thyroid dysfunction); heart disease and other serious health conditions; severe hearing impairment or blindness; use of antidepressants within a year prior to inclusion into the study. Patients were diagnosed by a treating psychiatrist in the clinic. The evaluation included the 17-item Hamilton Depression Rating scale (HAMD-17, Hamilton 1960), and only subjects with moderate to severe depressive symptoms were included. None of the subjects reported suicidal thoughts or history of suicide attempts. Previous depressive episodes were not considered as exclusion criteria for the MDD group, however precise clinical data on recurrent depressive episodes was not consistently available. A group of 43 age matched control subjects were recruited among healthy volunteers without depressive or other neuropsychiatric disorders using the same exclusion criteria.

Patients entered the study on the day of their hospitalization after a treating psychiatrist confirmed the diagnosis of MDD. All patients were assessed on the same day using the 17-item Hamilton Depression Rating Scale (HAMD-17). All subjects also filled out the self-report Beck Depression Inventory (BDI; Tarabrina 2007) and the Spielberger State Trait Anxiety inventory (STAI; Hanin and Spielberger 1983). Demographic information included age, sex, education level, economic status and body mass index (BMI). Control subjects filled out the same self-report scales.

The study protocol was reviewed and approved by the local Ethical Committee and all procedures were carried out in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Stress task protocol

All subjects underwent a stress inducing cognitive task and blood samples were collected immediately prior to the task and 60 min after task initiation. These procedures took place in the morning after hospitalization before food or medication intake, starting between 8:00 and 8:45 am.

The stress inducing task consisted of testing on Schulte tables, which is a visual search task, commonly used for exercising attention, peripheral vision and speed of reading skills, and may be used for measurement of attention stability. This task was selected based on effectiveness in inducing a stress response in a pilot study previously performed in our center (Freiman et al. 2015) as a non-invasive and non-traumatizing stressor. Subjects were instructed to find and point out numbers from 1 to 25 distributed randomly in a 5×5 table. In part 1 of the test, subjects had to complete five trials with a different Schulte table each time, and were asked to perform each consecutive trial faster than the previous one. In part 2, the investigator switched the Schulte tables every 15 s, and the subjects were instructed to start the test (8 tables in total) from the beginning after each switch. The procedure took place in a distracting environment in a common area of the ward and lasted between 8 and 12 min, depending on the individual tested.

Measurement of clinical, biochemical and hormonal parameters

Biochemical and hormonal parameters were measured in serum obtained from fasting morning venous blood. Samples were collected in Gel/Clotting activator S-Monovette tubes

and centrifuged at 2000 g for 10 min at 8 °C on a Labmaster ABC-GF35R centrifuge. Serum aliquots were frozen and stored at −80 °C. Thyroid stimulating hormone (TSH), free triiodothyronine (fT3) and free thyroxine (fT4) were measured in serum via competitive enzyme immunoassay using applicable kits from BECKMAN COULTER (USA) on an ACCESS® 2 immunoassay system (BECKMAN COULTER, USA). Ciliary neurotrophic factor (CNTF) and brain derived neurotrophic factor (BDNF) were measured in blood serum using corresponding Quantikine ELISA kits(RnD Systems); interleukin 6 (IL-6), interleukin 1β (IL-1β), and tumor necrosis factor-α (TNF-α) were determined with corresponding Human high sensitivity ELISA kits (eBioscience, Bender MedSystems). Adrenocorticotropic hormone (ACTH) and cortisol were assessed in EDTA plasma samples using enzyme immunoassay kits from Biomerica (USA). Cortisol was measured on the ACCESS® 2 immunoassay system (BECKMAN COULTER, USA); ACTH, BDNF, and all proinflammatory cytokines were measured on an automated enzyme immunoassay analyzer (ChemWell 2910, USA) by two-site sandwich assay.

Laboratory biochemical parameters (glucose, bilirubin, creatinine, triglycerides, cholesterol, urea, ALT, AST, GGT, ALP) were determined in blood serum on the automated biochemistry A-25 analyzer with corresponding kits from Biosystems S.A. (Spain).

Cardiometric parameters

We assessed heart rate variability (HRV) as a baseline indicator of autonomic function in patients and controls. The recording was scheduled during the first days after hospitalization, but not the same day as the stress task procedure. Single channel electrocardiography (ECG) 5-min recordings were registered using a portable device with automatic HRV analysis with Medicom MTD software (Medicom MTD, Russia). During the recording, subjects were seated at rest with clip electrodes placed on forearms. *Time-domain measures* included the average normal-to-normal interval (RRNN) and the standard deviation of the NN interval (SDNN). *Frequency-domain methods* were used to evaluate power spectrum components: total power (TP), absolute power of very low frequency (VLF, <0.04 H), low frequency (LF, 0.04–0.15 Hz), and high frequency components (HF, 0.15–0.4 Hz) expressed in ms^2. Relative power of the VLF, LF and HF components were calculated as percentage of total power.

Statistical analysis

Statistical analysis was performed using StatSoft Statistica 10 software. The data are presented as mean ± SD. Mann–Whitney U test was used for comparison of age, BMI and psychometric scores between groups. $\chi 2$ tests was used in comparisons of the nominal demographic parameters. Laboratory parameters were analyzed with ANOVA, using Neuman Kells post-hoc test for comparisons between groups and between base and 1 hour after stress test measurements. Correlations were tested between selected cytokines using Spearman's correlation coefficient.

Results

Group characteristics

Table 1 presents the demographic information and clinical characteristics for the MDD and control group. The groups did not differ in age, sex, BMI, economic and marital status. The MDD group consisted of patients with moderate to severe depression. Illness duration was reported as 60 months in 2 of the patients and between 0.5 and 24 months in the rest of the group. Concomitant anxiety symptoms were diagnosed in approximately 45% of patients with MDD.

Heart rate variability parameters

Baseline HRV parameters were decreased in the MDD group with the mean RRNN of 715 ± 82 ms vs. 792 ± 102 ms in controls; and SDNN of 39.6 ± 19.2 ms for patients, compared to 60.0 ± 20.5 ms in the control group. Analysis of spectral components demonstrated significantly lower absolute powers of VLF, LF and HF in MDD patients compared to controls (Table 2). The relative power VLF, however, was significantly higher in the group with depression (44.7% ± 15.6% vs. 36.9% ± 11.1%; $p = 0.03$), whereas the HF relative power was decreased in the MDD group (15.8% ± 8.39% vs. 21.1% ± 11.3% in controls; $p = 0.047$) (Fig. 1). The examined groups did not differ significantly in the relative power of LF spectral component (37.8% ± 12.6% in patients vs. 41.9% ± 12.4% in controls; $p = 0.2$).

Hormonal, Proinflammatory,and metabolic parameters

Baseline biochemical parameters

Measurements of baseline hormone parameters in the MDD group showed elevated levels of cortisol (472.24 ± 121.36 nmol/L in patients vs. 401.16 ± 110.50 nmol/L in controls; $p = 0.027$) and ACTH (59.11 ± 31.70 pg/ml in patients vs. 38.36 ± 22.53 pg/ml in controls; $p = 0.00038$).

An elevation of Il-6 baseline level was observed in the MDD group (1.72 ± 0.89 pg/ml vs. 1.34 ± 0.84 pg/ml in controls; $p = 0.01$), as well as significantly elevated baseline CNTF (4.87 ± 2.27 pg/ml in MDD vs. 3.34 ± 1.54 pg/ml in controls; $p = 0.01$). CNTF is a member of the same cytokine

Table 1 Patient and control group population characteristics

Characteristic	MDD ($n = 33$)	Control ($n = 43$)	p value
Age (mean ± SD)	32.89 ± 7.82	30.51 ± 5.50	0.32
Sex (% females)	58	56	0.88
BMI (mean ± SD)	24.09 ± 5.23	22.64 ± 3.34	0.30
Economic status (% low/middle/high income)	6/90/3	11/81/7	0.50
Marital status (% single/married/divorced)	36/48/15	35/53/12	0.87
Psychological assessment scores (mean ± SD)			
HAMD-17	20.12 ± 4.13		
STAI state	57.17 ± 9.11	33.00 ± 7.21	>0.0001
STAI trait	54.48 ± 9.29	39.33 ± 9.33	>0.0001
BDI	24.42 ± 8.01	4.15 ± 4.19	>0.0001
Duration of depressive episode (weeks, median and range)	12 (5–24)		
Anxiety symptoms present (%)	45		

family as IL-6, and in our pooled study population we observed a correlation between the levels of these cytokines ($r = 0.28$; $n = 59$; $p = 0.03$). This correlation remained as a trend in the MDD group ($r = 0.36$; $n = 27$; $p = 0.07$), but was absent in the control group ($r = -0.06$; $n = 32$; $p = 0.74$). We also observed a correlation between TNF-α and IL-1β in the control group ($r = 0.46$ $n = 30$; $p = 0.01$), but not in depressed individuals ($r = 0.075$; $n = 24$; $p = 0.73$). No significant differences were observed between the MDD and control groups in IL-1β or TNF-α levels (Fig. 2 e and f).

For major metabolic parameters, no significant baseline differences were observed between the MDD and control groups: glucose (4.93 ± 0.45 mmol/L in MDD vs. 5.14 ± 0.49 mmol/L in controls; $p = 0.058$) and triglycerides (1.29 ± 0.75 mmol/L in MDD vs. 1.12 ± 0.80 mmol/L in controls; $p = 0.60$; Fig. 2 g and h). We also did not find any significant difference in baseline BDNF levels in the MDD and control groups (26.93 ± 8.12 ng/ml vs.26.58 ± 6.91, respectively; $p = 0.85$) (Table 3 in Supplementary Material).

Table 2 HRV parameters in the MDD and control groups

Parameter	Units	Mean ± SD		p value
		Control	MDD	
RRNN	ms	792 ± 102	715 ± 82	0.0012
SDNN	ms	60.0 ± 20.5	39.6 ± 19.2	0.0001
VLF	ms^2	2827 ± 2338	1574 ± 2077	0.0005
LF	ms^2	2892 ± 1668	1578 ± 2323	0.0001
HF	ms^2	1551 ± 1381	1308 ± 4188	0.00003
relative VLF	%	36.9 ± 11.1	44.7 ± 15.6	0.03
relative LF	%	41.9 ± 12.4	37.8 ± 12.6	0.2
relative HF	%	21.1 ± 11.3	15.8 ± 8.39	0.047

Response to stress test (moderate cognitive task)

We observed a significant decrease of cortisol from baseline to 60 min after cognitive task in both patients and controls ($p = 0.04$ and $p = 0.00012$, respectively; Fig. 2a). Similarly, we observed a decrease in ACTH levels; however, this decrease was significant only in the MDD group (Fig. 2b).

Cognitive task induced a significant increase in the levels of TNF-α in the MDD group, without any significant response in controls (post-hoc test $p = 0.02$ and $p = 0.93$, respectively; Fig. 2f). We did not observe significant changes of IL-1β, Il-6 or CNTF 60 min after the test in either group (Fig. 2c, d and e).

We found a significant elevation of glucose levels 60 min after the stress in the MDD group (post-hoc test $p = 0.00015$; Fig. 2g), while its levels in controls remained close to baseline.

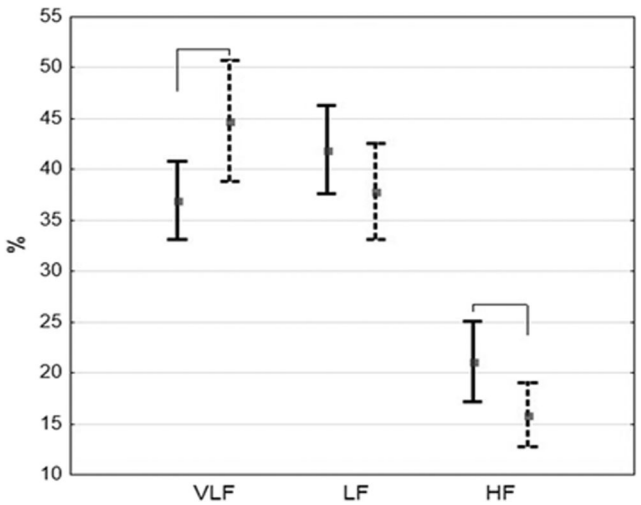

Fig. 1 Contribution of three spectral component in total power (%) for MDD patients (dotted line) and controls (solid line). Significance bars mark the difference between groups for the relative VLF ($p = 0.03$) and relative HF ($p = 0.047$) components

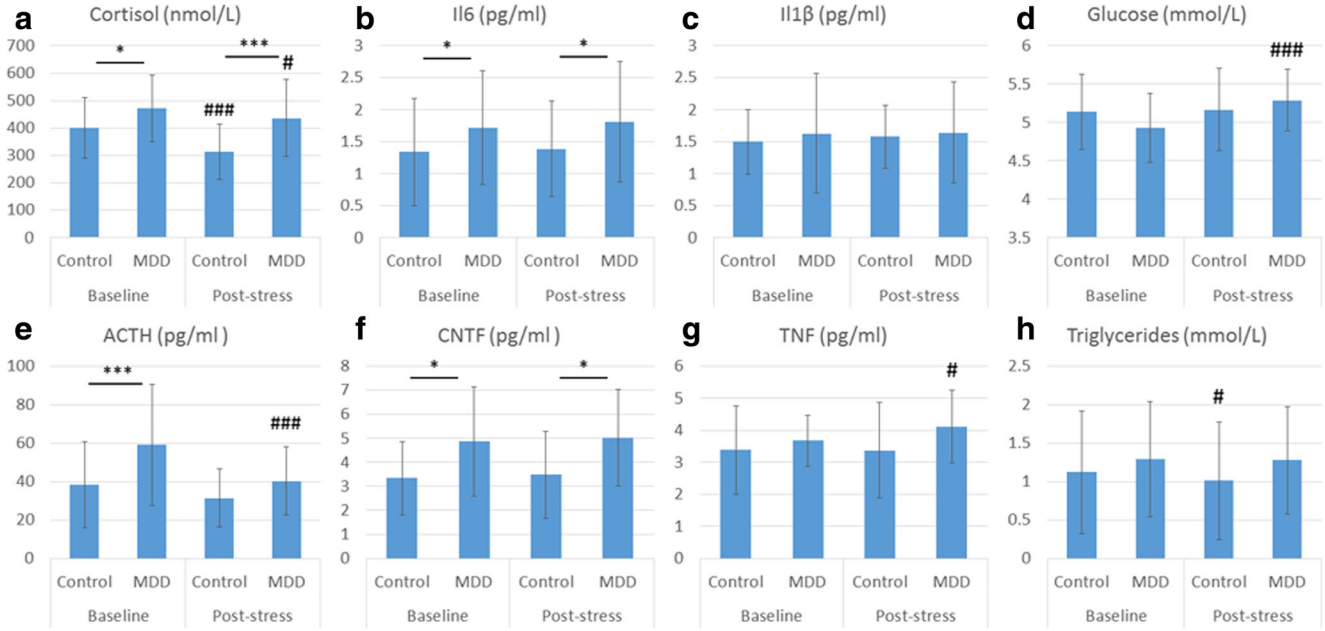

Fig. 2 Blood serum parameters at baseline and 60 min after cognitive task performance in healthy controls and patients with MDD. **a** Cortisol levels were elevated in the MDD group both at baseline and 60 min after cognitive stress (horizontal bars: $*p = 0.027$ and $***p = 0.00017$); changes in cortisol levels from baseline to 60 min in both controls and MDD ($###p = 0.00012$ and $\#p = 0.04$, respectively). **b** Adrenocorticotropic hormone (ACTH) levels were elevated in the MDD group at baseline ($***p = 0.00038$); ACTH levels decreased significantly in the MDD group after cognitive task ($###p = 0.00012$). **c** Interleukin 6 (IL-6) levels were elevated in the MDD group both at baseline and 60 min after cognitive stressor ($*p = 0.013$; $**p = 0.009$). **d** Ciliary neurotrophic factor (CNTF) levels were higher in the MDD group both at baseline ($*p = 0.01$) and at 60 min ($*p < 0.01$) after cognitive task. **e** Interleukin-1β (IL-1β) levels showed no difference between groups both before and after cognitive stress. **f** Tumor necrosis factor-α (TNF-α) levels were increased at 60 min following cognitive stress in the MDD group only ($*p = 0.02$). **g** Glucose levels were elevated at 60 min post-stress in the MDD group only ($###p = 0.00015$); for illustration purposes the diagram axis for glucose is shown from 3.5 since this is a homeostatic parameter with very narrow fluctuations borders in relatively healthy individuals. **h** Triglyceride levels were decreased at 60 min post-stress in the control group only ($##p = 0.0076$), remaining at similar levels in the MDD group

Conversely, triglyceride levels which tended to be higher at baseline in MDD patients as compared to controls, significantly decreased in the control group, with only a trend in the MDD group (post-hoc test $p = 0.09$ in MDD vs. $p = 0.0076$ in controls; Fig. 2h).

Table 3 (Supplementary Material) presents the complete results of the ANOVA analysis for the differences between groups before and after the cognitive task performance.

Discussion

The main finding in our study is the altered pattern in laboratory biochemical indices response to a mental stress in patients with moderate to severe depression as compared to healthy individuals. Baseline alteration in HPAA and cytokine activity, as well as in cardiometric parameters indicate well-known basal neuroendocrine and immune changes in the MDD group. The use of a non-traumatizing cognitive task as the stressor simulates a situation potentially encountered frequently in daily life, emphasizing that even in the absence of severe stress depression is likely to be associated with chronic stimulation of HPAA activity, cytokine production and shifts in autonomic regulation. The change in glucose and TNF response to a non-traumatizing stressor in MDD patients makes them potential markers of neuroendocrine, immune, and metabolic activity in the "depressed" brain, specifically, their reactivity to a mild challenge.

Glucose is an indicator of catabolic activity, which, in response to acute stress, is mediated by catecholamine release and sympathetic activity (De Boer et al. 1990). The adrenalin release is virtually immediate and activates the sympathetic system response as well as glucose metabolism; experimental data and data from healthy individuals demonstrate that glucose levels return to initial levels relatively quickly after an acute stress response (Moan et al. 1995; Sim et al. 2010; Jones et al. 2012). A study in healthy individuals with experimentally induced hyperinsulinemia and controlled euglycemia, demonstrated that individuals with the greatest sympathoadrenal response also manifested a greater rate of glucose uptake during mental stress conditions (Moan et al. 1995). At the same time, there many reports on a decreased sensitivity to insulin in conditions of chronic exposure to glucocorticoids (Steiner et al. 2014; review in Geer et al. 2014). It is likely, that in the MDD group we observed a delayed uptake of glucose, which was released during the initial

sympathoadrenal response. Our results confirm findings from a pilot study with a similar protocol comparing patients with depression and anxiety disorders with healthy controls, paralleled in an experimental rodent model of depression (Freiman et al. 2015).

So far, few data are available on the stress response of TNF in depressed individuals. Several studies demonstrate a stress response in persons without mood disorders (Slavish et al. 2015), however the stressors in these studies were significantly longer and different from our protocol (e.g. giving a 2 h lecture, 60 min exercise). Previously, Wieck et al. (2014) demonstrated a decrease in the levels of the TNFR1 receptors 40 min following acute psychological stress both in healthy and bipolar subjects. Taking into account available deta, our results and suggest that this cytokine is involved in the response to acute stress and that its response is different in MDD and healthy individuals; however, the extent and timing of its activity should be studied further. Depending on conditions and the receptor involved, TNF can activate pro-apoptotic or survival signaling pathways (Berthold-Losleben and Himmerich 2008). Savitz et al. (2013) performed a study of gene expression and MRI correlates; they found the TNF gene to be overexpressed in adult MDD and bipolar patients (age 35 ± 10 years), and this differential expression correlated with grey matter volume in the caudate nucleus. A pilot MRI study in elderly patients with MDD demonstrated an association between plasma TNF levels and white matter hyperintensity volumes (Smagula et al. 2017). These data suggest that excessive TNF release may possibly be a marker of damaged immune mechanisms in mood disorders and its assessment before and after a stress test, as in our study, may have potential diagnostic or prognostic value.

Pro-inflammatory drive is believed to be one of the key mechanisms of depression pathogenesis (Pace et al. 2006). Previous studies reported an elevation of TNF-α as well as IL-1β in depressed individuals (Dahl et al. 2014; Grassi-Oliveira et al. 2009), however in our study the baseline levels of these cytokines did not differ significantly between the MDD and control groups. This may be explained by differences in depression severity and some other specific features in our patient population and cohorts studied by other groups. Sloan et al. (2007) demonstrated that decreased parasympathetic vagal tone is associated with elevated cytokine production (specifically IL-6 and C-reactive protein), which corresponds to the baseline elevation of IL-6 in our patient group and is consistent with an activation of the immune response in depressed individuals (Miller et al. 2009; Sesayama et al., 2013). A recent review of salivary cytokine measurements in response to acute stressors demonstrated an increase in their levels to different degrees in studies with different approaches, with the greatest increase for IL-6 within the first 20–30 min following stressor application (Slavish et al. 2015). Few data was available on IL-1β response to acute stress, however in a single study the response was registered 10 min after a cognitive stressor (Mastrolonardo et al. 2007).

The role of CNTF levels in MDD is not extensively studied, with few inconsistent data from experimental and genetic polymorphism studies (Grünblat t et al. 2006; Peruga et al. 2012). Although we did not observe a statistically significant elevation of CNTF in response to stress, its levels would need to be measured at more time points for more detailed and deep investigation.

The reaction to acute stress in subjects with MDD regarding HPAA activity has been studied extensively both in healthy individuals and persons with depression and anxiety disorders (Peeters et al. 2003; Burke et al. 2005). It plays an important role in modulation of the inflammatory response to chronic stress (Miller et al. 2009). The increase in baseline cortisol and ACTH in our MDD group corresponds with chronic HPAA hyperactivity described by many groups (Miller et al. 2007; Wei et al. 2015; Pochigaeva et al. 2017), which may be linked to decreased HRV and lowered parasympathetic influence (Thayer and Sternberg 2006). It should be emphasized that in our protocol, direct interpretation of the cortisol and ACTH response to the cognitive stressor is limited by the relatively long 60 min time interval since there are expressed diurnal changes of these hormones during the morning hours when the procedure took place. The decline of ACTH 60 min after task performance only in the MDD group may be partially explained by the cortisol negative feedback suppression effect on ACTH secretion, potentiated by the elevated baseline cortisol levels in this group (Raff et al. 2014). In control subjects, the initially lower cortisol levels may have resulted in lesser suppression of ACTH in the course of its diurnal decrease.

The decline of triglycerides in the control group is difficult to interpret unequivocally. Wirtz et al. (2009) previously demonstrated an elevation and subsequent decline of triglyceride, cholesterol and low-density lipoprotein levels in hypertensive subjects with a enhanced sympathoadrenal response following a mental stress task, suggesting that the shift in autonomic regulation towards sympathetic influence (also described in MDD) might be associated with fluctuations in lipid levels when stress occurs. In normotensive subjects their levels dipped or declined steadily over 80 min, which corresponds with the result in our study. Assessments of the stress response of lipid parameters may be useful in understanding to what extent mildly stressful events promote the comorbidity between MDD and cardiovascular disease, as well as point to possible targets for prevention measures (Wirtz et al. 2009; Goldstein et al. 2015).

Evaluation of autonomic function, an accessible physiological marker associated with mood disorders, was used in our study as an additional parameter for characterizing the patient population. Steady decrease of parasympathetic tone, as

assessed by lower input of the HF power component, has previously been described both in adults and adolescents with depressive symptoms (Kemp et al. 2010; Blood et al. 2015), and a similar tendency is evident in our patient group. The relative power of the LF component was not significantly changed in MDD patients and we cannot directly infer change in sympathetic activity; however, lowered relative HF power indicates a decrease of parasympathetic inhibition on sympathetic signaling (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Sgoifo et al. 2015). The VLF component does not have a clear association with autonomic regulation and is usually not included in the assessment of sympathetic-parasympathetic balance (Sassi et al. 2015). Its prognostic value, however, was demonstrated in studies of outcomes in myocardial infarction and chronic heart failure (Huikuri et al. 2000; Guzzetti et al. 2005). Increase of the relative VLF power was also associated with severity of depressive symptoms in adolescents (Blood et al. 2015), which corresponds with the findings in our adult study population.

Our data confirm the impairments of stress response in MDD and suggest that the reaction of simple metabolic and pro-inflammatory indices to a mild stressogenic challenge may be indicative of a depressive state. However, there are several limitations of this study which may be relevant for the interpretation of the data. A limitation in our study was the relatively long time window between the testing stress onset and response assessment. It would be reasonable to confirm these results on larger groups of subjects, timing the stress-response protocol to reduce confounding from diurnal fluctuations. Although we did not include patients, who had been treated with antidepressants for the current episode or within a year prior to the study, data were not uniformly available on antidepressant use during previous years. The influence of childhood and recent stressful events was beyond the scope of our protocol; however, these are important factors in the neuroendocrine, immune and metabolic changes seen in depression (McEwen 2013), and any valid system of stress response biomarkers would have to account for age and gender norms, as well as evaluation of the lifetime allostatic load. The glucose and TNF responses seen in our study only in MDD patients suggest that these parameters may be useful as markers in mood disorders when measured at a defined time point after a standardized stress task.

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Compliance with ethical standards

Declaration of interest None of the authors had conflict of interest to declare.

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