**POSTERS**

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**Effect of psychosocial stress on FKBP5 and NR3C1 gene expression in healthy young men**

Stress diseases such as affective disorders are often characterized by a disturbed regulation of the hypothalamus-pituitary-adrenocortical (HPA) axis. This dysregulation can be explained by an impaired function of the receptors involved in the HPA-axis regulation, for example, the glucocorticoid receptors (GR). The regulation process of the HPA axis and the GR function are influenced by several genes, for instance by NR3C1 coding for the GR and also by FKBP5, a co-chaperone in the GR-complex. Binder et al. showed that common polymorphisms in FKBP5 are associated with increased FKBP5 protein expression as well as correlation between cortisol levels and peripheral blood FKBP5 mRNA expression. Regarding the effects of FKBP5 genotypes on psychosocial stress reaction, Ising and colleagues tested healthy subjects with the Trier Social Stress Test, a standardized paradigm to induce psychosocial stress. Subjects homozygous for any of the FKBP5 variants showed an incomplete normalization of the stress induced cortisol secretion.

Recent studies demonstrated that FKBP5 and NR3C1 are involved in the endocrine stress reaction. Therefore, we expected changes of FKBP5 and NR3C1 mRNA expression in peripheral blood after exposure to a psychosocial stress situation. To address this, we performed a pilot study where we tested six healthy young men without history of psychiatric or severe somatic disorders and applied the trier social stress test (TSST). Before and after two consecutive TSSTs, we took blood samples with a venous catheter in order to measure ACTH and cortisol in plasma and mRNA expression of the candidate genes in peripheral blood. Blood cells were stabilized using PAXgene tubes, and gene expression was processed by qPCR.

Briefly after the psychosocial stress the stress hormones ACTH and cortisol increased whereas the reaction to the second TSST was lower suggesting a habituation effect. These endocrine stress responses were followed by an alteration in FKBP5 gene expression, further underlining the importance of this gene for the neuroendocrine stress reaction. NR3C1 mRNA levels did not change after the TSST.

Our preliminary data indicate an effect of psychosocial stress on the FKBP5 mRNA levels. Further research with larger samples sizes is required to replicate and extend these results.

**Keywords:** HPA axis; FKBP5; NR3C1; gene expression; stress hormones; TSST

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**A delay and trace fear conditioning paradigm in humans: time-dependent effects of corticosteroids?**

**Background:** Corticosteroids are released in response to stress and have been shown to influence affective learning in rodents and humans. Many models of pathogenesis of affective and anxiety disorders have incorporated stress and cortisol as vulnerability factors. A well-established paradigm to investigate emotional learning and memory processes is classical fear conditioning.

**Method:** Here, we set out to investigate corticosteroid effects on fear acquisition and memory retention in healthy men (n = 63). We first successfully established a within-subjects paradigm to evaluate both delay and trace fear conditioning in humans, measuring electromyogram (EMG) startle responses, skin conductance responses, and unconditioned stimulus (US) expectancy scores. In delay conditioning, the presentation of the conditioned stimulus (CS) is directly followed by the US, whereas in trace conditioning, there is a stimulus-free period between the offset of the CS and the US. This distinction is of special interest because the hippocampus, a brain area that is important for learning and memory and one of the main targets for corticosteroids, is suggested to code temporal information during the stimulus-free period in trace conditioning.

**Results:** We specifically targeted time-dependent effects of corticosteroids on fear conditioning in this within-subjects delay and trace conditioning paradigm by administering 10 mg hydrocortisone either 4 h or 1 h before fear
acquisition. Twenty-four hours later, subjects came back for a fear memory retention test followed by extinction. Analyses show that hydrocortisone impaired trace acquisition specifically on EMG startle responses, regardless at which time point it was administered. However, we found an enhancement of EMG fear responses to the trace stimulus 24 h later only when corticosteroids were administered 4 h before acquisition.

**Conclusions:** This indicates that slow corticosteroid effects before acquisition lead to better retention of the fear memory for trace conditioning the next day.

Keywords: fear conditioning; EMG; hydrocortisone; startle response; cortisol

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**Psychological stress levels and autonomic activity in everyday life are related to stress responses in the laboratory**

**Rationale/Statement of the Problem:** Associations between stress levels in everyday life and controlled laboratory conditions remain a controversial topic. The aim of the present study was to compare psychological and physiological stress levels assessed in a real-life setting with laboratory stress levels.

**Methods:** Thirty-five healthy male students (age M = 24.4, SD = 2.6 years) took part in the study. The first part of the study consisted of a 2-day period within which subjects collected saliva and rated their stress levels on a visual analogue scale immediately after awakening, 30 min later, at 9am, and then every 2 hours for a total of nine times a day while maintaining their regular daily activities. Salivary alpha-amylase (sAA) was assessed as a marker for autonomic nervous system activity at each time point. In the second part, subjects were invited to two laboratory sessions on two separate days, with randomized exposure to either a standardized stress test (cold pressor test (CPT), stress condition) or a rest condition (reading magazines). Again, sAA and subjective stress were assessed repeatedly during both conditions.

**Results:** During both days, sAA levels showed a distinct diurnal rhythm, with a trough in the morning and a steady increase over the course of the day (time effect, \( p < 0.001 \)). Self-reported stress levels significantly fluctuated over the course of the 2 days (time effect, \( p = 0.022 \)). In the laboratory part, the CPT resulted in significant increases in sAA and in self-reported stress levels (time effect, \( p = 0.004 \); interaction effect, \( p = 0.001 \)). Regression analyses revealed that overall sAA levels in everyday life predicted sAA levels in both laboratory conditions (\( p < 0.01 \)). The same held true for subjective stress levels (\( p < 0.001 \)). It was also found that overall subjective stress levels in everyday life predicted the psychological laboratory stress response (\( p = 0.024 \)). Furthermore, a trend was found for the sAA awakening response predicting overall sAA in the stress condition (\( p = 0.067 \)).

**Conclusions:** Stress levels in everyday life were shown to predict psychological as well as physiological stress levels in the laboratory. Furthermore, subjects with high stress levels in everyday life experienced a more pronounced psychological stress response to a laboratory stressor.

Keywords: cold pressor test; alpha-amylase; stress response; daily stress; autonomic activity

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**Intercorrelations between serum-, salivary- and hair-cortisol and child-reported estimates of stress in elementary school girls**

To evaluate the impact of stress on children's well-being, it is important to have valid and reliable stress assessment methods. Nevertheless, selection of an appropriate method for a particular research question may not be straightforward, as there is currently no consensus on a reference method to measure stress in children. This paper examined to what extent childhood stress can be estimated accurately by commonly applied stress measures.
Two hundred and seventy-two girls between 5 and 11 years old participated in this study as part of the ChiBS project. Child-reported estimates of stress were collected through the Coddington Life Events Scale (CLES). Serum, saliva and hair samples were collected for cortisol analyses. The intercorrelations of cortisol in the different biological samples were investigated by Spearman rank correlations and Bland-Altman plots. Next, CLES-scores, salivary and hair cortisol concentrations were compared triangularly with the true, but unknown childhood stress using the Triads method, based on pair-wise Spearman's correlation coefficients and the calculation of validity coefficients.

Serum cortisol (free and total) was positively correlated with salivary morning and AUC cortisol. Hair cortisol correlated with salivary morning and AUC cortisol, but not with serum cortisol. In relation to recent childhood stress (0–3 months ago), the highest validity coefficients were observed for salivary cortisol measurements, while for periods more distant in the past hair cortisol measurements displayed the highest validity coefficients.

This paper investigated the relationship between cortisol measurements in different biological samples, showing a lack of association and disagreement between measures of single-point, short-term cortisol versus long(er)-term cortisol. In addition, this paper examined to what extent childhood stress can be accurately estimated by stressor questionnaires and biological markers in girls. Salivary cortisol was shown to most accurately indicate true childhood stress for short periods in the past (i.e. last three months), whereas hair cortisol may be preferred above salivary measurements for periods more distant and thus for chronic stress assessment.

Keywords: cortisol; child; stress; questionnaire; biomatrices

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Brief cognitive interventions interact with resilience to modulate ACTH response to the Trier Social Stress Test

Rationale/statement of the problem: Stress undermines health, perhaps via activation of the hypothalamic-pituitary adrenal (HPA) axis. There is evidence that psychological factors (i.e., sense of control, familiarity, effective coping, and social support) can buffer stress effects and HPA axis activation. There is also evidence that resilience and compassionate goal orientations (striving to help others rather than promoting the self) are associated with health and well-being, perhaps via HPA-buffering effects. We utilized a laboratory model of social evaluative threat (Trier Social Stress Test, TSST) to activate the HPA axis and study the stress-buffering effects of control, familiarity/coping, and compassionate goals, testing for interactions with resilience. Cortisol results were previously presented (41st International Society of Psychoneuroendocrinology (ISPNE) annual conference). Adrenocorticotropic hormone (ACTH) responses, which have now been analyzed, have strengthened the original findings.

Methods: Healthy participants ($n = 54$) were exposed to a TSST after receiving a standard instruction or one of three intervention instructions (access to control over threat exposure, cognitive intervention to increase familiarity and effective coping, or a compassion intervention designed to shift goal orientation from self-promotion to helping others). ACTH responses were analyzed using a median split into low and high resilient participants (CD-RISC, Connor and Davidson, 2003).

Results: Overall, the type of instruction significantly interacted with resilience in modulating ACTH responses throughout the TSST ($p = 0.006$). Low resilient participants receiving the coping intervention demonstrated higher ACTH baseline levels when compared to the other instruction groups. High resilient subjects given the compassion intervention showed reduced ACTH reactivity to the stressor relative to the other instructions.

Conclusion: The ACTH results mirror previously reported findings with cortisol responses to the TSST: Coping instructions increased anticipatory stress in low resilient participants, whereas compassionate goal instructions reduced stress reactivity to the TSST in high resilient participants. Further work assessing individual differences in resilience, and tailoring stress inoculation techniques accordingly, may facilitate development of more effective means of reducing the detrimental health effects of stress.

Keywords: HPA-axis; ACTH; TSST; resilience; cognitive intervention

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Salivary cortisol is not a valid marker of stress-related exhaustion

Salivary cortisol has frequently been used as a biomarker of chronic stress. The results have differed considerably between studies, which could to some extent be explained by the various definitions of chronic stress cases, ranging from patients with a clinically diagnosed condition to working individuals scoring high on burnout questionnaires. Thus, it is not possible to generalize findings in the literature to stress-related conditions encountered in the clinic and it is difficult to apply the knowledge in diagnosis and treatment. The aim of this study was to elucidate the usefulness of basal salivary cortisol as a marker of chronic stress in a clinical population with stress-related exhaustion.

We have measured salivary cortisol concentrations in two different samples of patients with a clinically diagnosed exhaustion disorder (ED). ED is defined as physical and mental exhaustion experienced for at least two weeks, caused by exposure to one or more stressors for a minimum of six months. In the first study, 162 patients (64% females) collected saliva samples at awakening and 15 minutes thereafter to assess the cortisol awakening response. This patient group was compared with 79 healthy controls (49% females). The patients repeated the saliva sampling at follow-up assessments after 3, 6, 12, and 18 months of treatment. The second study of 68 patients (79% females) included saliva samples taken at awakening, 30 minutes thereafter and at bedtime on two consecutive days to assess the diurnal profile, and follow-up assessments after 6 and 12 months. This study included 98 healthy controls (56% females). Age, sex, BMI, antidepressant use, and physical activity were considered as potential confounders.

No significant differences were found between patients and controls in salivary cortisol awakening response (first study) or diurnal profiles (second study). Furthermore, follow-up measurements in patients indicated that salivary cortisol concentrations did not change significantly during treatment.

Salivary cortisol levels, at least as measured in this study, apparently provide a rather poor reflection of the long-term stress exposure experienced by the patients in this study. Thus, basal salivary cortisol measurements are not recommended as a biomarker of stress-related exhaustion.

Keywords: burnout; exhaustion; HPA-axis; longitudinal; salivary cortisol

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Stress and the choice of competition in an economic tournament game

Rationale: Recent research on stress and decision making highlights the importance of considering the reciprocal relationship of these processes. Indeed, everyday experience suggests that economic decision situations can be stressful in and by themselves, particularly if they involve psychosocially stressful elements like competition. It is, however, at present not known whether or not physiological reactions elicited by the decision situation influence the decision that is reached. According to Salvador and Costa [Salvador, A. & Costa, R. (2009). Coping with competition: Neuroendocrine responses and cognitive variables. Neurosci Biobehav Rev, 33(2), 160–170], effects of competition (i.e., positive vs. negative outcomes) critically depend on the nature of applied coping strategies that are in turn related to specific physiological changes.

Methods: Our study examined the physiological and subjective changes induced by an established economic laboratory competition paradigm in a mixed-gender sample of 104 healthy participants. A mental arithmetic task was performed first under a piece-rate payment scheme and afterwards under a tournament (i.e., winner-takes-it-all) condition (i.e., forced competition). In a third round, subjects decided how to be paid (i.e., piece rate or tournament).

Results: Our results indicate that the laboratory paradigm indeed elicited physiological reactions that were related to the voluntary choice of competition. Participants that chose tournament were more likely to appraise the situation as challenging and showed higher sympathetic nervous system reactivity and higher testosterone increase during the game.
Conclusion: As these physiological changes are associated with an active coping mechanism (Salvador & Costa, 2009), we conclude that while competition is not per se treated as a harmful stressor, the reciprocal effect on the decision to compete again seems to depend on the use of an active coping strategy.

Keywords: competition; decision making; stress; heart rate; testosterone; economic tournament

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The calm mouse: an animal model of stress reduction

Chronic stress is associated with negative health outcomes and is linked with neuroendocrine changes, suppressed immunity, and central nervous system neuropathology. While human studies have illustrated the benefits of stress reduction, mechanistic understanding of how decreasing stress affects health, and disease progression remains unclear. Furthermore, prior animal studies have focused primarily on increasing stress, and few animal models of stress reduction have been fully developed. Therefore, we have developed a “calm mouse model” with caging enhancements designed to reduce murine stress.

Male BALB/c mice were divided into four groups (n = 10/group): Control (Cntl), standard caging; Calm (Calm), large caging to reduce animal density, a cardboard nest box for shelter, paper nesting material to promote innate nesting behavior, and a polycarbonate tube to mimic tunneling; Control Exercise (Cntl Ex), standard caging with a running wheel, known to reduce stress; Calm Exercise (Calm Ex), Calm caging with a running wheel.

Calm, Cntl Ex, and Calm Ex animals exhibited significantly less corticosterone production than Cntl (Day 49: Calm, Mdiff 20.5 ng corticosterone metabolites/0.05 g feces (CM), CI95 11.7–29.4, P < 0.0001; Cntl Ex, Mdiff 22.5 ng CM, CI95 13.4–31.5, P < 0.0001; Calm Ex, Mdiff 21.8 CM, CI95 11.7–32.0, P = 0.0003). Calm animals gained greater body mass than Cntl, although they had similar weekly energy intake. We also observed changes in body composition, spleen mass, and spleen composition. In particular, we found that Calm mice had a significantly greater proportion and absolute number of splenic CD19+ B lymphocytes when compared with Cntl (proportion: Mdiff 6.7% of splenocytes, P < 0.0001; absolute number: Mdiff 9.04 × 10^6 cells, CI95 8.3 × 10^6 – 9.8 × 10^6, P < 0.0001).

Our data indicate that both Calm and exercise caging generated reductions in physiologic stress measures in mice and that Calm animals exhibited increases in splenocyte subpopulations that may underlie changes in functional immunity. Collectively, the Calm model represents a promising approach to studying the biological effects of stress reduction in the context of health and in conjunction with disease models.

Keywords: neuroendocrine; stress reduction; animal model; immunology; glucocorticoid

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Stressful life events, perceived stress and morning plasma cortisol in subjects with early psychosis

Statement of the problem: Stressful life events have been shown to have great influence on the onset or recurrence of psychotic symptoms [1]. Increased stressful life events [2], perceived stress [3], and higher cortisol levels [4,5] have been described in subjects with a first psychotic episode. The main aim of our study was to explore the relationship between stress measures and cortisol levels in subjects with early psychoses.

Methods: We included 85 subjects, aged between 18 and 35 years, who attended the Early Psychosis Program from Reus (Tarragona, Spain). All subjects were assessed at baseline using a structured clinical interview (Schedules for Clinical Assessment in Neuropsychiatry) to obtain a clinical diagnosis. We stratified the sample into three groups: Group 1, first episode of psychosis (FEP, N = 36); Group 2, critical period (CP, defined as a
psychotic disorder >1 year of duration of illness, \(N=35\); and Group 3, ultra high risk (UHR, subjects with prodromal psychotic symptoms, \(N=14\)). Perceived stress was assessed with perceived stress scale (PSS). Stressful life events during the previous 6 months were assessed with the Holmes Rahe Social Readjustment Scale. A fasting morning blood sample (9 h) was obtained to determine total cortisol in plasma. SPSS v.17.0 was used for the statistical analyses. Spearman correlations were used to explore the association between continuous variables. Wilcoxon test was used to compare continuous variables between diagnostic groups. A \(p\)-value < 0.05 was considered significant.

**Results:** In all subjects, stressful life events were positively associated with perceived stress \((r = 0.244, p = 0.033)\) but not with plasma cortisol levels. In the stratified analysis by diagnoses, no significant differences in stressful life events were found between all three groups. Subjects at risk for psychosis (UHR) reported greater scores in PSS \((30.6 \pm 11.7)\) than other groups (FEP: 27.0 \pm 0.1; CP: 20.9), this result being statistically significant \((p = 0.003)\). Those subjects from the critical period group showed increased plasma cortisol \((20.7 \pm 4.8)\) when compared to UHR \((18.9 \pm 6.4)\) and FEP \((18.12 \pm 4.5)\) groups.

**Conclusion:** UHR subjects report greater levels of perceived stress when compared to those subjects with a psychotic disorder. Stressful life events and perceived stress are associated but not with plasma cortisol levels.

**Keywords:** stress; perceived stress; psychosis; cortisol levels

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Hyperresponse to acute stress and poorer memory in former preterm children

**Background:** Preterm birth is marked by stressful environment in intra- as well as extrauterine life. Furthermore, preterms are exposed to repeated painful procedures, loud noise, and restricted contact with parents in the neonatal intensive care unit. This environment can affect hormonal and physiological systems and lead to long-term negative outcomes. Despite this, little is known about how early-life stress affects preterms later on in childhood. The goals of the current study were threefold: (1) comparing cortisol profile, including cortisol awakening response (CAR), between preterm and full-term children; (2) assessing memory, behavior, and emotion of preterms; (3) evaluating if preterms are more responsive to an acute stressor.

**Methods:** Basal cortisol and \(\alpha\)-amylase (sAA) profiles, including CAR of 30 preterm children were evaluated. Salivary samples were measured on two consecutive days at four time points: awakening, 30 min post-awakening, 1600h, and 2100h. Furthermore, we assess memory functions by using the wide range assessment of memory and learning and screen behavior/emotion by using strengths and difficulties questionnaire. The results of preterms were compared to an age- and sex-matched control group \((n = 31)\). One week after, the participants were exposed to Trier Social Stress Test for Children (TSST-C).

**Results:** We specifically targeted time-dependent effects of corticosteroids on fear conditioning in this within-subjects delay and trace conditioning paradigm by administering 10 mg hydrocortisone either 4 h or 1 h before fear acquisition. Twenty-four hours later, subjects came back for a fear memory retention test followed by extinction. Analyses show that hydrocortisone impaired trace acquisition specifically on EMG startle responses, regardless at which time point it was administered. However, we found an enhancement of EMG fear responses to the trace stimulus 24 h later only when corticosteroids were administered 4 h before acquisition.

**Conclusions:** Our findings illustrate the long-lasting effects of preterm birth on the hypothalamic pituitary adrenal (HPA) axis, internalizing behavior, and memory. The findings are in line with the idea that early-life stress alters the set-point of the HPA axis thereby creating a more vulnerable phenotype.

**Keywords:** preterm birth; cortisol; CAR; \(\alpha\)-amylase; memory; behavior; childhood

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Beyond the HPA-axis: the role of the gonadal steroid hormone receptors in modulating stress related responses in an animal model of PTSD

**Rationale:** The activation of the neuroendocrine systems is a basic response to environmental perturbations, which threaten homeostasis. The HPA-axis is one of the primary effector systems, which functions to minimize deviations from the homeostatic state and help to return equilibrium following a disturbance. It has been well established that products of the HPA-axis can directly inhibit the hypothalamo-pituitary-gonadal (HPG)-axis. Consequently, following chronic stressors reproduction is impaired.

**Method:** Animals were exposed to predator scent stress for 15 min. Behaviors were assessed with the elevated plus-maze and acoustic startle response tests, 7 days later. Trauma-cue response, circulating corticosterone and testosterone, and localized brain expression of androgen receptor (AR) and estrogen receptors were subsequently assessed. All data were analyzed in relation to individual behavior patterns. The behavioral effects of testosterone agonist, testosterone receptor antagonist (flutamide), or vehicle-administered systemic one hour before and 7 days after PSS-exposure were evaluated in the same manner.

**Results:** Animals whose behavior was extremely disrupted (EBR) selectively displayed significant down-regulation of AR in the hippocampus compared to animals whose behavior was minimally (MBR) or partially (PBR) disrupted and to un-exposed controls. One-hour pre-exposure treatment with testosterone significantly increased prevalence rates of EBR and increased trauma-cue freezing responses, compared to vehicle controls. In contrast, immediate pre-exposure treatment with flutamide significantly reduced prevalence rates of extreme responders and reduced trauma-cue freezing responses compared to vehicle and testosterone treatments. Moreover, treatment with testosterone 7 days post exposure significantly reduced prevalence rates of extreme responders and reduced trauma-cue freezing responses compared to vehicle and testosterone treatments.

**Conclusions:** The gonadal steroid hormones are actively involved in the neurobiological response to predator scent stress and thus warrant further study as a potential therapeutic avenue for the treatment of anxiety-related disorders.

**Keywords:** PTSD; animal models; gonadal steroid hormones; stress response; HPA Axis

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Anxiety symptom severity differentiates HPA acute stress reactivity in children

**Rationale/Statement of the problem:** Considerable research has focused on the relationship of anxiety with alterations in the hypothalamic-pituitary-adrenal (HPA) acute stress response. Findings, however, differ among studies on adults and children, and among different types of anxiety. This study investigates the relationship of anxiety symptom severity with HPA reactivity to the cold pressor task (CPT) in preadolescent children. We hypothesize that children with increased symptoms of anxiety will have increased cortisol (HPA) reactivity to the CPT.

**Methods:** A social-evaluative adaptation of the CPT was used to elicit HPA acute stress reactivity among 42 children (26 female, 16 male) aged 8–12 years (mean age, 10 years) recruited from a child anxiety disorders clinic (n = 20) and from the community at large (n = 22). Repeated saliva samples were assayed for cortisol to determine maximum task response (TR) and area under the curve with respect to the increase from baseline (AUCi). Multi-dimensional anxiety measures included the Screen for Anxiety and Related Disorders (SCARED: parent and child report); State Trait Anxiety Inventory-Trait (STAI-T), and Children’s Anxiety Sensitivity Index (CASI). Subjects were grouped according to recruitment source and high/low symptom measures (all subjects by anxiety measure median split); groups were compared via independent samples t-tests.

**Results:** Maximum cortisol TR and AUCi did not differ between children recruited from the anxiety disorders clinic and the community. Among all subjects, maximum TR was significantly greater for those with high anxiety symptoms on the STAI-T (p = 0.006), SCARED-C (p = 0.012), and SCARED-P (p = 0.031), and approached significance on the CASI (p = 0.056), compared to those with low symptoms on these measures. AUCi was greater among those with high symptoms on the SCARED-C (p = 0.01) and SCARED-P (p = 0.011), but not on the STAI-T (p = 0.113) or CASI (p = 0.072).
Conclusion: Results suggest that increased anxiety symptom severity is associated with greater cortisol reactivity to acute stress in preadolescent children. Moreover, findings were similar among youth recruited from the clinic and the community, thus providing additional evidence of the high prevalence of anxiety in children and the potential associated risk of alterations in physiological stress reactivity among those with more severe symptoms.

Keywords: anxiety; children; stress; cortisol; cold pressor task

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Effects of chronic family stress during development on attentional bias and psychobiological stress reactivity in women

Prior theory and research suggests that psychosocial stress during development may contribute to vulnerability to problems in adulthood in domains of both mental and physical health through alterations in both automatic attentional and psychobiological stress reactivity processes. We hypothesized that childhood exposure to family conflict would be related to variations in hypothalamic–pituitary–adrenal (HPA)-axis activity patterns and would moderate the relation between attentional bias to threat and biological stress reactivity to acute laboratory stress exposure.

A sample of young adult female participants (*n* = 116; mean age = 18.96 years, SD = 1.13 years) was classified based on their past exposure to family conflict during childhood and randomized in a crossover design to complete both a mild laboratory social stress task and a computerized task assessing attentional bias to threatening words. Salivary cortisol was measured continuously throughout the study.

Exposure to family conflict during development was significantly positively correlated with baseline cortisol in the sample as a whole (*r* = 0.35, *p* < 0.001) and total cortisol area under the curve (*r* = 0.26, *p* = 0.005). A linear regression analysis indicated a negative main effect of conflict exposure, *β*(3, 45) = −0.36, *p* = 0.022, and a significant interaction of the effects of conflict exposure and attentional bias to conflict stimuli on cortisol, *β*(3, 45) = −0.30, *p* = 0.42. Specifically, attentional bias to conflict stimuli was positively related to cortisol reactivity to an acute stressor, but only for individuals exposed to lower levels of family conflict during development.

Results suggest that exposure to chronic stress early in development shapes later perception and interpretation of environmental cues as stressful and has an enduring impact on biological reactivity to acute stress. These findings expand on earlier work by Luecken and colleagues presenting a combined cognitive-affective model to link characteristics of the family environment during development to alterations in psychological and physiological stress reactivity processes in adulthood, which may ultimately underlie illness vulnerability.

Keywords: chronic stress; cortisol; attentional bias; family conflict; attention

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Combination of early life stress and traumatic experiences across the lifespan are associated with shorter leukocyte telomere length in later adulthood: the Helsinki Birth Cohort Study

**Rationale:** Early life stress (ELS) poses a risk for mental disorders and aging-related physical diseases. Accelerated biological aging reflected in shorter leukocyte telomere length (LTL) may underlie these risks. Yet, studies examining associations between ELS and LTL have been scanty, elusive, and retrospective. We examined if objectively documented ELS in childhood, retrospectively, reported traumatic experiences across the lifespan and whether their combination is associated with LTL in later adulthood.

**Methods:** ELS, traumatic experiences, and LTL were present in 1,486 participants of the Helsinki Birth Cohort Study, born between 1934 and 1944 in Helsinki, Finland. Of them 215 were recorded as separated temporarily from their parents in childhood. The separations took place during World War II when Finnish children were voluntarily evacuated unaccompanied by their parents to temporary foster care abroad (mean age at and length of separation 4.6 and 1.7 years, respectively). Traumatic experiences across the lifespan were self-reported at age 63.2 years (SD = 2.8) using the Traumatic Experiences Checklist, and LTL was measured at age 61.5 years (SD = 2.9) using real-time quantitative polymerase chain reaction (PCR) method.

**Results:** LTL did not differ significantly by separation status or by having experienced traumas (p > 0.151). However, ELS and traumatic experiences interacted significantly in the analyses of LTL (p < 0.008). Those participants who were separated and had experienced an emotional trauma across the lifespan displayed shorter LTL than those who were not separated regardless of their traumatic experiences. In contrast, those participants who were separated but who had not experienced an emotional trauma did not differ in LTL from the non-separated.

**Conclusion:** ELS and traumatic experiences may, in combination, contribute to accelerated cellular aging and shed light into the underlying mechanisms linking ELS and early traumatic experiences with mental disorders and aging-related diseases.

Keywords: telomere length; early life stress; trauma; cellular aging; aging-related disorders

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**Enhanced increase in cortisol/DHEA ratio under prolonged stress in individuals with irritable bowel syndrome**

Recently, the hypothalamic–pituitary–adrenal axis activated by psychological stress has been reported to be involved in irritable bowel syndrome (IBS) symptoms. In the present study, we investigated the effect of prolonged stress (for two weeks) on salivary adrenal hormones in individuals with IBS. The participants were 23 female college students (mean age = 18.8 years), including 10 individuals with IBS met Rome II criteria and 13 individuals without IBS (control group), and they were scheduled for a two-week teaching practice at kindergarten. Participants were asked to collect their saliva immediately (T1), 30 min after awakening (T2), and before sleep (T3) at date of a month before (D1), 3 days after (D2), 7 days after beginning of teaching practice (D3), and several days after the end of it (D4). They also completed perceived stress scale (PSS) (D1–D4). Comparisons between groups and between dates in PSS score were done using 2-way analysis of variance. Linear mixed model was applied to analyze the effects of the presence of IBS, time, and date on salivary adrenal hormones (cortisol, dehydroepiandrosterone [DHEA], DHEA-sulfate [DHEA-S]). There were significant effects of day in PSS (p < 0.0001), cortisol (p = 0.002), and DHEA (p = 0.02) and significant effects of time in cortisol (p < 0.0001), DHEA (p < 0.0001), DHEA-S (p < 0.0001), and DHEA-S:DHEA ratio (p < 0.0001). A significant interaction between group and time was found in cortisol:DHEA ratio (F = 6.9, p = 0.001). Cortisol:DHEA ratio at T2 was higher than ratio at T1 and T3, and ratio at T1 was higher than ratio at T3 in both groups. Cortisol:DHEA ratio at T2 in IBS group was higher than that in control group. Cortisol:DHEA ratio in participants of the present study responded to prolonged stress, and individuals with IBS showed higher cortisol:DHEA ratio at 30 min after awakening than individuals without IBS during experiment period. These results of this study using prolonged stressor differs from that of our previous study using acute stressor that individuals with IBS showed lower DHEA-S level and DHEA-S:DHEA ratio throughout the experiment.
Glucocorticoids in hair in relation to cardiometabolic risk markers

Altered long-term secretion of glucocorticoid hormones is believed to play a pivotal role in linking chronic stress to cardiometabolic risk. Despite experimental data supporting this link, previous epidemiological field studies have often yielded inconsistent results. Amongst other things, this is likely to be related to methodological limitations in the assessment of glucocorticoid secretion over prolonged periods of time. The measurement of glucocorticoids in hair may constitute a major advancement here, enabling the assessment of cumulative hormone levels over periods of up to six months. Here we will present first data from a large industry-funded cohort study investigating links between work-related stress, long-term glucocorticoid secretion and cardiometabolic risk factors.

Hair samples were obtained from 1315 employees of the airline manufacturing industry and assayed for cortisol (F) and cortisone (E) concentrations using liquid chromatography with tandem mass spectrometry detection (LC-MS/MS). In addition, relevant anthropometric, psychosocial and physiological biomarkers of cardiometabolic risk were assessed.

Results reveal positive associations of hair F and E concentrations with measures of central obesity (body mass index, waist-to-hip ratio), resting systolic and diastolic blood pressure as well as fasting morning blood levels of glucose, glycated haemoglobin (HbA1c), C-reactive protein and high-density lipoprotein (negative). Significant positive associations with low-density lipoprotein and triglyceride levels were only seen for hair E but not for hair F. These findings are in line with current conceptions suggesting an important role of aberrant glucocorticoid secretion in the development of cardiometabolic risk. Implications of these data for hair analysis as an important future tool in epidemiological field research will be discussed.

Keywords: hair; cardiometabolic syndrome; glucocorticoid; stress; cortisol; cortisone
fulfilled the PTSD criteria. On SCL-90-R there was a significant reduction on four subscales; the obsessive-compulsive, interpersonal sensitivity, psychotism and the global severity index ($p$’s $< 0.05$). The total depression score on BDI-II were significantly reduced ($p < 0.05$), also intrusion on IES-R and its total score ($p < 0.05$). 6 months after treatment 7 of 14 patients (50%) (3 drop-outs) did not have PTSD according to CAPS, DES overall score was significant reduced ($p < 0.05$), as well as all scales on IES-R ($p$’s $< 0.01–0.05$) and CAPS ($p$’s $< 0.01–0.05$) except criterion B (re-experience symptoms). However, there was no longer a significant reduction on BDI-II total score or the SCL-90-R in total.

The results indicate that even in a relatively small sample, NET has value of transference and can also be a useful treatment for outpatients living in a nonthreatening environment. Further investigations are needed to assess more extended effects, in particular on depression.

Keywords: Narrative Exposure Therapy; treatment effect; PTSD; outpatients; depression

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Salivary cortisol profiles in multiple sclerosis patients with comorbid depression and posttraumatic stress disorder

Objectives: Multiple sclerosis (MS) as an inflammatory demyelinating disease of the brain and the spinal cord is associated with a high prevalence rate of major depressive disorder (MDD). Psychological stress has been linked to MS pathogenesis as well as relapse risk in established disease. Moreover, MS diagnosis itself may be a potential trigger for the development of posttraumatic stress disorder (PTSD). Both MDD as well as PTSD have been linked to altered hypothalamic-pituitary-adrenal (HPA) axis regulation and consecutively to elevated or lowered cortisol secretion. This study explores associations of PTSD and MDD with HPA activity in patients with MS.

Methods: In a cross-sectional sample of female MS patients, psychological comorbidities were diagnosed using the structured clinical interview (SCID). Circadian salivary cortisol profiles (AUC) and the cortisol awakening response (CAR) as markers of HPA axis activity were assessed over the course of 2 days. On the third day, low dose oral dexamethasone suppression was examined (post-Dex CAR/AUC).

Results: Forty-nine patients with relapsing-remitting MS were included. Eleven patients fulfilled diagnostic criteria for current MDD. A total of 14 patients were diagnosed with PTSD, 7 of whom developed PTSD related to MS-diagnosis. Patients with PTSD were not currently depressed. Importantly, patients with comorbid psychological disorders showed significantly lower coping resources such as self-efficacy, sense of coherence, and social support. While no significant differences were found in most measures of cortisol secretion between the three groups, we observed a trend for higher CAR after dexamethasone suppression in MS patients with PTSD.

Conclusion: The present study indicates a high frequency of MDD and PTSD in MS and associations to reduced salutogenetic resources. These comorbidities might be linked to different aspects of HPA axis dysregulation and could be associated to different biological pathways.

Keywords: multiple sclerosis; salivary cortisol; depression; PTSD; coping resources

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Effect of chronic stress and in vivo cortisol measures on immune cell glucocorticoid receptor expression and cellular immune activation

Chronic psychological stress increases inflammation, providing a mechanism for the elevated risk of infectious, autoimmune and cardiovascular diseases in chronically stressed persons. While the HPA axis plays an important role in mediating the link between stressful events and inflammatory processes, it is becoming increasingly clear that immune cells can become resistant to cortisol, resulting in diminished regulation of inflammation. One potential mechanism of cortisol resistance results from decreased glucocorticoid receptor (GR) expression in immune cells during elevated cortisol exposure.

Chronic stress results in chronic high cortisol exposure leading to decreased immune cell GR expression that in turn is associated with greater immune activation. Using flow cytometry we measured immune activation and GR expression (geometric mean fluorescence intensity [gMFI]) in 10 immune cell subsets in 25 post-menopausal females (10 caregivers [CGs] and 15 controls [CNTLs]). Mann–Whitney and Pearson correlations were employed for statistical analysis with \( p < 0.05 \) considered significant.

No statistically significant difference in daily cortisol exposure was observed between CGs and CNTLs; however, CGs did exhibit greater T cell immune activation (\( p = 0.029 \)). Contrary to our hypothesis, T cell immune activation was not associated with decreased GR expression. In fact, CGs had equal or a trend toward greater GR expression compared to CNTLs. CGs did demonstrate a statistically significant negative correlation between total daily in vivo cortisol levels and GR expression in CD4\(^+\) and CD8\(^+\) T cells (\(-0.74 (p < 0.02)\) and \(-0.81 (p < 0.02)\), respectively). Combining groups, we observed a positive trend in GR expression and perceived stress in two monocyte subsets (CD14\(^{br}\) and CD14\(^{dim}\)CD16\(^+\)). A statistically significant negative correlation between GR expression in the pro-inflammatory CD14\(^{br}\)CD16\(^+\) and CD14\(^{dim}\)CD16\(^+\) monocyte subsets and their relative frequency was also observed (\(-0.47 (p = 0.02)\) and \(-0.52 (p = 0.01)\), respectively). Elevated inflammation during chronic stress may not result simply from down-regulation of GR in immune cells. Cortisol and GR expression may influence the frequencies of pro-inflammatory monocyte subsets (CD14\(^{br}\)CD16\(^+\) and CD14\(^{dim}\)CD16\(^+\)) that may be important in regulating chronic inflammation.

Keywords: chronic stress; glucocorticoid receptor; inflammation; cortisol; immune activation; flow cytometry; HPA axis

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Impact of antenatal synthetic glucocorticoid exposure on endocrine stress reactivity in term born children

Background: Antenatal glucocorticoid (GC) exposure has been discussed as a potent programming factor of hypothalamus–pituitary–adrenal (HPA)-axis activity producing sustained alterations in cortisol secretion throughout life. So far, the assessment of HPA-axis activity in offspring of mothers treated with synthetic GCs has been limited to a time period shortly after birth, with prematurity being an important confound in most prior studies.

Method: The present study aimed to investigate HPA-axis reactivity of term-born children with antenatal GC exposure in a larger sample (\(N = 209\) children between 6 and 10 years of age), allowing to further address sex and drug specific effects. Cortisol secretion patterns in response to a standardized laboratory stressor (Trier Social Stress Test for Children) were assessed in children with antenatal GC exposure (a single course of either dexamethasone or betamethasone) and compared to different control groups.

Results: We observed significantly increased cortisol reactivity to acute psychosocial stress in 6–11 years old, term-born children exposed to antenatal synthetic GC treatment compared to controls (\(F(3.4,345.9) = 5.8, p < 0.001\)). This finding appeared to be independent of the specific synthetic GC used and was found to be more pronounced in females.

Conclusions: The present study provides first evidence for long-lasting effects of antenatal synthetic GC exposure on HPA-axis reactivity in term-born children. These findings may bear important implications regarding the vulnerability for stress-related physical and psychiatric disorders, for which dysregulation of the HPA-axis has been discussed as a potential causal factor.
Rationale: Problematic peer relationships in adolescence have long been linked with various psychological disorders, but there remain questions as to why adolescents with similar social experiences may suffer no psychological effects or why some respond with depression or anxiety while others become aggressive. Parenting style and level of chaos in the home environment have also been shown to have protective or detrimental effects in conjunction with social stressors. Adolescence is typified by substantial hormonal changes and maturation of both the pubertal and the stress systems. Ian Goodyer has suggested that atypical ratios of stress and pubertal hormones may be indicative of vulnerability for psychopathology. High cortisol and low DHEAS have been linked to depression, whereas the opposite has been found in those with aggression. This study is the first to examine the cortisol/DHEAS ratio as a moderator of peer stress in the development of psychopathology in adolescents. This investigation uses a biopsychosocial model to test the moderating role of parenting style, environmental chaos, and adrenal hormone ratios on the association between social stress and aggression or depression over a 1-year period.

Methods: Participants were 156 young adolescents (50% f; M age = 11 years, SD = 0.7), ethnically diverse, and predominantly middle to lower SES. Depressive symptoms, aggression, social stress, and environmental chaos were assessed via survey and interview reports from mothers and children. Parenting characteristics were assessed via mother survey. Saliva and urine samples were collected on multiple mornings to measure cortisol and DHEAS, respectively.

Results: Cross-sectional and longitudinal analyses indicate significant main effects of parenting style, chaos, and adrenal hormone ratios in predicting depressive symptoms and aggression and significant moderating effects on the relationship between social stressors and psychopathology. High cortisol/DHEAS ratio predicted depressive symptoms and enhanced the effects of peer problems; low ratio was predictive of aggression in adolescents with high levels of peer problems.

Conclusion: The results of this study shed light on factors that may better explain the varying responses adolescents have to social stressors, thereby identifying adolescents at risk for psychological problems.

Keywords: cortisol; DHEAS; ratio; family; depression; aggression; peer

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Imaging Stress Task (MIST)) performed under and accompanied by social pressure, 50–60% uncontrollable failure rate and negative feedback.

**Results:** Salivary cortisol secretion relative to ground (AUCg) was significantly different between groups and within subjects. Gender showed a significant main effect ($F(1,39) = 0.6816, p = 0.013$), with females showing greater cortisol response than males. Further, a significant trait-by-gender-by-condition interaction effect was observed ($F(1,39) = 6.414, p = 0.015$), where F_AS showed elevated AUCg under placebo, a response was largely blunted by alcohol. This interaction effect was also significant in terms of amygdalae and orbitofrontal cortical activation under MIST; both regions where significantly deactivated under alcohol in F_AS (parameter estimates, $p < 0.05$ respectively: $-2.103; -2.229$).

**Conclusions:** These findings provide evidence for the notion that distinct risk personality profiles are associated with differential vulnerability for AUDs. They further support the self-medication theory, whereby AS individuals drink to dampen stress, rendering the former a negative reinforcer targeting and inhibiting their neural and hormonal stress circuitry.

Keywords: alcohol; sensation seeking; anxiety sensitivity; fMRI; cortisol; stress response; amygdale; orbitofrontal cortex

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Peripheral indices of oxidative stress are correlated with hippocampal volume in major depression and in controls

Oxidative stress (an imbalance between free radicals and the ability to neutralize them with antioxidants) occurs in several mental illnesses, including major depression (MDD). A major antioxidant in humans is glutathione peroxidase, which reduces GSSH to GSH, increasing glutathione's ability to scavenge free radicals. The brain, and the hippocampus (HC) in particular, is particularly sensitive to oxidative stress, and HC oxidative stress (particularly in the CA1 and CA3 & dentate gyrus [CA3&DG] subfields) may contribute to major depression.

Nineteen medication-free subjects with MDD and 19 matched controls underwent 4T MRI scanning of the HC and had fasting morning venipuncture for peripheral oxidative stress assessment. Two of the MDD subjects did not have glutathione (GSH) and/or glutathione disulfide (GSSG) data. Because of the preliminary nature of the study, no corrections for multiple comparisons were applied.

Across all subjects, the antioxidant Vitamin C was directly correlated with total HC ($p < 0.03$) and CA3&DG ($p < 0.04$) subfield volumes. Glutathione peroxidase was directly correlated with total HC ($p < 0.006$) and CA1 ($p < 0.009$) and CA3&DG ($p < 0.002$) subfield volumes. Levels of the antioxidant and GSH were directly correlated with CA2 ($p < 0.02$) and CA3&DG ($p < 0.03$) subfield volumes. In the controls, a similar pattern was observed at or near the significance threshold. In the MDD group alone, glutathione peroxidase activity was directly correlated with total HC volume ($p < 0.05$) and tended to be directly correlated with CA3&DG subfield volume ($p < 0.07$). The antioxidant ratio of GSH/GSSG (an index of antioxidant reserves) was directly correlated with CA2 ($p < 0.02$) and CA3&DG ($p < 0.03$) subfield volumes. These exploratory data are consistent with the hypothesis that oxidative stress is related to diminished hippocampal volume, with the CA3&DG subfield perhaps being the most sensitive. The relationship of peripheral oxidative stress to local oxidative stress in the HC is unknown, but studies in humans have suggested some degree of direct correlation between blood and cerebrospinal fluid (CSF) oxidative markers, and peripheral oxidative stress measures are increased in several neurodegenerative diseases.

Keywords: oxidative stress; depression; hippocampus; glutathione peroxidase

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Acute stress prompts riskier decisions in young men

There is evidence that acute stress impacts decision making (DM) under risk. It has been concluded that stress prompts riskier decisions in men. However, in the DM tasks used thus far, the expected value (EV) of reward and risk of decision options are confounded and it is, therefore, unclear which component is being affected by acute stress.

We developed a new DM paradigm, in which EV of reward and risk of decision options are independent and quantifiable. Subjects (5 men, age: 31.2 ± 1.92 years) completed 220 trials in which they had to repeatedly choose between a safe and a risky option associated with different EV of reward and risk. Stress was induced using the Socially Evaluated Cold Pressor Test (SECPT). Each subject received the SECPT and the corresponding control condition in random order.

Comparing the stress and control condition on a trial-by-trial basis, we found that, descriptively, gamble variance, a measure for the risk associated with decision options, was about 10% higher when subjects were stressed compared with when they received the control manipulation. EV of reward on which subjects gambled did not differ between stress and control manipulation.

Our data provide a first hint that risk but not reward processing in healthy young men might be affected by acute stress.

Keywords: stress; cortisol; decision making under risk; reward

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Serum leptin concentrations and telomere length in MDD and in controls

Obesity and the metabolic syndrome (MetS) predispose to multiple diseases and to accelerated cell aging as indexed by accelerated shortening of telomeres in peripheral blood mononuclear cells (PBMC’s). Major depressive disorder (MDD) is often associated with MetS and is also associated with increased disease risk and PBMC telomere shortening. A potential role of leptin in telomere shortening has been suggested, but prior results have been inconsistent and no study has yet assessed this relationship in MDD. The goal of this study was to assess the relationship between serum leptin concentrations and PBMC telomere length in MDD and in controls and to assess whether this relationship is mediated by body-mass index (BMI) or the homeostatic model assessment of insulin resistance (HOMA-IR), two principal components of the MetS.

Eighteen medication-free MDD subjects (11 female, 7 male, mean age 37.1 ± 2.7 years) and 17 healthy controls (11 female, 6 male, mean age 37.8 ± 3.0 years) had blood drawn for assay of fasting morning levels of leptin, glucose, and insulin and PBMC telomere length. The groups did not differ on BMI (24.66 ± 3.72 vs. 24.77 ± 4.29, respectively, n.s.). Analyses were co-varied for age and sex, with and without BMI.

In the combined group, serum leptin concentrations were inversely correlated with telomere length ($r = -0.33$, $p < 0.02$), with and without co-varying for BMI. This relationship remained significant in the MDD group alone ($r = -0.54$, $p < 0.04$) but missed significance in the controls ($r = -0.23$, ns). Hierarchical linear regression, entering BMI and HOMA-IR prior to leptin (with telomere length the dependent variable) showed that BMI and HOMA-IR were not significantly correlated with telomere length ($t = 1.04, \ p > 0.30$, and $t = 1.49, \ p > 0.10$, respectively), but leptin concentrations remained significantly correlated with telomere length ($t = -2.88, \ p = 0.007$).

Relatively high leptin concentrations, in the presence or absence of increased BMI and insulin resistance, may be a risk factor for telomere shortening. While this was demonstrated here in individuals with MDD, a similar relationship in non-depressed individuals cannot be ruled out because of the small sample size.

Keywords: leptin; telomeres; depression; body-mass index; insulin resistance; metabolic syndrome; obesity

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Diminished vagal activity and blunted circadian heart rate dynamics in posttraumatic stress disorder assessed through 24-h linear and unifractal analysis

Background: Affected autonomic heart regulation is implicated in the pathophysiology of cardiovascular diseases and is also associated with posttraumatic stress disorder (PTSD). However, although sympathetic hyperactivation has been repeatedly shown in PTSD, research has neglected the parasympathetic branch. The objective of this study is the long-term assessment of heart rate (HR) dynamics and its circadian changes as an index of autonomic imbalance in PTSD. Since tonic parasympathetic activity underlies long-range correlation of heartbeat interval fluctuations in healthy state, we included nonlinear (unifractal) analysis as an important and sensitive readout to assess functional alterations.

Methods: Electrocardiogram recordings over a 24-h period were conducted in 15 deployed male subjects with moderate to high levels of combat exposure (PTSD: n=7; combat controls: n=8). Analysis of HR dynamics included time domain, frequency domain and non-linear analysis based on detrended fluctuation analysis. Psychiatric symptoms were assessed using structured interviews, including the Clinician Administered PTSD Scale.

Results: Subjects with PTSD showed significantly higher baseline HR, higher LF/HF ratio in frequency domain analysis, blunted differences between daytime and nighttime measures, as well as higher scaling coefficient $a_{fast}$ during the day, indicating diminished tonic parasympathetic activity.

Conclusions: This study appears to be the first combining linear and non-linear methods to assess long-period autonomic and circadian differences in HR dynamics between combatants with and without PTSD. Diminished circadian differences and blunted tonic parasympathetic activity altering HR dynamics suggest central neuro-autonomic dysregulation that could represent a possible link to increased cardiovascular mortality in PTSD.

Keywords: autonomic nervous system; detrended fluctuation analysis; heart rate variability; parasympathetic nervous system; posttraumatic stress disorder; sympathetic nervous system

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Post-stress rumination after initial psychosocial stress predicts cortisol responses to repeated stress exposure

Background: Rumination, defined as past-centered negative thinking, has been linked to stress physiology and suggested to affect mental and physical health. Research has shown that both state and trait rumination is correlated with cortisol responses to psychosocial stress. It has not been addressed if state rumination is associated with cortisol responses to repeated stress.

Methods: Nineteen participants (aged 21–65, mean age = 53.5; nine males) were exposed to the Trier Social Stress Test (TSST) twice on consecutive days. Salivary cortisol was measured 1 min before and 1, 10, 30, 60 and 120 min post-TSST on both days. Participants provided self-reports of post-stress state rumination on both days. Participants further provided information about early adversity using the Childhood Trauma Questionnaire and self-rated depression and perceived chronic stress.

Results: Cortisol responses were successfully induced on both days of testing ($F[1.5, 54.5] = 4.4, p = .032$). State rumination scores on day 1 were significantly correlated with cortisol increases ($r = .615, p = .005$); interestingly, state rumination scores on day 1 of testing were related to cortisol increases the following day ($r = .594, p = .007$). No gender differences were found in rumination on either day (all $p = n.s.$). Childhood trauma, although reported at a very low level, was found to be strongly related to rumination on both days (rumination day 1: $r = .547, p = .02$; rumination day 2: $r = .712, p = .009$). Childhood trauma was further related to cortisol responses on the first, but not second, day of testing (day 1: $r = .503, p = .047$; day 2: $r = .31, p = n.s.$).
Conclusions: Post-stress rumination on day 1 was correlated with hypothalamic–pituitary–adrenal (HPA) axis reactivity. Day 1 post-stress rumination was correlated with day 2 responses to the same stressor, but day 2 rumination was unrelated to the stress response on that day. This suggests that rumination has prolonged effects on stress reactivity. Other variables, such as subclinical childhood trauma, were also related to state rumination and cortisol responses. These factors are potential mediators of the relationship between state rumination and HPA axis stress reactivity.

Keywords: rumination; stress; cortisol; HPA axis

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Salivary cortisol and alpha-amylase during traumatic memory encoding—relationships with intrusions and pre-existing characteristics

Rationale/statement of the problem: Cortisol levels have been extensively studied in patients with posttraumatic stress disorder (PTSD), but their specific relationship to intrusive memory symptoms is unknown. Salivary alpha-amylase (sAA), an index of sympathetic activation, has never been studied in the context of PTSD. This study adopted the Trauma Film Paradigm to assess how changes in cortisol and sAA levels during memory encoding are related both to subsequent intrusive memories of the film and to individuals’ pre-existing characteristics.

Methods: Saliva samples were collected in the afternoon (considering the circadian rhythm of cortisol and sAA) from 58 healthy adult participants at baseline, during the film, and post-film. Measurements of pre-existing PTSD symptoms, dissociation and anxiety traits as well as intrusions of the traumatic film over the week following film viewing were assessed.

Results: Results showed that cortisol levels increased, whereas sAA levels decreased in response to the film. The vividness of intrusive memories was negatively correlated with cortisol levels during and after the film. Pre-existing PTSD symptom severity was negatively correlated with cortisol levels at the post-film stage and positively correlated with sAA in both during the film and post-film stages. Moreover, dissociative traits (especially dissociative amnesia) were negatively correlated with sAA levels at baseline and during the film, while anxiety traits were positively correlated with post-film sAA levels.

Conclusions: This is the first study to investigate the relationship between cortisol, sAA, intrusive trauma memories and pre-existing psychological traits. The results supported the hypothesis that insufficient cortisol release in the immediate aftermath of trauma is a risk factor for the development of intrusive symptoms. The findings also shed light on how pre-existing characteristics affect physiological reactions to traumatic stimuli.

Keywords: PTSD; cortisol; alpha-amylase; trauma; dissociation; memory

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Boosting the oxytocin system in acute trauma victims at risk for PTSD: the rationale and design of a randomized controlled trial

Rationale: Currently, there are no effective interventions that prevent the development of posttraumatic stress disorder (PTSD) in recently traumatized individuals. The neuropeptide oxytocin is a potent regulator of two important processes disturbed in PTSD: it regulates physiological and behavioural stress and fear responses. In addition, oxytocin administration influences socio-emotional processes. Interestingly, high levels of acute distress after trauma and a lack of social support are risk factors for developing PTSD. Therefore, oxytocin administration appears to be a promising preventive treatment for PTSD, by hypothetically ameliorating dysregulated stress and fear responses as well as facilitating adaptive social functioning.
Methods: We have initiated a randomized controlled trial (RCT) to investigate the effectiveness of an intranasal oxytocin treatment regimen in preventing the development of PTSD in recently traumatized individuals at increased risk for PTSD. In addition, in the same population we are conducting an fMRI study, which will create deeper insights into the neural mechanisms through which oxytocin and social context may regulate fear responses to traumatic stress.

Results: In this presentation, the rationale behind stimulation of the oxytocin system in recently trauma-exposed individuals at risk for PTSD will be discussed, and an outline of the RCT will be presented. In addition, preliminary pilot data of the RCT will be shown.

Keywords: PTSD; traumatic stress; oxytocin; RCT; fMRI; social support

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Lower fasting plasma glucose levels in patients with stress-related exhaustion

In a recent study, we unexpectedly found lower fasting plasma glucose concentrations in patients with stress-related exhaustion compared with healthy controls. To further elucidate the reliability of these findings we now investigated possible differences in glucose and glycated haemoglobin (HbA1c) levels between all patients with Exhaustion Disorder (ED) that entered the treatment program at the Institute of Stress Medicine, Gothenburg, Sweden between 2004 and 2010 and a healthy control population. We also investigated the development of plasma glucose during 18 months of multimodal treatment and related it to changes in symptoms of burnout, depression and anxiety.

The study included 383 patients (71% females, age 21–66 years) and 199 healthy controls (50% females, age 25–54 years). All patients fulfilled the criteria for ED, which include physical and mental exhaustion experienced for at least two weeks, caused by exposure to one or more stressors for a minimum of six months. Cardinal features are markedly reduced mental energy, impaired memory and reduced capacity to meet demands.

Blood samples were drawn in the morning after fasting since 22:00 the day before. Follow-up measurements were performed after 3, 6, 12, and 18 months of treatment in the patient group. Fasting plasma glucose was significantly lower in the patients (4.7 ± 0.4 mmol/L) compared with healthy controls (5.0 ± 0.5 mmol/L), both in women and men. HbA1c did not differ between patients and controls. These results remained after controlling for age, BMI, WHR, physical activity, and antidepressant use.

In the patient group, plasma glucose levels increased significantly from inclusion to the follow-up measurements after 12 and 18 months. Changes in glucose during treatment were not related to improvement of symptoms of depression, anxiety or burnout.

We confirm our previous finding that plasma glucose levels are lower in patients with stress-related exhaustion compared with healthy controls. The increase during treatment could indicate that lower level of glucose might be a consequence of long-term stress, which is normalised during treatments. Further studies are needed to confirm if this is the case and whether this relatively small difference in glucose levels is of clinical relevance.

Keywords: blood sugar; burnout; exhaustion disorder; fatigue; stress

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The contagion of physiological stress: causes and consequences

Rationale/Statement of the problem: The contagion of psychological states such as arousal, pain, and distress has been well established and is consistent with perception–action models of empathy. However, the recent demonstration of contagious physiological stress is more confounding because cortisol responses have been...
historically difficult to trace to specific subjective states or overt behaviors. Thus, it is currently unclear how someone could detect another’s physiological stress (i.e., cortisol and sympathetic nervous system responses) through mere observation to produce resonating levels in themselves. It is also unclear if such resonating stress has any implications for subsequent prosocial behavior, as it does for typical empathic states like shared pain or distress.

**Methods:** In two separate studies, we assessed salivary cortisol and salivary alpha-amylase in both speakers and observers during a modified Trier Social Stress Test (TSST). In Study One, we coded a set of nonverbal behaviors from TSST speakers to determine the behavioral indices that may signal stress reactivity between individuals. In Study Two, to examine the influence of contagious stress on prosocial behavior, participants completed poststress measures of empathy and altruism.

**Results:** In both studies, observers and speakers showed evidence of contagious physiological stress responses. In Study One, speakers who displayed more gaze aversions showed the greatest cortisol reactivity. In Study Two, both speakers and observers showed evidence of increased prosocial behavior after the TSST.

**Conclusion:** These findings demonstrate that the contagion of physiological stress is a robust phenomenon, which may be mediated through the observation of behaviors like gaze aversion that indicate another’s level of stress. The experience and resonance of stress also appears to have implications for prosocial behavior.

Keywords: physiological stress; salivary cortisol; salivary alpha-amylase; prosocial behavior; Trier Social Stress Test (TSST)

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**Predicting internalizing outcomes based on psychophysiological dynamics**

**Background:** Our insight into the neurobiological dynamics underlying the processes that may over time cumulate into syndromes like burn-out and depression is rapidly developing. A recent, though important, step has been to combine the relevant parameters of multiple domains (physiological, endocrine, social/emotional) to optimize prognostic accuracy. This is of relevance as initially subtle neurobiological disturbances associated with stress may indicate the start of a negative and potentially dangerous trend, both for physical and psychological health.

**Methods:** On the basis of the regular monitoring of key variables of allostatic processes (like heart rate variability, corticosteroid concentrations, and psychosocial status), risks scores for internalizing development can be calculated. When repeatedly collected by means of a standardized assessment protocol, it becomes possible to conduct trend analyses, which may potentially indicate development towards aversive outcomes like burn-out (in labour environments) or for example depression.

**Results:** On the basis of available data, algorithms have been developed combining diverse allostatic key variables into multi-level prognostic models (low–medium–high risk for internalizing development). On the basis of these models, a standardized assessment protocol is developed using state-of-the-art information technology to make the application as consumer friendly as possible.

**Conclusions:** Although some technical developments are necessary to optimize the potency of assessment protocols like the present one (e.g., sensor technology able to measure or estimate corticosteroid concentrations “on the spot”), the used algorithms do not only seem to provide valid prognostic information, though essential indicators for easy to apply preventive strategies as well. These could be instrumental in averting long-term negative psychological outcomes.

Keywords: depression; burn-out; prognostic modelling; allostasis; health

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Tell me what you read and I will tell you if you are stressed: stress reactivity in consumers of self-help books

Background: The self-help book industry is one of the most lucrative in North America generating profits of $10 billion annually. The main purpose of self-help books is to increase the sense of worth of the readers as well as to provide them with adequate coping strategies, so they can better negotiate their stress. Despite the popularity of this literature, no study has investigated whether it impacts on people's stress reactivity. Consequently, the goal of this study was to compare consumers and non-consumers of self-help books with regard to their physiological stress response.

Methods: Thirty-one healthy men and women aged between 18 and 65 took part in this study. Of this group, 16 reported being consumers of self-help books, whereas the other 15 participants reported not being consumers nor attracted by these books. During their afternoon visit to the laboratory, all participants were exposed to the Trier Social Stress Test, a validated psychosocial stressor. Salivary samples were taken throughout the session in order to quantify their cortisol levels. Participants also filled out different questionnaires assessing self-esteem, depressive symptomatology and personality traits.

Results: In terms of stress reactivity, the area under the curve with respect to increase was significantly higher in consumers when compared to non-consumers. The two groups did not differ from each other in terms of depressive symptomatology and self-esteem. The consumer group scored lower on the “extraversion” personality trait compared to the non-consumer group.

Conclusions: Healthy consumers of self-help books are more stress reactive when facing a psychosocial stressor than non-consumers of self-help books. Although the current study design does not allow concluding about the efficacy of these books, the results nonetheless suggest that further investigation about the impact of this literature is necessary. Moreover, given the considerable amount of consumers of self-help books and their poor ability to cope with stress, there is clearly a need of increasing public awareness about effective coping strategies.

Keywords: stress; cortisol; self-help books; auto-therapy

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Subjective sleep is associated with the diurnal cortisol profile in children and adolescents

Rationale/Statement of the Problem: In adults, there is a robust, immediate effect of sleep on the diurnal cortisol profile. Shorter sleep duration and poorer sleep quality are associated with greater awakening response, flatter diurnal slope, and higher evening cortisol levels. Because of methodological limitations, this relation is less well-established in children and adolescents. Specifically, the use of single cortisol samples and sampling at unconventional times limit the generalizability of these findings. This study examines the influence of sleep duration, sleep quality, and daytime sleepiness on the diurnal cortisol profile in children and adolescents.

Methods: Children and adolescents aged 8-18 (N = 227, M = 12.61, SD = 2.04, 45.8% female) participated in the Healthy Heart Project at Concordia University. Children and adolescents rated their sleep quality on a 1-10 scale (1 = poor, 10 = excellent) and completed the Pediatric Daytime Sleepiness Scale. Parents completed the Child’s Sleep Habits Questionnaire and reported their children’s bedtime and waketime to derive sleep duration. Six saliva samples were collected over 2 days. Single sample (bedtime, maximum) and aggregate measures (AUC AG, AUC TG, diurnal slope) of the diurnal cortisol profile were derived.

Results: After controlling for age and day of the week, higher bedtime cortisol was associated with shorter sleep duration (r = -0.17, p = .01), poorer sleep quality (r = -0.19, p = .01), and greater child-report daytime sleepiness (r = 0.16, p = .02). Higher AUC TG was associated with poorer sleep quality (r = -0.15, p = .02); higher AUC I was related to greater child-report daytime sleepiness (r = 0.14, p = .03). Parent-report sleep problems and daytime sleepiness were not associated with any cortisol measure. Maximum sample, AUC AG, and diurnal slope were not related to any sleep measure.

Conclusion: Poorer sleep quality, greater daytime sleepiness, and shorter sleep duration were related to higher bedtime cortisol. Poorer sleep quality and greater daytime sleepiness were associated with higher AUC TG and AUC I, respectively. While child-report measures of sleep were associated with cortisol, parent-report measures were not.
Current findings offer insight into possible pathways linking sleep and health. Future studies should further elucidate this association by examining objective measures of sleep.

Keywords: sleep duration; sleep quality; diurnal cortisol profile; children and adolescents; parent-report

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Sympathetic nerve activity in takotsubo cardiomyopathy

The maintenance of cardiovascular and cerebrovascular health is based on a complex relationship between the heart and the brain. While some responses to stress are vital for survival, mental stress has also been claimed to cause cardiovascular disease. The Japanese observation from the early 1990s of a reversible stress-induced cardiomyopathy, the takotsubo cardiomyopathy (TC), a peculiar type of left ventricular (LV) dysfunction triggered by an acute strong emotional or physical stressor, supports this notion. The syndrome, mostly affecting postmenopausal women, presents signs and symptoms of acute coronary syndrome without evidence of obstructive coronary artery disease. Though the definite pathophysiology of TC remains to be identified, a catecholamine overstimulation of the myocardium is thought to underlie the pathogenesis and forms the basis for treatment of this medical entity.

Direct recordings of multiunit efferent postganglionic muscle sympathetic nerve activity (MSNA) were obtained from 12 female patients, 5 in the acute (24-48 hours) and 7 in the recovery phase (1-6 months), with apical ballooning pattern and 12 healthy matched controls. MSNA was expressed as burst frequency (BF), burst incidence (BI) and relative median burst amplitude (RMB%). All patients were investigated with ongoing medication. MSNA was lower in patients with TC as compared to matched controls, but did not differ between the acute and recovery phase of TC. RMB%, blood pressure and heart rate did not differ between the groups. MSNA is shown to be lower in patients with TC compared to healthy controls, suggesting that sympathetic neuronal outflow is rapidly reduced following the initial phase of TC. A distension of the ventricular myocardium, due to excessive catecholamine release over the heart in the acute phase may increase the firing rate of unmyelinated cardiac c-fibre afferents resulting in widespread sympathetic inhibition. Such a mechanism may underlie the lower MSNA reported in our patients.

Keywords: sympathetic nerve activity; takotsubo cardiomyopathy; emotional stress; women; postmenopaus; blood pressure

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Lower DHEA and DHEA-S response during acute psychosocial stress is related to higher perceived stress at work

Background: Dehydroepiandrosterone (DHEA) and Dehydroepiandrosterone Sulfate (DHEA-S) increase during acute psychosocial stress is suggested to have a protective role against the negative consequences of cortisol. We have previously reported that, in adults, the capacity to produce DHEA and DHEA-S during acute psychosocial stress declines with age. Changes in DHEA and DHEA-S levels with ageing depend on changes in the zona reticularis area in the adrenal cortex, which is responsible for DHEA and DHEA-S production. Prolonged psychosocial stress may be a factor that negatively affects the zona reticularis area. This study aimed to investigate whether self-reported prolonged stress affect the capacity to produce DHEA and DHEA-S during acute psychosocial stress.

Methods: 20 men and 19 women (age 30-50 years) underwent Trier Social Stress Test (TSST). Physiological measurements were performed before, directly after the stress test and after 30 min of recovery. Perceived stress at work (during the last week) was measured by the Stress-Energy (SE) questionnaire. The participants were divided into three groups based on their scores. A general linear model (multiple regression analysis) was performed, using
the magnitude of stress-induced increase of DHEA and DHEA (log) as dependent variable and age and stress level group as independent variables.

**Results:** Both the medium stress group and the high stress group had lower DHEA and DHEA-S increase during acute psychosocial stress compared to individuals reporting low stress levels at work \((p = 0.027 \text{ and } p = 0.036, \text{ respectively})\).

**Conclusions:** This study indicates that prolonged stress is a factor that negatively affects the zona reticularis area in the adrenal cortex and its capacity to produce DHEA and DHEA-S during acute psychosocial stress.

Keywords: acute stress; DHEA and DHEA-S response; prolonged stress

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**Symptom improvement in deep brain stimulation for obsessive-compulsive disorder is related to cortisol changes**

**Background:** Deep brain stimulation (DBS) is an effective treatment for obsessive-compulsive disorder (OCD), but its mechanism of action is largely unknown. Since DBS may induce rapid symptomatic changes and the pathophysiology of OCD has been suggested to be related to the hypothalamic-pituitary-adrenal (HPA)-axis, we set out to study whether/how DBS affects the HPA-axis in OCD patients.

**Methods:** We studied 16 therapy-refractory OCD patients treated with DBS of the accumbal area for at least 1 year in an “on” and “off” stimulation phase, with a 1-week interval. We measured 24-h urinary excretion of cortisol, adrenaline, and noradrenaline as well as obsessive-compulsive (Y-BOCS), depressive (Ham-D), and anxiety (HAM-A) symptom scores.

**Results:** Eight patients who completed the study were included in the final analysis. The comparison between DBS on and off phase revealed a change in Y-BOCS (39%), HAM-D (78%), and HAM-A (56%) scores. Median cortisol levels increased by 53% in the off phase, from 93 to 143 nmol/24 h, and correlated strongly with Y-BOCS and HAM-D changes. There was no significant change in urinary adrenaline or noradrenaline excretion.

**Conclusions:** Our findings indicate that symptom improvement in DBS for OCD patients is associated with changes in cortisol levels.

Keywords: deep brain stimulation; nucleus accumbens; hypothalamic-pituitary-adrenal axis; cortisol; catecholamines; obsessive-compulsive disorder

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The effects of sexual orientation on stress-reactive cortisol: are sexual minority women ruminative and men resilient?

**Rationale/statement of the problem:** Lesbian (L), gay (G), and bisexual (B) individuals frequently report heightened distress due to discrimination, yet investigations into their physiological stress responsivity are missing from the literature. Our group recently showed that disclosing one's sexual orientation corresponds with comparatively lower psychiatric symptoms and morning cortisol levels than those who remain “in the closet.” Extending from our

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earlier studies, the current study investigated whether sexual minorities might manifest differential cortisol levels than heterosexuals (Hs) in response to social-evaluative threat.

**Methods:** Participants included 87 healthy adults (mean age 25, 54% men) identifying as L/G/B ($n=46$) or as Hs ($n=41$). Stress was induced using the Trier Social Stress Test (TSST), and 10 salivary cortisol samples were collected throughout a 2-hour afternoon visit. Results were analyzed through ANOVA split by sex with sexual orientation as the between-subject factor and cortisol as the with-subject factor while controlling for age, self-esteem, and disclosure status.

**Results:** Results reveal that L/B women had higher cortisol levels than Hs women 40 min after stress exposure. As a group, G/B men had significantly lower cortisol levels in contrast to Hs men. The covarying effects of age, self-esteem, and disclosure status intermittently contributed to time and group effects for both sexes.

**Conclusions:** Our findings demonstrate that relative to Hs controls (1) L/B women displayed higher cortisol levels late after TSST exposure, whereas (2) G/B men displayed lower overall cortisol levels throughout testing. We previously reported that G/B men in our sample manifested lower depressive symptoms and allostatic load based on 20 biomarkers compared to Hs men. It is possible that G/B men who are able to successfully overcome stigma may be resistant to chronic stress and stress reactivity. Yet, the opposite might be true for L/B women who displayed heightened distress during recovery that may indicate ruminative processes. These results suggest that it is important to include intrasex variations such as sexual orientation as well as unique developmental challenges such as disclosure processes in future psychoneuroendocrine studies.

Keywords: sexual minority stress; cortisol; Trier Social Stress Test; stress reactivity; disclosure; rumination; resiliency

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**Low lead levels associated with blunted cortisol reactivity in a sample of elders from the general population**

**Background:** A few weeks ago and for the first time in 20 years, US health officials have lowered the threshold for lead (Pb) poisoning from 10 to 5 g/dL in blood, but only in young children. However, elders are also a high-risk population when considering adverse effects of lead exposure. The association between low-level lead exposure and cognitive variability is well documented in elderly people, e.g. in the domain of attention and memory. Toxicokinetic studies have also demonstrated that the skeleton is the site of storage for around 95% of lead in the adult human body, resulting in a release of lead in blood in elderly people with bone demineralization. One potential mechanism explaining adverse health effects of lead exposure stands in its endocrine disrupting function, and a recent study has found significant associations in children between low-lead levels and cortisol reactivity to the cold pressure task. We hypothesized that this association between lead exposure and hypothalamo–pituitary–adrenal functioning could be observed in elders from the general population.

**Methods:** Pb levels were determined from blood samples of 78 elderly individuals (mean age = 58.37, SE = 4.01) without previous occupational Pb exposure. Diurnal cortisol was measured using salivary cortisol samples collected at home over two working days at awakening, 30 min after waking, 14: 00 h, 16: 00 h and before bedtime (~10 pm) periods. Salivary cortisol reactivity was assessed in response to the Trier Social Stress Test (TSST).

**Results:** All participants showed blood Pb levels below the threshold limit recommended by the CDC with a mean Pb of 2.6 g/dL, SE = 1.4. No association was found between lead exposure and diurnal cortisol activity ($n=75$, $r = -0.02$, $p = 0.98$). However, the more exposed to lead, the lower the cortisol response following TSST was found in participants ($n=74$, $r = -0.26$, $p < 0.03$), even when controlling for age, and levels of education ($n=73$, $\beta = -0.24$, $p = 0.05$).

**Conclusions:** Lead levels, even at a very low level of exposure, are associated with a blunted cortisol response to the TSST. These findings support the relationship between environmental contaminants and stress, and support the idea that regulation should be applied to the aging population. The next step will be to determine whether the association between lead exposure and cognitive variability could be explained by impairment of the stress system.
Sociodemographic variables, life style and cortisol levels in a sample of Mexicans

Kudielka, Hellhammer and Wüst (2009) identified studies about how a wide sample of variables affect the measure of the concentration of cortisol; in the first place are the age and gender of participants, in women, the phase of the menstrual cycle, consume of oral contraception, and if they were pregnant or nursing, among others. Indeed, the variations of immediate physical conditions—like a sleep hours after the take of the saliva sample, strong physical activity, or if they consumed coffee, nicotine, dietary or any kind of drugs prior to the research. Finally, due to the influence of more distal variables, such as intense emotional experiences of the mother during the pregnancy and hereditary factors in general (see Bartels, de Geus, Kirshbaum, Sluyter & Boomsma, 2003) and the type of procedures, like the hour of the take of the saliva sample, because of the variation of the circadian rhythm of the cortisol.

Problem: If we recognize the influence of these variables, from a methodological view, it is important to control these variables in the context of a research where we use the measure of salivary cortisol.

Methods: The overall average and the circadian cycle of cortisol in 3,414 salivary samples taken in 12 studies in Mexico, that were discussed this hormone differences based on age, gender and consumption or not cigars variables were analysed.

Results: It was observed a decrease in the concentration of cortisol as the participants were advancing in age; also identified a circadian normal pattern but with higher levels in the studied sample. Finally, no significant differences were found between the concentrations of cortisol between women and men, as well as between smokers and non-smokers.

Conclusion: It discusses the conceptual, methodological implications and practices resulting from the findings, both for the development of future research for his study in relation to the phenomena of health and disease. Take into account the age as a factor that affects the salivary cortisol measurements.

Evaluation of classification criteria for the detection of cortisol pulses in repeated-measures designs

Rationale: Hypothalamus–pituitary–adrenal (HPA) axis reactivity, which has been considered a potential endophenotype for psychiatric disorders, is commonly investigated by repeated-measures designs utilizing frequent sampling of salivary cortisol in temporal proximity to psychosocial stressors. To remove sources of cortisol variance, which are not related to HPA axis reactivity, researchers often utilize classification criteria to identify individuals who show no cortisol response (non-responders), for example, baseline-to-peak distances of 2.5 nmol/l. However, such classification criteria have not been systematically evaluated with regard to their classification performance.

Methods: As a first step, we fitted an autoregressive latent trajectory model to cortisol data, which was obtained from longitudinally sampled saliva of 504 participants, of which 309 were exposed to the Trier Social Stress Test. Different sources of time-series variance were accounted for by modeling of initial cortisol levels, amplitude of the subsequently occurring secretory episodes, and continuous cortisol elimination. Assuming zero-amplitudes for individuals who show no stress response, a mixture distribution was implemented for secretory episodes, resulting in appropriate classifications of cortisol responders, or non-responders. Then, as a second step, we evaluated the classification performance of various proposed classifiers by constructing receiving operator characteristics.
**Results:** Results reveal (a) that covariance and mean structure of cortisol time-series can be sufficiently accounted for by the proposed model, allowing to infer on endocrine parameters that can barely be extracted by conventional analyses and (b) that the 2.5 nmol/l criterion is suboptimal in terms of simultaneously minimizing false-positive and false-negative classifications and inferior as opposed to other classifiers.

**Conclusion:** To maintain the low number of false positives, but to increase true-positive classifications, we suggest to lower the conventional baseline-to-peak classification threshold to 1.5 nmol/l. Furthermore, classification performance can be increased by adjusting baseline-to-peak differences for initial cortisol levels.

Keywords: autoregressive latent trajectory model; cortisol; longitudinally; Trier Social Stress Test; time-series variance

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**Animal model of differential susceptibility to stress in development: implications for schizophrenia**

**Rationale/Statement of the problem:** Common gene variants predisposing for altered dopamine (DA) neurotransmission are candidates for schizophrenia-susceptibility genes, although genome-wide studies so far showed a weak association of these variants with schizophrenia. It has actually become apparent that the expression of psychotic symptoms in schizophrenia is associated with the exposure of the genetically predisposed individuals to environmental risk factors during development such as early life adversity and upbringing in an unfavorable social environment. Furthermore, it has been postulated that genetic predisposition can promote not only vulnerability in response to negative environmental input, but also resilience in response to positive environmental stimulation.

**Methods:** We decided to test this hypothesis in the apomorphine-susceptible (APO-SUS) rat line, which was selected from Wistar rats on the basis of an extremely enhanced stereotypic gnawing response to administration of the dopamine agonist, apomorphine (APO-gnawing). The parental strain was used for comparison. Adult rats exposed as pups to poor maternal care and to post-weaning social-isolation rearing were examined for pre-pulse inhibition of acoustic startle (PPI), T-maze spontaneous alternation, contextual fear-conditioning and stress hormonal responses to a conditioned emotional stressor.

**Results:** Adult APO-SUS rats that had experienced poor maternal care as judged from low maternal licking and grooming (LG) scores showed dramatically enhanced stress-induced ACTH levels in the face of modest increases in circulating corticosterone (CORT) and prolactin levels. These low LG offspring also developed a basal PPI-deficit, reduced acoustic startle and impaired contextual fear-conditioning, but showed enhanced short-term memory. Additional isolation rearing abolished entirely basal PPI and impaired short-term memory in these individuals. High LG offspring, on the contrary, displayed enhanced PPI in both rearing conditions that was reduced only after CORT-challenge, while the low LG was resistant to CORT. Maternal LG history alone in Wistar rats had limited effects on the behaviour or stress response of offspring. When low maternal LG history was combined with post-weaning social isolation, basal APO-gnawing was decreased and PPI increased. High LG offspring reared in isolation displayed, however, the highest APO-gnawing and the lowest PPI levels among rats reared in social isolation. An injection of high dose CORT in the adult low LG offspring reduced PPI, whereas the high LG group was resistant to the acute effects of CORT.

**Conclusion:** If exposure to negative social environment accumulates, a schizophrenia-like phenotype, characterized by a severe deficit in sensorimotor gating and brain glucocorticoid-resistance, precipitates in the genetically predisposed individuals while the non-predisposed individuals are resilient. However, the same genetically predisposed individuals are sensitive to positive environment as well, where they improve their phenotype and outperform the controls, which do not change. This is the first animal model to find strong evidence for a differential susceptibility to stress in development depending on genetic predisposition.

Keywords: animal model; schizophrenia; maternal behavior; cortisol; offspring

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**Early life obesity, maternal depression, and telomere length in Latino children**

Telomere length (TL) is an important marker of cellular aging that can be examined from birth to death and provide information about health status and disease risk. TL shortens in early childhood with the majority of the shortening occurring by age 4. TL is associated with stress and obesity in adults. It is possible that exposure to early life stressors and excess adiposity from birth and the first year of life may impact the rate of telomere shortening. Few studies have examined TL in the first years of life, and none of them have examined stress and obesity in infants. We examined TL by qPCR using genomic DNA from dried blood spots in a sample of 109 four-year-old, low-income Latino children and their mothers. TL is expressed as T/S (the ratio of telomeric product vs. single copy gene product). This group of children and their mothers were recruited prenatally in San Francisco at which time socio-demographic and health history was assessed. In addition, child weight and length and maternal body mass index (BMI) have been assessed annually from birth with the child’s weight and length measured also at birth and 6 months of age. Maternal depressive symptoms were assessed prenatally, at 4-6 weeks postpartum and annually throughout the follow-up period. Child behavior was evaluated using the child behavior checklist (CBCL) at 3 and 4 years of age for internalizing and externalizing behaviors. Student’s t-tests were performed to compare TL in relationship to different childhood exposures – maternal depression, child overweight and obesity, and socio-demographic factors such as child sex, ethnicity, and socioeconomic status. Factors that were significant at p < 0.10 were subsequently entered into a multivariate regression model to evaluate independent predictors for shortened TL.

In bivariate analysis, being obese at 6 months of age (weight/length ≥ 95th percentile) and being obese at both 6 and 12 months of age were associated with shorter TL at age 4 (1.62 ± 0.36 versus 1.84 ± 0.34, p = 0.02 and 1.44 ± 0.30 versus 1.82 ± 0.34, p = 0.02, respectively). Exposure to maternal depressive symptoms at age 3 was also associated with shorter TL (1.66 ± 0.25 versus 1.81 ± 0.33, p = 0.07). Children of Mexican descent tended to have longer telomeres than those of Central American ancestry (1.85 ± 0.31 versus 1.73 ± 0.38, p < 0.07). Exposure to maternal depressive symptoms at other timepoints in early childhood and internalizing or externalizing behavior was not associated with shorter TL. In linear multiple regression analysis, female sex (Coeff = 0.18, 95% CI: 0.04-0.31) as and maternal TL (Coeff = 0.18, 95% CI: 0.04-0.31) predicted longer TL, whereas being obese at 6 and 12 months (Coeff = −0.49, 95% CI: −0.79 to 0.19) predicted shorter TL. In this population of low-income Latino children, obesity in the first year of life was associated with shorter telomere length at age 4, independent of sex mother’s TL and mother’s depression. Thus, obesity early in life may shape TL, whereas obesity in the toddler and preschool years may be less associated with obesity at age 4.

**Keywords:** childhood; obesity; stress; maternal depression; Latino

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**Childhood trauma and comorbid mood and anxiety disorders in adult patients with post-traumatic stress disorder**

Childhood trauma (CT) is associated with mood and anxiety disorders in adulthood, especially with posttraumatic stress disorder (PTSD). These disorders frequently co-occur, yet few PTSD comorbidity studies have focused on samples with a range of CT severity and none have included participants with adulthood-only trauma in the same study. We investigated SCID diagnoses of comorbid mood and anxiety disorders among 69 adult PTSD patients (M age = 37.94, SD = 11.13; 53.6% female), with CT exposures (CTQ scores) ranging from absent to extreme. The CAPS and QIDS-SR measured PTSD and depression severity, respectively. Total CT exposure correlated with having at least one comorbid anxiety disorder diagnosis (r_pb = .42, p < .001) and logistic regression indicated that CT exposure predicted comorbid anxiety disorder diagnosis after controlling for demographics, mood disorder, and PTSD severity. Significant correlations were also identified between particular CT subtypes and the presence of a comorbid anxiety disorder. Total CT exposure did not predict current or past mood disorder diagnosis or depression severity. These findings support a relationship between CT and the presence of additional anxiety...
disorders in adult patients with PTSD, and highlight the need for thorough diagnostic assessment and special treatment planning to address the full spectrum of psychopathology in adult PTSD patients with significant histories of CT.

Keywords: childhood trauma; PTSD; mood disorders; anxiety disorders

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**Systems biology of post-traumatic stress disorder: characterization of pathways and networks involved in the development of PTSD**

**Rationale:** Life-threatening experiences, including the observations of severe trauma and/or violence, coupled with feelings of extreme fear and helplessness can result in posttraumatic stress disorder (PTSD). Unpredictability, uncontrollability, and novelty are considered key factors in eliciting and influencing the intensities of the stress responses. Personal coping strategies may affect resilience and susceptibility to stressors and, in PTSD patients, may also affect responses to stressors such as cortisol secretion. Recent interest in PTSD models focuses on the drivers of susceptibility versus resilience factors and the identification of potential targets for prevention and/or treatment of PTSD. Following a traumatic event, most individuals experience at least some symptoms of PTSD. However, many trauma survivors who develop PTSD recover over the course of months.

**Methods:** Systems and integrative biology approaches were applied to characterize the development of PTSD using an animal model of repeated social trauma/stress. Behavioral, physiological, and histopathological consequences of repeated social stress were evaluated using a modified “6 hour box-in-box resident-intruder” model. At the end of the stress episodes, mouse blood samples and organs were collected and brains were dissected into 17 different regions. Transcriptomic, metabolomic, proteomic, and epigenomic changes were analyzed using microarrays.

**Results:** Pan-omic analyses of this mouse model that simulate aspects of PTSD revealed that genes involved in axonal guidance signaling, apoptosis, inflammation, corticotropin releasing hormone signaling, synaptic long-term depression, dendritic branching, and cardiac hypertrophy were upregulated in stressed mice compared to the control. Suppressed transcripts were involved in synaptic long-term potentiation, lymphocyte activation, gap junction signaling, and glucocorticoid receptor pathway.

**Conclusions:** We characterized the regulation patterns of genes, metabolites, protein, DNA methylation, and their associated networks in a mouse model of PTSD. These patterns can be used as part of a diagnostic panel for the development of PTSD and for the validation of therapeutic interventions.

Keywords: genetics; DNA methylation; animal model; trauma; PTSD

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**Nicotine exposure results in food consumption differences between adolescent and adult female mice**

**Background:** Individuals with disordered eating have the highest mortality rate of any psychiatric disorder and females make up the majority of the eating disordered population. Tobacco smokers have lower BMIs than do their non-smoking counterparts, and adolescent and adult females report using tobacco to lose or maintain body weight. Multiple biobehavioural factors contribute to this nicotine-body weight relationship, rodent studies suggest that reduced food intake following nicotine exposure may be a primary factor.

**Objective:** To examine the effects of nicotine on body weight changes in response to different food types.

**Methods:** We used an oral nicotine administration paradigm to investigate body weight changes in the presence of standard chow, high sweet and high fat foods in adolescent (N=63) and adult (N=60) female C57BL/6J mice. Mice were exposed to nicotine (200 μg/ml) or water along with one of three food types for 7 days.

**Results:** Adult mice weighed more but ate less food than did adolescents (p<0.05). Mice exposed to high fat food weighed the most, but ate the least (p<0.05). While there were no main effects of nicotine on body weight in either
age group, nicotine-exposed adults consumed less food than did water-exposed adults \((p<0.05)\), this effect was not seen in adolescents. Among the nicotine-exposed mice, adolescents consumed more food than did adults \((p<0.05)\).

**Conclusions:** These findings suggest, in females, the appetite suppression qualities of nicotine differ based on age, with nicotine exposure actually increasing food consumption in adolescents. Nicotine’s effects on food intake do not result in body weight changes in either age group.

Keywords: nicotine exposure; food consumption; adolescent; adult; female; mice

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**Altered glucocorticoid action in obese pregnancy is modulated by diet and is associated with gestational weight gain but has similar influences on birthweight in males and females**

**Rationale/ statement of the problem:** One in five UK women is obese at antenatal booking. Maternal obesity increases risk of offspring obesity, behavioural and metabolic disorders. Animal studies suggest male offspring are more vulnerable to these effects than females. We hypothesised that this is mediated by altered action of maternal glucocorticoids, key regulators of development and stimulators of appetite and weight gain.

**Methods:** Serum cortisol levels were measured at 16, 28 and 36 weeks gestation in \(n=156\) class III obese (BMI \(>40\) kg/m\(^2\)) and \(n=87\) lean (BMI \(<25\) kg/m\(^2\)) pregnant women. mRNA levels of \(11\)-beta hydroxysteroid dehydrogenase type 2 (\(11\beta\)HSD2), which inactivates cortisol, were measured in \(n=36\) first trimester and \(n=61\) term placental samples.

**Results:** Cortisol levels were significantly lower throughout pregnancy in obese than lean \((p<0.05)\). Obese reported similar appetite and total calorie intake to lean but had significantly less gestational weight gain \((10.1 \pm 3.7\) kg vs. \(5.5 \pm 5.6\) kg, \(p<0.01)\); this inversely correlated with cortisol levels \((r=-0.27, p<0.01)\). Cortisol levels correlated positively with reported pregnancy intake of protein, fat, saturated fatty acids and sugars in lean \((all\ p<0.05)\). Placental expression of \(11\beta\)HSD2 increased in association with increasing obesity in early pregnancy \((r=0.21, p<0.05)\) and was highest in term placenta in obese women with macrosomic (\(>4000\) g) offspring \((p<0.05)\). There were no gender-specific effects of maternal overnutrition on birthweight, placental gene expression or maternal glucocorticoid levels.

**Conclusions:** Lower circulating cortisol levels in obese pregnancy, together with the more effective placental barrier to maternal glucocorticoids may be a mechanism contributing to higher birthweight in offspring of obese women. In lean women, dietary composition may regulate cortisol levels during pregnancy.

Keywords: maternal obesity; cortisol levels; birthweight; gestational weight gain

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**Sex differences in fear conditioning: a role of the forebrain mineralocorticoid receptor**

**Rationale:** A recent study showed that a mineralocorticoid receptor (MR) gene variant, MR haplotype 2, was associated with higher levels of dispositional optimism, less thoughts of hopelessness, and lower risk of depression in women but not in men. Mice lacking the MR in the forebrain, MR\(^{CaMKCre}\) mice, were generated to further investigate behavioral sex differences with and without the MR. Here, the hypothesis that sex differences would disappear after deletion of the MR was tested.

**Methods:** We used male \((n=8–9)\) and female \((n=9–14)\) MR\(^{CaMKCre}\) mice and control littermates to study fear conditioning, memory performance, and extinction. The fear-conditioning paradigm assessed both context- and cue-related fear within one experimental procedure.

**Results:** At the end of the conditioning, all mice acquired the fear-motivated response. During the first minutes of the memory test, both male and female MR\(^{CaMKCre}\) mice remembered and feared the context more than the control mice. Furthermore, female MR\(^{CaMKCre}\) mice were not able to extinguish this memory even on the second day of
memory testing. The female mutants could also not discriminate between cue (more freezing) and context periods (less freezing). In contrast, male MR<sup>CaMKCre</sup> and control mice showed extinction and were capable to discriminate, although extinction of the MR<sup>CaMKCre</sup> mice started slower.

**Conclusion:** The loss of forebrain MR does not eliminate sex differences but rather results in large differences in emotional and cognitive behaviors between female and male mice. This finding suggests a role of this receptor in the female prevalence of stress- and anxiety-regulated disorders.

Keywords: fear conditioning; sex differences; mineralocorticoid receptor

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Maternal mood and neuroendocrine programming: effects of time of exposure and sex

**Rationale/ statement of the problem:** Adverse exposures that influence growth in prenatal and early postnatal periods are thought to influence vulnerability to chronic diseases via their effects on the neuroendocrine system. In humans, assessment of the underlying mechanisms has been restricted. The aim of the present study was to investigate the effects of adverse early life exposures, specifically maternal mood, on hypothalamic–pituitary–adrenal (HPA) axis, sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) responses to an acute physiological stressor. In addition, we conducted a preliminary examination into whether effects varied by time of exposure and sex.

**Methods:** A total of 139 individuals (mean age 15.12 years) were recruited from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. Participants underwent the CO<sub>2</sub> stress test, and indices of the PNS, SNS and HPA axis were measured. Pre-existing data on mothers’ demographic and psychosocial factors during pregnancy (18 and 32 weeks) and postnatally (8 weeks and 8 months) were extracted, as were participants’ clinical and demographic data at birth.

**Results:** Increases in both prenatal and postnatal anxiety and depression were associated with greater SNS reactivity to the stressor and slower recovery, as well as blunted HPA axis responses. Programming effects on the SNS appeared restricted to male offspring only. No consistent relationships were evident for any of the measures of pre-stress function.

**Conclusion:** We have found preliminary evidence that both pre- and postnatal maternal anxiety and depression have sustained programming effects on the SNS and HPA axis. Effects on the SNS were restricted to male offspring.

Keywords: maternal mood; HPA; SNS; foetal programming hypothesis

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The lingering effect of childhood socioeconomic status: parental education predicts diurnal cortisol trajectory in adulthood

Socioeconomic disadvantage during childhood has lasting effects on adult health. Children raised by less educated parents are at higher risk for later cardiovascular disease (CVD), Alzheimer’s disease, and type 2 diabetes mellitus. The mechanisms through which childhood socioeconomic status (SES) affect health are unclear. Childhood SES may shape stress physiology, including neuroendocrine processes, which may negatively impact health in adulthood. Prior literature shows that less educated individuals have flatter cortisol slopes across the day compared to those higher in education. Flattened slopes have been linked to chronic stress, CVD outcomes, breast cancer mortality, and both all-cause and CVD mortality. It is unknown whether one’s childhood SES, approximated by parental education level, predicts diurnal cortisol trajectories independent of one’s individual education. To this end, we recruited 20 Black and 20 White women who previously participated in the National
Heart, Lung, and Blood Institute (NHLBI)-supported National Growth and Health Study (NGHS) to complete a
daily stress assessment, which included salivary cortisol sampling at four times per day over two consecutive days.
Mixed modeling indicated that cortisol slope across the day was a function of individual education \((b_{\text{time \times individual education}} = -0.04, \ SE = 0.02, \ p = 0.045)\). Simple slope analyses revealed that women with only a high school diploma had significantly flatter cortisol slopes \((b = -0.22, \ SE = 0.06, \ p < 0.001)\) than those with more than a high school diploma \((b = -0.26, \ SE = 0.02, \ p < 0.001)\). Cortisol slopes were also a function of parental education \((b_{\text{time \times parental education}} = -0.04, \ SE = 0.02, \ p = 0.038)\). Simple slopes analyses revealed that women with parents who received only high school educations had significantly flatter cortisol slopes \((b = -0.20, \ SE = 0.06, \ p < 0.001)\) compared to those with parents who received more than a high school diploma \((b = -0.24, \ SE = 0.02, \ p < 0.001)\). Importantly, the effect of parental education was independent of individual education. These findings provide preliminary evidence that parental education, a marker of childhood SES, can influence neuroendocrine activity beyond childhood, having lasting effects into adulthood with important implications for health.

Keywords: cortisol; diurnal slope; HPA-axis; childhood SES; parent education

Rationale/statement of the problem: Although tricyclic antidepressants (TCAs) are not recommended as first line
therapy for depression in patients with coronary heart disease (CHD), they are still occasionally prescribed.
Rationales may include resistance to other classes of antidepressants, previous response to TCAs, or treatment
continuation after onset of a CHD. Despite their antidepressive effectiveness, TCAs may worsen cardiovascular
prognosis because of autonomic side effects. Here, we examined potential adverse effects of TCAs on autonomic
function as marked by heart rate variability (HRV) and norepinephrine (NE) levels.

Methods: A total of 956 outpatients with stable CHD, 44 used TCAs. All patients were prospectively followed for
7.2 ± 2.6 years. Standard deviation of all normal RR intervals (SDNN) as a measure of HRV was calculated from
24 h-electrocardiographic recordings. NE levels were measured in plasma and 24 h-urinary samples. We also
calculated hazard ratios for all-cause mortality.

Results: Users of TCAs had an increased risk of mortality compared to non-users \((p = 0.01)\) in a model adjusted for age, sex, smoking, diabetes, congestive heart failure and depressive symptoms).
When additionally adjusted for HRV and plasma NE, there was no significant association of TCA use and
mortality. TCA users had an increased risk of being in the lowest tertile of HRV \((p < 0.01)\) and in the highest tertile
of urinary NE \((p < 0.01)\) and plasma NE \((p < 0.01)\). Adjustment for age, sex, smoking, diabetes, congestive heart
failure and depressive symptoms did not significantly change the results.

Conclusion: Use of TCAs was associated with increased mortality in patients with CHD. Unfavourable changes in
autonomic function as marked by low HRV and high NE levels might be a potential mechanism.

Keywords: depression; coronary heart disease; tricyclic antidepressants; heart rate variability; norepinephrine

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Cortisol awakening response is associated with hippocampus-dependent cognitive impairment in major depression

**Rationale:** Cognitive deficits and alterations in cortisol secretion are characteristic features of major depression disorder (MDD). The cortisol awakening response (CAR) is altered in depression and crucially depends on hippocampus function, a brain area closely related to cognitive function.

**Methods:** We examined 21 MDD patients without medication, 20 MDD patients treated with antidepressants, and 41 healthy control subjects (HC), matched for age, gender, and years of education. We applied several neuropsychological tests. Salivary cortisol levels were measured on two consecutive days at awakening, and 30 min and 60 min after awakening.

**Results:** Both patient groups did not differ in severity of depression ($p = 0.20$). Analysis of variance (ANOVA) with CAR as dependant variable revealed a significant effect of group ($p = 0.01$). Post-hoc tests confirmed that medicated patients exhibited a smaller CAR compared to unmedicated patients ($p = 0.04$) and HC ($p = 0.01$), whereas differences between unmedicated patients and HC were not significant. ANOVA for Auditory Verbal Learning Task total score revealed a significant effect of group ($p = 0.03$). Post hoc tests confirmed that unmedicated patients were significantly impaired in verbal memory ($p = 0.01$) whereas medicated patients were impaired on trend-level ($p = 0.09$) when compared to HC. Differences between both patients groups were not statistically significant. Repeated-measures ANOVA revealed a significant effect for group ($p = 0.04$) regarding non-verbal memory as measured with the Rey figure. Post hoc tests showed that unmedicated patients were significantly impaired compared to medicated patients ($p = 0.02$) and compared to HC ($p = 0.06$), whereas medicated patients and HC did not differ ($p = 0.32$). In depressed patients, but not in HC, we found a negative correlation between CAR and memory function, which was driven by the unmedicated depressed patients.

**Conclusion:** The magnitude of the CAR is strongly associated with impaired memory function in unmedicated depressed patients even though CAR was not significantly increased in these patients. In contrast, medicated patients showed a blunted CAR and unimpaired cognitive function compared to controls. These results suggest that antidepressant treatment may reduce CAR and partially restore memory function even if depressive psychopathology is still present.

Keywords: cortisol awakening response; depression; memory

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Cortisol is associated with longer telomeres in human lymphocytes cultured in folate-replete and deficient conditions

**Background:** Telomeres cap and protect the ends of chromosomes from fusion. Excessively shortened telomeres are associated with telomere dysfunction and chromosomal instability (CIN), DNA damage and an increased risk of degenerative diseases of ageing. Psychological stress has been strongly associated with accelerated telomere shortening, consistent with a wealth of evidence that chronic stress impacts negatively on health, possibly contributing to initiation of cancers, cardiovascular disease and neurodegenerative disorders such as Alzheimer’s disease. Risk for these disorders is increased by deficiency in micronutrients, such as folate, an essential co-factor required for accurate replication of DNA and maintenance of methylation (epigenome) patterns, providing protection against CIN.

**Methods:** The aim of this preliminary study was to test the hypothesis that chronic exposure to the stress hormone cortisol impacts deleteriously on telomere length (TL) and that this effect would be further aggravated by folate (Vitamin B9) deficiency. Human lymphocytes from 3 males and 3 females (aged 53 ± 3 years) were cultured in vitro for 12 days in medium containing either 25 or 120 nM folic acid (FA), together with either 0, 550, 1300 or 3500 nM cortisol. TL (by QFISH flow cytometry), cell growth and viability were measured.

**Results:** Cells cultured in FA-replete medium and chronically exposed to 550 or 1300 nM cortisol displayed longer TL at day 12 than cortisol-free controls ($p < 0.03$). In FA-deficient cultures TL increased with increasing cortisol, however, this effect was not significant in this sample size. TL was longer in lymphocytes cultured in low FA conditions, compared with those in FA-replete medium ($p < 0.0001$). The strongest cell growth was recorded in FA-replete cultures, with cortisol having no effect. Cell viability (%) was higher in cells exposed to cortisol, and this
effect was strongest in FA-deficient cultures, with 16% of variance being attributable to treatment ($p = 0.0002$), and 72% to time ($p < 0.0001$).

**Conclusions:** The results of this study do not support the hypothesis that cortisol, folate deficiency or their interaction can explain telomere shortening associated with psychological stress. Further analyses are being performed to determine if cortisol causes changes in CIN or epigenome status and the extent to which these effects correlate with TL.

Keywords: telomere; cortisol; folate; DNA damage; methylation; lymphocytes

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The effect of intranasal oxytocin on perceiving and understanding emotion on the Mayer-Salovey-Caruso Emotional Intelligence Test

**Background:** There is increasing evidence that oxytocin promotes empathy in humans. However, research on oxytocin and emotion recognition, a fundamental component of empathy, has yielded inconsistent results. Part of the problem is that studies have focused on limited, and varying, categories of emotional stimuli. Therefore, we investigated the effect of intranasal oxytocin on the identification of seven basic emotions (happiness, sadness, fear, excitement, surprise, disgust, and anger) using social and non-social stimuli, and we explored the effect of oxytocin on conceptual understanding of emotion.

**Method:** Eighty-two participants were administered a 24IU dose of intranasal oxytocin or placebo in a double-blind experiment. Participants completed the perceiving (faces, designs) and understanding (blends, changes) emotion components of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) 120 minutes after drug administration.

**Results:** Contrary to our prediction, standardized scores for accurately detecting emotions during the faces task of the MSCEIT were lower following oxytocin administration than placebo ($F(1,80) = 8.861, p < .01, \eta^2 = .10$). Accuracy ratings worsened following oxytocin because participants rated all emotions with greater intensity, particularly facial expressions of surprise and disgust. Oxytocin did not influence performance on tasks related to understanding emotions or tasks using non-social stimuli.

**Conclusions:** Oxytocin appears to influence the recognition of facial expressions of emotion by increasing the perceived intensity of the emotion, while having no effect on more complex processing (i.e., understanding emotion). The present findings further support the view that oxytocin influences social information processing by increasing the salience of emotional stimuli, which may have positive or negative effects depending on context.

Keywords: MSCEIT; intranasal oxytocin; surprise; disgust; emotion recognition; faces

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Methylphenidate does not restore the reduced serum BDNF levels in ADHD children

**Statement of the problem:** Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of trophic factors, which is the most abundant neurotrophin in the brain. BDNF exerts its effects by binding to the tropomyosin-related kinase B (TrkB) receptor. It enhances the growth and maintenance of several neuronal systems, serves as a neurotransmitter modulator, and participates in mechanisms of neuronal plasticity, such as long-term potentiation and learning. We aim to quantify the basal concentration and daily fluctuation of serum BDNF, as well as its possible change in response to prolonged release methylphenidate in an open, quasi-experimental and controlled study.
Methods: A total of 148 (115 males, 33 females) patients, of 9.77 (2.56) years old, were subdivided in two group. (1) Control group (n = 37; 27 males, 10 females); healthy siblings of the Attention deficit hyperactivity disorder (ADHD) patients. (2) ADHD group (n = 111; 88 males, 23 females), without epilepsy and with a normal value in an abbreviated intelligence test Kaufman Brief Intelligence Test (KBIT). In all subjects, after written informed consent, we performed identical clinical, psychometric and biochemical study, before and after (only ADHD group) treatment. ADHD group were diagnosed according Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria and sub-classified in the primary ADHD subtypes by EDAH scale.

Measurement: BDNF by ELISA (IBL International, ref. RB59041), in serum samples obtained at 09:00 and 20:00 h, before and after 4.63 (2.3) months of the daily morning ingestion of PRMPH. Statistic: factorial analyses using statistical package STATA 12.0. Funding: Grant of Spanish government, FIS-P107-0603.

Results:

| Control group | Serum BDNF (ng/ml) in ADHD children | Pre-PRMPH | Post-PRMPH |
|---------------|------------------------------------|-----------|------------|
| Day          | Night                          | Day       | Night      | Day       | Night      |
| 36.36 ± 11.62| 31.78 ± 11.92                   | 31.96 ± 12.57 | 28.40 ± 12.50 | 29.43 ± 12.00 | 26.73 ± 12.32 |

Basal measurements: Day/night comparisons: \( z = -2.76, p = 0.006 \). Group comparison: \( z = -2.19, p = 0.028 \). ADHD pre vs. post: \( \chi^2 = 2.64, p = 0.1042 \); day vs. night: \( \chi^2 = 9.8, p = 0.0017 \).

Conclusion: The ADHD patients show reduced BDNF serum concentrations in relation with siblings controls, concordant with the known pathophysiological mechanisms. Our results do not support the only previous contribution that indicates an increase of BDNF in untreated ADHD children, with positive correlation with the severity of the symptoms of inattention. In addition, we report for the first time “basal” response to treatment with PRMPH, with somewhat surprising results, because as neuronal trophic factor, one might expect an increase in serum in response to methylphenidate, that ameliorates neuropsychological and organic immaturity, proven the last in studies of volumetric magnetic resonance imaging (MRI).

Keywords: methylphenidate; reduced serum; BDNF levels; ADHD; children

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Different basal concentration and different response of BDNF to prolonged release methylphenidate between ADHD subtypes

Statement of the problem: Brain-derived neurotrophic factor (BDNF), a member of the family of neurotrophic receptors, appears to intervene in the pathogenesis and treatment response in Attention deficit hyperactivity disorder (ADHD), hypothesis based on the conceptualization of ADHD as a neurodevelopmental disorder and the importance of the BDNF for normal neural development. In addition, in experimental models, psychostimulants and antidepressants increase the brain concentration of BDNF. Genetic polymorphisms related with the activity of the BDNF seem to correlate with the incidence, clinical manifestations, endophenotypes or the treatment response in ADHD. We aim to define if the response to prolonged release methylphenidate treatment is different in the main ADHD subtypes, in an open, quasi-experimental and controlled study.

Methods: A total of 148 (115 males, 33 females) patients, of 9.77 (2.56) years old, were subdivided in two group. (1) Control group (n = 37; 27 males, 10 females); healthy siblings of the ADHD patients. (2) ADHD group (n = 111; 88 males, 23 females), without epilepsy and with a normal value in an abbreviated intelligence test (KBIT). In all subjects, after written informed consent, we performed identical clinical, psychometric and biochemical study, before and after (only ADHD group) treatment. ADHD group were diagnosed according Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria and sub-classified in the primary ADHD subtypes by EDAH scale (). Measurement: BDNF by ELISA (IBL International, ref. RB59041), in serum samples obtained
at 09:00 and 20:00 h, before and after 4.63 (2.3) months of the daily morning ingestion of PRMPH. Statistic: factorial analyses using statistical package STATA 12.0. Funding: Grant of Spanish government, FIS-Pi07-0603.

**Results:** In the control group serum BDNF concentration in the morning (36.36 ± 11.62 ng/ml) was very similar to the value seen in the predominantly inattentive subgroup of ADHD children, although evening concentration was higher (31.78 ± 11.92 ng/ml). The treatment with prolonged release methylphenidate do not modify the daily fluctuation of BDNF in the children with hyperactive/impulsive/conduct disorder children, whereas in children with predominantly inattentive disorder PRMPH induces a significant decrease ($\chi^2 = 6.62, p = 0.010$).

| ADHD subtype | Pre-MPH Day | Pre-MPH Night | Post-MPH Day | Post-MPH Night |
|--------------|-------------|---------------|--------------|---------------|
| PHI/CD       | 30.76 ± 12.34 | 29.09 ± 12.82 | 30.29 ± 12.5 | 27.25 ± 12.93 |
| PDA          | 35.31 ± 12.85 | 26.41 ± 11.55 | 26.97 ± 10.3 | 25.05 ± 10.21 |

PDA: Day vs. Night, pre: $\chi^2 = 11.63, p = 0.0019$. ADHD pre- vs. post-treatment, day: $\chi^2 = 6.62, p = 0.010$. All statistical values for comparisons not shown were non-significant.

Our results show both similar morning concentrations and daily fluctuation of BDNF, between predominantly inattentive ADHD children and healthy sibling controls. The PRMPH treatment does not modify the reduced BDNF concentration (vs. controls) in hyperactive/conduct disorder children, nor the absence of daily fluctuation; but contrary to expectation reduces the concentration in the predominantly inattentive patients to values similar to that observed at night, disappearing the highly significant basal day/night fluctuation also noted in the control group.

**Conclusion:** Besides our data in hyperactive/conduct disorder children has been reported that the major depression is also associated with a decrease in BDNF concentration. As serum BDNF seem parallel with intra-cerebral concentration, especially in mesencephalic areas, this neurotrophin could be the link between ADHD and major depression, and provide a new pathway for the development of drugs for ADHD.

Keywords: basal concentration; response of BDNF; prolonged release; methylphenidate; ADHD subtypes

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“Differential effects of three classes of antidiabetic drugs on olanzapine-induced glucose dysregulation and insulin resistance in female rats”

Rationale/Statement of the Problem: The second generation antipsychotic drug olanzapine is an effective pharmacological treatment for psychosis. However, there is an increasing awareness that the use of the drug is commonly associated with serious metabolic side-effects in patients, including hyperglycemia, glucose intolerance and insulin resistance, and places patients at risk for developing cardiometabolic disorders, such as Type 2 diabetes. These side effects have been accurately modelled in rodent paradigms. We and other groups have demonstrated previously that olanzapine causes significant glucose intolerance and insulin resistance in rats.

**Methods:** In the present study, we directly compared three distinct classes of antidiabetic drugs, which included metformin (100 and 500 mg/kg, PO), rosiglitazone (6 and 30 mg/kg, PO) and glyburide (2 and 20 mg/kg, PO), on olanzapine-induced glucose dysregulation and insulin resistance. Adult female rats (n = 8–10 per group) were acutely treated with lower (7.5 mg/kg) or higher (15.0 mg/kg) doses of olanzapine, and glucose intolerance was assessed using the glucose tolerance test, while insulin resistance was measured using the HOMA-IR equation.

**Results:** Both doses of olanzapine caused pronounced glucose dysregulation and insulin resistance that were significantly reduced by treatment with metformin and rosiglitazone; however, glucose tolerance did not fully
return to control levels. In contrast, glyburide failed to reverse olanzapine-induced glucose intolerance, despite significantly increasing insulin levels.

**Conclusion:** These findings indicate that oral hypoglycemic drugs which influence hepatic glucose metabolism, such as metformin and rosiglitazone, are more effective in regulating olanzapine-induced glucose dysregulation than those affecting primarily insulin secretion, such as glyburide. The current model may also be used to better understand the biological mechanism of glucose dysregulation caused by olanzapine and how it can be reversed.

Keywords: olanzapine; metformin; rosiglitazone; glyburide; glucose intolerance; insulin resistance

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**Early cortisol awakening response as a biological risk marker in young children**

**Background:** Recent research suggests that atypical cortisol awakening response (CAR) is an outcome of negative factors, such as post traumatic stress disorder (PTSD) (Johnson et al., 2008) and insomnia (Backhaus et al., 2004), in adults. While a positive CAR is present in the vast majority of adults, less is known about the normal development of this response in children. Without a clear sense of typical emergence in early childhood, it is uncertain if risk factors can be standardly associated with the magnitude of CAR during development. Our study aims to expand current research on CAR to children under the age of 8 years. We aim to understand how CAR manifests in young children and how methodological, familial, and child-specific factors contribute to positive CAR (responders).

**Methods:** Fifty-two children (54% female) and mothers participated, ranging in age from 1 to 8 years (M: 4.88, SD: 1.72). Mothers were asked to complete several questionnaires and were sent a “cortisol packet” with instructions to obtain child saliva samples when they awoke (T1) and 45 minutes later (T2) across 2 days. “Responders” were identified as children whose cortisol levels increased from T1 to T2.

**Results:** No difference in responder group by child age was found in this sample. It may suggest a step-like model, such that emergence of positive CAR would begin in infancy (38%; Saridjan, 2010) and that rates may start to increase only around age 10 (60%; Freitag, 2009) until they stabilize in adulthood (75%; Wust, 2000). In contrast to previous literature, methodological variables, such as daily routine and time between samples (Griefahn & Robens, 2011), were not significantly associated with responder status. However, results were consistent with Saridjan and colleagues (2010), demonstrating that lower family income was associated with greater likelihood of being a responder. Maternal psychopathology had no effect on child CAR status. Interestingly, for child-specific factors, internalizing and externalizing scores had the opposite effect such that, for every increase in externalizing score the risk of being in the responder group increased by 13.5%; however, for every increase in internalizing score, the risk of being a responder decreased by 10%.

**Conclusions:** Future research should aim to understand the effects of pure internalizing and externalizing versus comorbidity on cortisol in larger samples.

Keywords: preschoolers; cortisol awakening response; stress; risk factors; internalizing problems; externalizing problems

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**The hypothalamus–pituitary–adrenal axis in patients with CRPS type 1: molar cortisol to DHEA ratio increases with disease duration**

**Background:** The main complaint symptom of complex regional pain syndrome type 1 (CRPS-1) is neuropathic pain. There is significant co-morbidity between neuropathic pain and neuropsychiatric disorders, including anxiety and depression. A decrease in dehydroepiandrosterone (DHEA) or increase in the molar
cortisol to DHEA ratio (molar F/D ratio) is commonly found in patients with psychiatric disorders, such as major depression and posttraumatic stress disorder. However, no information about DHEA secretion is available for patients with CRPS-1. The present study determined the molar F/D ratio within the first hour after awakening in patients with CRPS-1 undergoing combined antidepressant treatment with analgesics and non-steroidal anti-inflammatory drugs.

**Method:** To do this, cortisol and DHEA concentrations were determined from saliva samples, which were collected immediately upon awakening, 30 and 60 min after awakening and at nighttime from patients with CRPS-1 ($n=26$) and age-matched healthy subjects ($n=25$). The beck depression inventory (BDI) was used to quantify depression levels in the medicated patients. The net increase in cortisol levels within the first hour after awakening (CARi) and the area under the cortisol curve with respect to ground within the first hour after awakening (CARauc) were calculated and used as an index of cortisol secretion. The area under the DHEA curve with respect to ground within the first hour after awakening (DHEAauc) was used as an index of DHEA secretion.

**Results:** The mean BDI scores of patients were $19.0\pm9.0$ (range, $5$–$41$). The BDI scores were not associated with any parameters for cortisol, DHEA secretion or other disease-related parameters such as disease duration, frequency of spontaneous pain, or extension of disease spread. We did not observe a difference in indices for cortisol and DHEA secretion between patients who had a value higher than the cut-off for chronic pain (BDI score $21$, $n=10$) or patients who had lower than cut off BDI scores ($n=16$). Among indices for cortisol and DHEA secretion, the molar CARauc to DHEAauc (molar F/Dauc) ratio was associated with disease duration. Patients who suffered from disease for relatively longer time (subgroup 4 month $\geq$) had a higher molar F/Dauc ratio than both controls and patients who suffered for a relatively shorter time (subgroup 4 month $\leq$). There was no difference in BDI scores between subgroups.

**Conclusion:** We used combined analgesic treatment with tricyclic antidepressants, anticonvulsants and non-steroidal anti-inflammatory drugs to relieve pain and pain-related symptoms, such as depression, in patients with CRPS-1, but these results indicate that DHEA secretion after the awakening period decreases in the combined treatment condition.

Keywords: CRPS-1; BDI scores; CAR; molar cortisol to DHEA ratio; disease duration; medication condition

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Changes in prolactin levels and sexual functioning after switching from long-acting injectable risperidone to paliperidone palmitate in young psychotic patients: a case series

**Statement of the problem:** Long-acting injectable (LAI) antipsychotics have been developed to increase compliance in schizophrenia. Risperidone-LAI was the first LAI atypical antipsychotic, as a biweekly injection. Paliperidone Palmitate (PP) is a recently developed LAI atypical antipsychotic that is administered monthly. PP is hydrolized to paliperidone (9-hydroxyrisperidone), the primary active metabolite of risperidone. Although both risperidone and paliperidone are associated with increases in prolactin levels, there is limited information regarding whether there are differences in sexual functioning between both compounds. We aimed to study whether there are changes in prolactin levels and/or sexual function after switching from LAI-risperidone to LAI-paliperidone.

**Methods:** We have studied 12 psychopathologically stable subjects with a psychotic disorder ($n=10$ schizophrenia, 1 schizoaffective, 1 psychosis N.O.S.) attending to the Early Psychosis Program from Reus (HPU Institut Pere Mata, Spain) treated with long-acting risperidone for at least 6 months. All participants were switched to LAI. Clinical assessment was conducted at baseline and 3 months after the switch with measures of psychopathological status (Positive and Negative Symptom Scale [PANSS], Calgary Depression Scale) and sexual dysfunction (Arizona Sexual Experiences Scale [ASEX]). Two fasting blood samples (baseline and 3 months post-switch) were obtained to determine prolactin levels in plasma. SPSS version 17.0 was used to perform the statistical analyses. Wilcoxon test was used to explore changes in continuous variables (e.g. prolactin levels, ASEX scores) during the period of the study. A $p$-value $<0.05$ was considered to be significant.

**Results:** There was a significant reduction in prolactin levels from baseline to the 3-month assessment. Those subjects with higher prolactin levels seemed to show a greater reduction. In relation to sexual dysfunction, although
In some cases improved notably in ASEX scores, the reduction was not significant in all the samples. None of the subjects reported worsening in psychotic symptoms.

**Conclusions:** In our sample, the switch from LAI-risperidone to paliperidone reduced prolactin levels during a 3-month period. However, changes in prolactin levels were not associated with a significant improvement in sexual functioning.

Keywords: prolactin levels; sexual functioning; risperidone; paliperidone palmitate; a case series; psychosis

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**Statement of the problem:** Subjects with psychosis are at risk for metabolic syndrome, mainly secondary to antipsychotic treatment although overeating also plays a role. The hypothalamic–pituitary–adrenal axis, which is involved in visceral obesity, may also affect energy balance through affecting energy intake and the risk for stress-induced hyperphagia. The main aim of the study was to study the association between salivary cortisol, overeating, and obesity in a sample of subjects with early psychosis.

**Methods:** We evaluated 53 participants (mean age: 23.5 years, 42% females) who were attending to the Early Psychosis Program from Reus (HPU Institut Pere Mata, Tarragona, Spain). All participants met criteria for a psychotic disorder or were considered at risk mental states after administration of the Schedules of Clinical Assessment in Neuropsychiatry (SCAN) or the Comprehensive Assessment of At Risk Mental States (CAARMS). Dietary habits were assessed by a dietician who administered the Eating Disorders module of the SCAN to explore two types of overeating: (1) Grazing, defined as repeatedly eating small amounts of food between mean meals (2) Binging, defined as consuming large quantities of food in a very short period of time. As grazing and binging can coexist in the same patient, we recoded overeating in four categories: (1) no overeating, (2) only grazing, (3) only binging and (4) grazing and binging. BMI and waist circumference were registered. A fasting morning saliva sample (9 h) was obtained. Salivary cortisol levels were determined by ELISA. Statistical analyses were performed with SPSS v.17.0. Kruskal–Wallis test was used to test differences between groups in continuous variables. Chi-squared tests were used to test differences between groups in categorical data.

**Results:** Of 53 participants, 37 (69.8%) reported grazing and/or binging. Salivary cortisol was not associated with BMI or waist circumference. Of all participants, the group reporting both grazing and binging showed increased salivary cortisol levels ($p = 0.004$) and greater BMI ($p = 0.035$).

**Conclusions:** In young participants with early psychosis, overeating (coexistence of grazing and binging episodes) is associated with greater BMI and increased morning salivary cortisol levels.

Keywords: prolactin levels; sexual functioning; a case series; psychosis patients; risperidone

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**Rationale/ statement of the problem:** Research has attempted to link atypical hormone patterns to behavior problems in adolescents with varying success. Exploring the interactive effects of hypothalamic–pituitary–adrenal (HPA) and hypothalamic–pituitary–gonadal (HPG) hormones may help clarify findings. Given the lasting influence of early life stress on hormones and mental health, considering the effect maternal depression (MD) may lend additional clarification.

**Clarifying divergent hormone-behavior associations: the influence of neuroendocrine measures and early maternal depression on adolescent mental health trajectories

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**Clarifying divergent hormone-behavior associations: the influence of neuroendocrine measures and early maternal depression on adolescent mental health trajectories

**Rationale/ statement of the problem:** Research has attempted to link atypical hormone patterns to behavior problems in adolescents with varying success. Exploring the interactive effects of hypothalamic–pituitary–adrenal (HPA) and hypothalamic–pituitary–gonadal (HPG) hormones may help clarify findings. Given the lasting influence of early life stress on hormones and mental health, considering the effect maternal depression (MD) may lend additional clarification.
Methods: Longitudinal data from 346 youth (171 males) were used to examine these associations. MD was measured during infancy and preschool with the Center for Epidemiologic Studies Depression scale. Morning levels of cortisol, dehydroepiandrosterone (DHEA), and testosterone were assessed at age 15 years. Internalizing and externalizing at 15, 16, 17, and 18 years were assessed with multi-informant report on the MacArthur Health and Behaviors Questionnaire using variables measuring number of symptoms (severity) and preponderance of one symptom type over the other (directionality). A two-level hierarchical linear model examined how neuroendocrine measures, early MD, and sex independently and jointly influenced mental health trajectories.

Results: For severity, a two-way interaction \((B = -0.095, t = -2.25, p < 0.05)\) revealed that adolescents with high cortisol-low testosterone displayed elevated mental health symptoms and a significant three-way interaction \((B = -0.019, t = -2.05, p < 0.05)\) revealed that adolescents exposed to early MD with high cortisol-high DHEA also displayed more symptoms. A significant three-way interaction \((B = -0.213, t = -2.01, p < 0.05)\) revealed that girls with high cortisol-low testosterone displayed elevated mental health symptoms and a significant four-way interaction \((B = -0.080, t = -2.60, p = 0.01)\) revealed that girls exposed to early MD with low cortisol and high testosterone also displayed increased mental health symptoms. Directionality findings revealed altered hormone patterns predicted internalizing symptoms for girls but externalizing for boys.

Conclusions: Results support the benefits of examining multiple hormones in the prediction of mental health problems and suggest additional hormone risk patterns are present in individuals exposed to early life MD.

Keywords: cortisol; testosterone; DHEA; early maternal depression; mental health; adolescence

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Serotonin 2c receptor gene expression in the rhesus amygdala predicts anxious temperament

Rationale/statement of the problem: In the central nervous system, the serotonin (5HT) neurotransmitter system plays a key role in the regulation of mood and emotion. Alterations in the 5HT system are thought to contribute to psychopathologies. In addition, drugs targeting the 5HT system are effective in the treatment of depression and anxiety disorders. Children with anxious temperament (AT) are characterized by excessive shyness, worrying, and avoidant behavior. This temperament, when stable across development, increases the risk of later developing depression and anxiety disorders. Using a well-established, nonhuman primate model of AT, we tested whether variations in the 5HT system predict individual differences in AT. We focused on the central nucleus region of the amygdala (CeA) because we have established that metabolic activity in this region is predictive of AT.

Methods: Using Affymetrix GeneChip® rhesus macaque genome arrays, we assessed gene expression from CeA tissue in 24 young male rhesus monkeys phenotyped for AT. Robust regression analysis was performed with correction for multiple comparisons across all annotated transcripts that are part of the neuroactive ligand pathway (KO04080) in the Kyoto Encyclopedia of Genes and Genomes (KEGG) database.

Results: As hypothesized, variation in gene expression predicted individual differences in AT. Specifically, of the thirteen 5HT receptors assessed, only the 5HT2C receptor (5HT2C; \(r = -0.57, p < 0.01\)) was identified in the microarray analysis as significantly negatively correlated with AT. Quantitative real-time polymerase chain reaction analysis using the same CeA RNA samples confirmed this association \((r = -0.65, p < 0.001)\). Underscoring the anatomical specificity of this effect, the significant relationship between 5HT2C receptor mRNA levels and AT was not observed in the motor cortex, a brain region not associated with AT \((r = 0.10, p = 0.64)\).

Conclusions: Previous work by others has shown robust levels of 5HT2C receptor mRNA and radioligand binding in the monkey CeA. In addition, rodent models have indicated a role for the 5HT2C receptor in anxiety-like responding. Our findings suggest that higher levels of 5HT2C receptor gene expression are associated with lower levels of AT. Increased expression of the gene encoding for this receptor may facilitate 5HT signaling in the amygdala thereby promoting adaptive responses and resilience to potentially anxiety provoking situations.

Keywords: serotonin; 2c receptor; gene expression; rhesus amygdale; anxiety; temperament

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Sweating the big stuff: dispositional pessimism exacerbates the deleterious effects of life stress on metabolic health

Rationale: Although pessimistic individuals are at increased risk for developing cardiovascular disease, the biological mechanisms underlying this effect, and the social-environmental factors that modify these effects, remain unclear. To address this issue, we examined how pessimism, defined as the generalized tendency to expect negative outcomes, interacts with life stress exposure to predict metabolic health.

Methods: Seventy-one pre-menopausal mothers who had a child with autism and 36 did not participated in the study. They ranged from 28 to 51 years-old (M = 41.3, SD = 5.1), had body mass indices from 17.2 to 43 (M = 25.58, SD = 5.76), and were free of major chronic illnesses, including diabetes and metabolic syndrome. Participants provided fasting blood samples, had their body measurements taken, completed the Life Orientation Test-Revised to assess their level of pessimism (M = 6.37, SD = 2.96) and the Stress and Adversity Inventory to assess their exposure to chronic stress over the life course (M = 7.76, SD = 4.35). Participants’ “metabolic risk” was indexed based on waist circumference, glucose, ratio of total cholesterol to HDL, triglyceride levels, and systolic blood pressure.

Results: As predicted, pessimism and cumulative life stress exposure were each independently associated with greater metabolic risk, independent of age, income and caregiver status (Pessimism: b = 0.49, p < 0.001; Stress: b = 0.33, p = 0.003). Moreover, when adjusting for age, income and caregiver status, pessimism interacted with cumulative stress exposure to predict greater metabolic risk (F = 7.29, p = 0.01). Decomposing this interaction effect revealed that pessimistic individuals experiencing high levels of cumulative life stress had the poorest metabolic health.

Conclusions: These results suggest that pessimistic individuals living under high levels of stress may have the greatest risk for cardiovascular disease and highlight pessimistic beliefs as a possible treatment target for reducing stress-related disease burden.

Keywords: pessimism; life stress; metabolic health; cardiovascular disease

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Lower heart rate variability is associated with cancer-related fatigue in breast cancer survivors

Background: Fatigue is the most common and distressing symptom reported by breast cancer survivors and yet the pathophysiology of cancer-related fatigue remains largely unknown. Fatigue is associated with lower parasympathetic and higher sympathetic nervous system activity in non-cancer samples, but only one study has demonstrated this same relationship in breast cancer survivors. This study evaluates the relationship between fatigue and basal autonomic nervous system activity as measured by heart rate variability (HRV) in a sample of breast cancer survivors.

Methods: Women who had been diagnosed with early stage breast cancer before the age of 50 were recruited from the UCLA tumor registry and completed psychological questionnaires, including measures of fatigue. A subset of these women (n = 30) participated in a follow-up study in which they completed measures of fatigue, energy and mood four times per day for 5 days using electronic diaries, provided 3 days of saliva samples for cortisol assessment and underwent physiological assessment including electrocardiogram (ECG). HRV was assessed via ECG R-R wave spectral and time sequence analysis.

Results: Questionnaire measures of fatigue were negatively associated with indices of parasympathetic nervous system activity, B = -3.85, p = 0.04 for RMSSD (root of the mean squared difference of successive normal to normal waves) and B = -76.97, p = 0.04 for LF power % (low-frequency wave power percentage). Daily fatigue was also associated with lower basal HRV, B = -15.1, p = 0.04 for RMSSD. However, fatigue indices were not associated with sympathetic nervous system activity as measured by low- to high-frequency wave ratio. Of note, fatigue was not associated with average daily cortisol output (AUC).

Conclusions: Lower HRV has been associated with increased chronic inflammation, which is elevated in cancer survivors reporting persistent fatigue, thus providing insight into potential system interactions underlying the mechanisms for cancer-related fatigue.
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Gender-dependent effects of body esteem and appraisal on cortisol stress responses

**Background:** The Social Self Preservation Theory posits that situations that threaten the ‘social self’ elicit shame which, in turn, is linked to cortisol stress response. Body esteem may be one predictor of the propensity to respond with shame to stress. Hence, the present study aimed at assessing whether body esteem is associated with cortisol stress responses, and further, whether this relationship is mediated by cognitive appraisals of challenge and threat.

**Methods:** We exposed 44 participants (21 F, 21 M; 22 years) to the Trier Social Stress Test (TSST). Salivary cortisol was assessed at -1, +1, +10, +30, and +50 min. Body esteem (BE) as well as subscales addressing appearance, weight, and attribution of others’ judgments were assessed with the Body Esteem Scale for Adolescents and Adults (BESAA). Appraisals of challenge and threat were assessed with the Primary and Secondary Appraisal Scale (PASA).

**Results:** While the TSST successfully elicited cortisol stress responses ($F = 6.85, p = 0.001$), hierarchical regression analysis revealed that females with low BE showed higher cortisol stress responses than females with high BE, while the opposite was true for males ($\beta = 0.44, p = 0.047$). The same pattern was found for the two BE subscales addressing weight and overall appearance ($\beta = 0.42, p = 0.04; \beta = 0.42, p = 0.04$), but not for the attribution subscale ($p < 0.24$). Body esteem was also associated with challenge appraisals in a gender-dependent manner: males with high BE reported feeling less challenged, while females with high BE reported feeling more challenged ($\beta = -0.63, p = 0.005$). Neither threat nor challenge scores were themselves linked to cortisol responses.

**Conclusions:** Despite the strong social-evaluative component of our stress test, these findings suggest that how one feels about one’s weight and overall physical appearance matters more than what one thinks others may think in this regard. Interestingly, those feelings and beliefs may be associated with gender differences in stress appraisal, such that for females, high BE may be stress protective, while for men, low BE may lead to disengagement from a stressful situation.

Keywords: cortisol; stress; body esteem; threat; challenge; appraisal

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Hyperprolactinemia and amenorrhea associated with risperidone normalized after switching to olanzapine: a case report

**Background:** Hyperprolactinemia as one of the frequent adverse effects associated with the use of antipsychotics is often neglected but can interrupt the compliance of treatment (1,2). Antipsychotic-induced hyperprolactinemia in women with schizophrenia frequently results in menstrual dysfunction (3) despite its potential to block D2 receptors. However, little (or less?) is known about the effect of olanzapine on prolactin levels in women.

**Methods:** Ms. S, military white-collar, a 35-year-old woman with psychosis, experienced amenorrhea shortly after beginning as well as during treatment with risperidone, 6 mg/day. Previously, she had been treated with haloperidol; she recalled one other occasion when her menses had ceased for 3 months. Before treatment with risperidone, however, Ms. S had been having regular monthly menstrual periods. Medical evaluation revealed an elevated serum prolactin level (100 ng/ml), a negative pregnancy test, and normal thyroid function tests. Magnetic resonance imaging showed no evidence of pituitary adenoma. Alternative treatment with olanzapine was initiated and titrated to 20 mg/day.

**Results:** After 2 months of olanzapine treatment, Ms. S's monthly menses resumed. Serum prolactin levels, although still elevated, trended downward to 86 ng/ml and 52 ng/ml after 2 and 4 months of olanzapine treatment, respectively. Although she has olanzapine-induced weight gain, her psychiatric condition remained in remission.

Keywords: hyperprolactinemia; amenorrhea; risperidone; olanzapine

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Conclusions: There are clinical trials regarding improvement of hyperprolactinemia after switching to olanzapine (4). We reviewed a case in which risperidone-induced hyperprolactinemia–amenorrhea normalized without clinical worsening after switching to olanzapine.

Keywords: olanzapine; risperidone; hyperprolactinemia; amenorrhea; treatment; psychosis

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Amenorrhea associated with olanzapine normalized after switching to aripiprazole: a case report

Background: Amenorrhea as one of frequent adverse effects associated with the use of atypical antipsychotics is often neglected but can interrupt the compliance of treatment. There are clinical trials regarding improvement of hyperprolactinemia after switching to olanzapine while some trials regarding the opposite and the improvement with aripiprazole. Aripiprazole is an antipsychotic with partial dopamine antagonism and agonism. Its advantageous side effect profile has been described earlier. We reviewed a case in which olanzapine induced amenorrhea normalized without clinical worsening after switching to aripiprazole.

Methods: Ms. C, a 36-year-old woman with psychosis, developed menstrual dysfunction and galactorrhea soon after beginning a treatment of olanzapine, 20 mg/day. She reported having monthly menses before regimen. After 3 month of treatment, menses were absent and galactorrhea began. Ms. C was not pregnant. Her prolactin level was 157.20 ng/ml, and an MRI showed no sign of pituitary adenoma. Olanzapine medication was discontinued in the patients because of galactorrhea, and raised liver enzyme activities. Aripiprazole was initiated and titrated to 15 mg/day.

Results: After 1 month of aripiprazole treatment, monthly menses resumed and galactorrhea resolved. The serum prolactin fell to a normal level (27.20 ng/ml). Ms. C’s psychiatric condition improved and she has remission.

Conclusions: Aripiprazole’s reduced potential to elevate prolactin may provide a treatment advantage for women with schizophrenia. Moreover, since menstrual cycles may normalize during treatment with aripiprazole, women treated with this drug may have improved fertility when compared with women receiving typical antipsychotics and olanzapine. In this case, aripiprazole treatment resulted in reduction of serum prolactin levels and resolution of galactorrhea. Further studies will be required to assess the comparative effects of aripiprazole and other antipsychotics on prolactin levels and resolution of galactorrhea.

Keywords: aripiprazole; olanzapine; amenorrhea; treatment; psychosis

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Understanding the impact of sleep duration on cortisol awakening response during early adulthood

Background: The impact of sleep on basal Hypothalamic–Pituitary–Adrenal (HPA)-axis functioning has been well documented. Specifically, decreased sleep quality and quantity are associated with higher basal cortisol levels, one index of HPA-axis functioning. Few studies, however, have examined the impact of sleep quality and quantity on the cortisol awakening response (CAR), or the diurnal peak in cortisol that occurs shortly after awakening. Investigating this association is important given that a higher CAR is associated with an increased risk for mental and physical health problems. Therefore, the current study aims to further examine the relationship between sleep and CAR in order to gain a better understanding of sleep’s impact on HPA-axis functioning.

Methods: 58 undergraduate students (29 males; mean age = 18.74) were assessed over two consecutive mornings. Each morning, participants completed a daily sleep diary to assess self-reported sleep quality and total sleep time (TST) from the previous night. Saliva samples were used to obtain morning cortisol levels. Participants were asked to provide four saliva samples by spitting into salivettes. The first sample was obtained immediately after
awakening. The following three samples were obtained at 30, 45, and 60 minutes after the first sample. Participants repeated this procedure on Day 2.

**Results:** Multilevel growth curve modeling was used in order to examine the impact of sleep quality and quantity on CAR. Results from the current study demonstrate that TST, or the total minutes slept during the preceding night on each day was significantly associated with both the intercept and slope of the model. More specifically, lower TST was associated with lower cortisol levels at awakening ($t = 5.40, p < 0.0001$), but a steeper post-awakening cortisol slope ($t = −2.55, p = 0.01$). After accounting for TST, however, sleep quality did not significantly predict any parameters in the model.

**Conclusions:** Contrary to prior research that has reported no or a small association between sleep duration and CAR, our study shows that participants with shorter sleep duration have lower cortisol levels at awakening and a faster rate of cortisol increase following awakening. Thus, these findings suggest that the amount a person sleeps may directly impact their diurnal cortisol pattern the subsequent morning.

Keywords: HPA axis; cortisol; sleep; college students

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**Determination of steroid hormones in human hair as a retrospective biomarker with HPLC-MS/MS**

**Statement of the problem:** The analysis of steroid hormones in hair is increasingly used in psychoneuroendocrinological research as a valid and easily implementable method for the retrospective assessment of cumulative long-term hormone secretion. To determine steroid hormone concentrations in hair, most laboratories have so far relied on immunochemical assays which are fast and easy to perform, but have a reduced reliability and analytical specificity due to cross-reactivity with other substances. Furthermore, immunoassay can only measure a single steroid at one time. By contrast, liquid chromatography tandem mass spectrometry (LC-MS/MS) has better specificity, sensitivity and reproducibility, and can measure a wide spectrum of steroid hormones simultaneously. Here, we report data on the development of a new LC-MS/MS-based method for the identification of endogenous concentrations of seven steroid hormones (cortisol, cortisone, testosterone, progesterone, corticosterone, DHEA, androstendione) in human hair.

**Methods:** Hair samples were first washed with isopropanol. Steroid hormones were extracted from 10 mg whole hair by 1.8 ml methanol incubation at room temperature. One milliliter methanol was transferred to a new tube and evaporated to dryness. Then the extraction was resuspended with 0.25 ml water, 0.20 ml of which was injected into the machine for analysis.

**Results:** The limits of detection were 0.1 pg/mg (cortisol), 0.1 pg/mg (cortisone), 0.4 pg/mg (testosterone), 0.9 pg/mg (progesterone), 0.4 pg/mg (corticosterone), 9.0 pg/mg (DHEA), 0.1 pg/mg (androstendione). Linear ranges were 0.5–100 pg/mg (cortisol), 0.5–100 pg/mg (cortisone), 2–100 pg/mg (testosterone), 4–100 pg/mg (progesterone), 2–100 pg/mg (corticosterone), 40–1000 pg/mg (DHEA) and 0.5–100 pg/mg (androstendione).

**Conclusions:** This LC-MS/MS method provides a highly specific analytical strategy for the detection of seven endogenous hormones in human hair and is thus likely to further enhance the accuracy of future research in this field.

Keywords: human hair; steroid hormones; high performance liquid chromatography; mass spectrometry

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Distinct panicogenic activity of sodium lactate and cholecystokinin tetrapeptide in patients with panic disorder

**Rationale:** The validity of experimentally induced panic attacks as a model to study the pathophysiology of panic disorder has been questioned. Unspecific, unpleasant and aversive effects as well as specific patterns of psycho vegetative symptoms pointing to different subtypes of panic disorder have been observed. These findings raise the question of challenge paradigms as a valuable tool to identify different vulnerabilities in patients with panic disorder.

**Methods:** We compared the two most widely studied panicogenic drugs sodium lactate and cholecystokinin tetrapeptide (CCK-4) with placebo in 25 patients with panic disorder and age- and gender-matched healthy control subjects. To measure psychophysiological changes, we repeatedly administered the Acute Panic Inventory (API) and visual analogue scales for anxiety and arousal. Cardiovascular (heart rate and blood pressure) and neuroendocrine (ACTH, Cortisol and prolactin) data were recorded simultaneously.

**Results:** In patients with panic disorder, 18 out of 26 experienced a sodium lactate- or a CCK-4 induced panic attack. Lactate or CCK-4-induced symptoms and induced panic attacks were only correlated in healthy controls, but not in patients with panic disorder. (Analysis of sodium lactate- and CCK-4-induced changes of cardiovascular and neuroendocrine parameters is in progress at the moment and results will be presented).

**Conclusions:** The mechanisms of lactate and CCK-4 induced panic attacks are distinct in panic disorder patients but not in healthy controls. Different neurobiological vulnerabilities may be uncovered by different challenges and may indicate differential response to specific therapeutic interventions as well.

Keywords: panic disorder; CCK-4; lactate; acute panic inventory; panicogenic activity

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Acute psychosocial stress determines cognitive control states in dual-task performance

**Rationale/Statement of the problem:** A major control demand in successful dual-task performance is the task-specific separation of task-goal representations and of the related stimulus-response translation processes. Although these cognitive control processes of task shielding and the physiological effects of acute stress share substantial neural commonalities such as their relation to the prefrontal cortex (PFC), direct empirical evidence of how specific PFC-related cognitive control processes involved in dual-tasking are influenced by acute stress is still missing. Therefore, the present study investigated the impact of acute psychosocial stress on task shielding in dual-task performance.

**Methods:** Fifty-six healthy subjects were exposed to either an acute psychosocial stressor (the Trier Social Stress Test) or a standardised control situation prior to a dual task. The individual physiological stress response was monitored by analysing salivary α-amylase (sAA) and cortisol as markers of sympathetic nervous-system and hypothalamus–pituitary–adrenal (HPA)-axis activity, respectively. Task shielding was assessed by the amount of interference of Task 2 processing on prioritised Task 1 performance (between-task interference).

**Results:** Following successful stress induction, as indicated by increases in sAA and cortisol, stressed individuals displayed increased between-task interference relative to controls. This result was further substantiated by a correlation between treatment-related increase in cortisol, but not sAA, and between-task interference.

**Conclusion:** Acute psychosocial stress reduces task shielding, and thus allows for more between-task interference in dual-task performance. We interpret this finding as a shift in cognitive control states from a more serial resource-demanding to a more parallel resource-efficient task-processing mode. The results further suggest a potential role of the HPA-stress response for the development of the observed control adjustment.

Keywords: psychosocial stress; cognitive control; dual task performance; HPA axis; physiological stress

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Depressive symptoms are not associated with leukocyte telomere length: findings from the Nova Scotia Health Survey (NSHS95) population-based study

Rationale/statement of the problem: Leukocyte telomere length (LTL), a marker of cellular aging, has been proposed as a pathogenic mechanism by which depression may confer increased risk of adverse cardiovascular events. Prior studies have suggested that depression and depressive symptoms are associated with shorter LTL, but these studies are limited by small sample sizes, selective enrollment of participants (e.g., psychiatric outpatients), and lack of adjustment for cardiovascular risk factors and other covariates. The present study examines the association of LTL with depression and depressive symptoms in a large, populations-based cohort.

Methods: Participants included 2225 apparently healthy individuals from the 1995 Nova Scotia Health Survey (NSHS95) population-based study. Depressive symptoms were assessed by the Center for Epidemiological Studies-Depression (CES-D) scale. LTL was assessed by a real-time polymerase chain reaction method. Linear regression analyses were used to examine the association between LTL and depressive symptoms, probable depressive disorder (CES-D ≥10 or CES-D ≥16), and specific depressive symptom clusters (depressed affect, somatic concerns, positive affect, and interpersonal problems). These analyses were adjusted for clinical and demographic factors thought to potentially confound the association between depression and LTL, including: age, sex, body mass index, Framingham risk score, and previous ischemic heart disease.

Results: In an unadjusted model, each 1-point increase on the CES-D was significantly associated with a 3.49 base pair increase in LTL (95% CI = 0.39–6.60, p = 0.03). However, this association was not significant after adjustment for age and sex (β = 1.20, 95% CI = −1.85–4.25, p = 0.44) and further adjustment for other covariates (all p’s ≥0.37). Neither probable depressive disorder nor specific depressive symptom clusters were independently associated with LTL after adjustment for covariates.

Conclusion: Concurrent depressive symptoms were not independently associated with LTL in a large population-based study. These results suggest that the excess risk of cardiovascular disease risk associated with concurrent depression may not be due to accelerated cellular aging.

Keywords: depression; depressive symptoms; telomere; cardiovascular disease; cellular aging

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Cortisol predicts decreased cerebral cortical volume in 592 young non-human primates

Background: Cortisol is a stress-related hormone that interacts with peripheral and neural systems. Although cortisol is important for short-term stress responses, chronically high cortisol is hypothesised to underlie the long-term effects of chronic stress, including decreased dendritic arborisation in rodent prefrontal cortex (PFC). Here we examined the relationship between variation in stress-induced cortisol levels and regional brain volume in 592 young rhesus monkeys.

Methods: Cortisol was quantified from blood samples taken from 592 rhesus monkeys (μ-age: 1.88 years; sex: 265 F) immediately after a human intruder presented their profile to the monkey for 30 min. T1-weighted structural MRI scans, taken within 2 weeks of testing, were transformed to an atlas-based study specific template using ANTS (http://www.picsl.upenn.edu/ANTS/). For each subject, we decomposed the final standard-space transformation into affine (linear) and deformable (nonlinear) components. We then produced a 3D map of the relative volume change from the deformable transformation, which accounts for whole-brain differences. Voxelwise robust regression analyses assessed the relationship between cortisol and brain volume, as measured using the log-jacobian determinant.

Results: Those subjects with higher cortisol had significant decreases in cortical volume. More specifically, there was a significant negative relationship (FDR, q<0.05, two-tailed) between the log-jacobian and cortisol in cytoarchitectonic areas 47o, 46/9, 46 and 8 within the PFC, as well as motor area 4 and parietal area PGa (MIP).
Conclusions: These results provide novel evidence that higher cortisol is associated with less PFC volume in young primates, and builds on previous work examining the relationship between stress and cortical thickness in older adult humans. These data, collected in very young animals, demonstrate that PFC volume and cortisol are negatively associated early in life. These findings are particularly interesting because the PFC regions identified here undergo substantial development throughout late childhood and early adulthood. Moreover, because changes in PFC are thought to underlie the emergence of adult-like cognitive and emotional functioning, our findings may have great relevance to the later development of affective psychopathology.

Keywords: cortisol; prefrontal cortex; primate; imaging; anxiety

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Cortisol predicts increased internal capsule integrity in a large sample of non-human primates

Background: Cortisol is critical for survival and reflects a primary mechanism by which emotions can influence immune responses throughout the periphery. Although cortisol release is adaptive in response to stress, chronically increased cortisol is known to have negative effects on both body and brain. Here we use a large sample of rhesus monkeys to examine individual differences in stress-related cortisol, in relation to white matter (WM) structure within a distributed brain network. We correlated individual differences in stress-induced cortisol with diffusion tensor imaging (DTI) measures of WM microstructure in 330 young rhesus monkeys.

Methods: 330 young rhesus macaques were scanned. Diffusion-weighted imaging was performed using a GE SIGNA 3T scanner. Scanning parameters were $b = 1000 \text{ s/mm}^2$, $\text{TR} = 10 \text{ s}$, $\text{TE} = 77.2 \text{ ms}$, $\text{FOV} = 14 \text{ cm}$, matrix $= 128 \times 128$, 2.5 mm slices. Brains were transformed to a standard space using DTI-TK normalization tool (http://www.nitrc.org/projects/dtitk), which iteratively constructs a nonlinear template from the tensor files. Fractional anisotropy maps were computed in standard space. Cortisol was measured from the blood after a No Eye Contact (NEC) challenge, where a human intruder entered the room for 30 minutes without having eye contact with the monkey. We used robust regression to examine the relationship between fractional anisotropy (FA) and cortisol levels while controlling for age and sex.

Results: Individual differences in cortisol were correlated with DTI-measured FA in the internal capsule ($p < 0.001$, two-tailed test, uncorrected), among other regions. The internal capsule is widely connected to distributed brain regions. Therefore, we used deterministic tractography to specifically identify the regions that were connected to the internal capsule region that predicted plasma cortisol levels. Results demonstrated connectivity with the dorsal putamen, anterior cingulate, hypothalamus, and brainstem structures.

Conclusions: Our data suggest that naturally occurring increased levels of cortisol are associated with structural differences in key WM regions that coordinate long-range connectivity. Because these connections are important for adaptive and maladaptive stress responses, these findings are highly relevant to understanding the development of stress-related psychopathology.

Keywords: cortisol; diffusion tensor imaging; DTI; primate; anxiety

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Cell aging and resilience: associations between daily emotion regulation and increased telomerase activity

Rationale: Chronic stress has been related to lower telomerase, an enzyme that helps preserve the integrity of DNA and slow immunological aging. However, it is unknown whether daily psychological processes reflecting healthy emotion regulation protect against stress-related immune-aging.
Methods: We examined basal telomerase activity in a sample of 72 healthy premenopausal women across a range of stress levels, including 35 mothers caring for a child with autism and 37 low-stress control mothers of healthy children. Participants completed a nightly diary over the course of a week, reporting their exposure to positive and negative events. Then they rated the extent to which they employed various emotion-regulation strategies in response to these events. Within-subject weekly means for all measures were calculated. In addition, composite scores for positive affect in response to positive daily events and negative affect in response to daily stressors were calculated, and weekly means obtained. Depressive symptoms were assessed using the Inventory of Depressive Symptoms. On day 4 of the study week, a fasting blood draw was performed to measure peripheral blood mononuclear cells (PBMC) telomerase activity.

Results: Higher telomerase activity was significantly associated with the use of more resilient emotion regulation strategies, including more positive emotional responses to positive daily events ($r = 0.27, p = 0.02$) and increased savoring of positive daily events ($r = 0.24, p = 0.04$). In general, negative emotional responses and rumination in response to daily stressors were not related to telomerase with two exceptions: lower telomerase was associated with greater emotional suppression ($r = -0.34, p < 0.01$) and higher levels of depressive symptoms ($r = -0.24, p = 0.05$). There were no overall differences in telomerase activity between caregivers versus controls.

Conclusion: These are the first findings to link daily emotion-regulation processes to telomerase activity. Daily emotion regulation strategies characterized by greater engagement with the positive and lower emotional suppression are associated with increases in telomerase, which may contribute to resilient immune cell aging. Emotion regulation, particularly in relation to the use of strategies that maintains a positive outlook in the face of stressful life exposures, may protect against cell aging.

Keywords: emotion regulation; cell aging; telomerase; telomeres; coping; positive psychology; chronic stress; psychoneuroimmunology; resilience

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Polygenic risk accelerates the developmental progression to persistent heavy smoking and nicotine dependence: evidence from a 4-decade longitudinal study

Background: To test how genomic loci identified in genome-wide association studies (GWAS) influence the developmental progression of smoking behavior.

Design: A 38-year prospective longitudinal study of a representative birth-cohort.

Setting: The Dunedin Multidisciplinary Health and Development Study was conducted in Dunedin, New Zealand.

Participants: A total of 1037 male and female study members participated in this study.

Main exposures: We assessed genetic risk with a multi-locus genetic risk score (GRS). The GRS was composed of single-nucleotide polymorphisms identified in three meta-analyses of GWAS of smoking quantity phenotypes.

Outcome measures: Smoking initiation, conversion to daily smoking, progression to heavy smoking, nicotine dependence (Fagerstrom Test of Nicotine Dependence), and cessation difficulties were evaluated at eight assessments spanning ages 11–38 years.

Results: GRS was unrelated to smoking initiation. However, individuals at higher genetic risk were more likely to convert to daily smoking as teenagers, progressed more rapidly from smoking initiation to heavy smoking, persisted longer in smoking heavily, developed nicotine dependence more frequently, were more reliant on smoking to cope with stress, and were more likely to fail in their cessation attempts. Further analysis revealed that two adolescent developmental phenotypes—early conversion to daily smoking and rapid progression to heavy smoking—mediated associations between the GRS and mature phenotypes of persistent heavy smoking, nicotine dependence, and cessation failure. The GRS predicted smoking risk over and above family history.

Conclusions: Initiatives that disrupt the developmental progression of smoking behavior among adolescents may mitigate genetic risks for developing adult smoking problems. Future genetic research may maximize discovery potential by focusing on smoking behavior soon after smoking initiation and by studying young smokers.

Keywords: smoking behavior; genetic risk; longitudinal study; adolescent development

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PBMC telomerase activity correlates with hippocampal volume in major depression

The cellular enzyme elomerase replenishes telomeric DNA, which can be lost during repeated mitoses or during exposure to inflammation and oxidation. However, telomerase may have other, non-canonical functions, including (in animal models) antidepressant and neurogenesis-enhancing effects. In this study, we determined the relationship between telomerase activity [(measured in peripheral blood mononuclear cells (PBMCs))] and hippocampal (HC) volume in depressed individuals (MDDs) and matched controls. Nineteen medication-free subjects with MDD and 17 matched healthy controls underwent 4T MRI scanning and fasting morning venipuncture for assessment of unstimulated PBMC telomerase activity. Due to the exploratory nature of the study, corrections for multiple comparisons were not applied.

Hippocampal volume was smaller, but not significantly so, in the MDDs than the controls. As reported previously, MDD subjects had significantly higher PBMC telomerase activity than the controls ($p < 0.007$). Within the MDD group (but not in the control group or in the combined sample), PBMC telomerase activity was positively correlated with HC volume ($r = 0.49$, $p < 0.04$).

The relationship between telomerase activity in PBMCs and telomerase activity in the HC is unknown. Nonetheless, these results are consistent with emerging preclinical data that telomerase may have neurotrophic and antidepressant effects, may facilitate the neurotrophic effects of brain derived neruotrophic factor (BDNF) and may reverse certain signs of aging, and with clinical data that telomerase may be associated with favorable antidepressant responses. Our finding of significant telomerase/HC correlations only in the MDD subjects raises the possibility that telomerase may play a compensatory or reparative role in this disease.

Keywords: telomerase; depression; hippocampal volume; antidepressant effects

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Cortisol awakening response and cortisol/DHEA ratio associations with hippocampal volume in MDD

Prior studies of Hypothalamic-Pituitary-Adrenal (HPA) associations with hippocampal (HC) volume have yielded inconsistent results. This might be due to the use of basal cortisol rather than cortisol reactivity measures and to the use of cortisol in isolation from related steroids. Therefore, in this study, we assessed the relationship of HC volume to cortisol awakening responses (CARs) and to the ratio of cortisol/DHEA in depressed (MDD) subjects and healthy controls. We additionally assessed cortisol correlations with individual HC subfield volumes.

A 4 Tesla T1 MR imaging was conducted for HC volume for 19 MDD subjects and 19 matched controls. Fasting morning serum was assayed for cortisol and DHEA. In addition, salivary samples were assayed for cortisol for 17 MDDs and 15 controls across 3 days: at Waking (Sample 1) and at +30 minutes after waking (Sample 2). The CAR is the difference between daily Sample 1 and Sample 2 salivary concentrations. The slope of the CARin increase was obtained by dividing the CAR by the actual length of time between the two sample collections.

Serum cortisol was not significantly correlated with HC volume. However, in the MDD group, serum DHEA, a putative anti-glucocorticoid, was positively correlated with HC volume ($p < 0.04$). In the combined sample and in the MDD group separately, the serum ratio of cortisol/DHEA was inversely correlated with HC volume ($p < 0.002$ and $p = 0.009$, respectively).

The average CAR slope across all three days of collection was not significantly correlated with HC volume. However, consistent with reports that CAR reactivity is greatest on the first day of collection, CAR slopes on Day 1 were negatively correlated with total HC volume ($p < 0.02$) and with CA1 subfield volume ($p < 0.05$). Correlation
coefficients were similar in the separate MDD and control groups but were not statistically significant, given the smaller sample sizes. This exploratory study (small sample with no correction for multiple comparisons) suggests that stimulated (e.g., CAR) cortisol levels and consideration of cortisol in relation to DHEA, are more likely to reveal significant correlations with HC volume. HC volume may be especially sensitive to stimulated peak levels of cortisol and to cortisol actions when unmitigated by DHEA actions.

Keywords: cortisol; depression; hippocampus; DHEA; cortisol awakening response

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Influence of physical activity and acute exercise on cognitive performance and saliva testosterone in preadolescent school children

Background: We investigated whether the habitual physical activity (PA) level had an impact on the acute effects of a short bout of 12 minutes of intensive exercise on cognitive performance and testosterone (T) concentration in primary school children. We further looked for associations between the T concentration and cognitive performance.

Methods: 42 students of a fourth grade (9–10 years of age) were randomly assigned to an experimental group (EG, n=27) and a control group (CG, n=15). The first saliva collection took place after a normal school lesson in which the students filled out a habitual physical activity questionnaire and completed the d2-test, a test of selective attention (pre-test). While the intervention (12 min) the EG performed an intensive exercise at a heart rate (HR) of 180–190 bpm and the CG participants watched a non-arousing movie. Afterwards, saliva samples were taken and both groups again completed the d2-test (post-test). Saliva was analyzed for testosterone. The whole sample was divided in low- and high physically active subjects by a median split. A 2 × 2 × 2 mixed factor ANOVA design with repeated measures was used to test for differences. Analyses were controlled for sex and BMI.

Results: After the intervention participants of the experimental group showed better performances in the d2-test of concentration compared to control. We further observed a significant group (EG, CG), test (pre, post), activity level (high, low) interaction indicating a different pre- to post-test development in T concentration for high- and low-active participants in the EG and CG. Post hoc pairwise comparisons revealed that after acute exercise the T concentration decreased only in habitually low-active children.

Conclusions: The results indicate that the intensive exercise only interacted with the hypothalamic-pituitary-gonadal (HPG) axis in habitually low-active preadolescents, but had a beneficial effect on cognitive performance for all participants independent of their activity level.

Keywords: testosterone; acute exercise; children; school; cognition; physical activity

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The serotonin transporter gene-linked polymorphic region (5-HTTLPR) and cortisol stress reactivity: a meta-analysis

Background: Recent meta-analyses have stimulated an active debate on whether the serotonin transporter gene-linked polymorphic region (5-HTTLPR) is associated with an elevated vulnerability to psychiatric diseases on exposure to environmental adversity. As a potential mechanism explaining genotype-dependent differences in stress sensitivity, altered stress-induced activation of the hypothalamus-pituitary-adrenal (HPA) axis has been investigated in several experimental studies, with most of the studies comprising small samples.

Methods: We evaluated the association of 5-HTTLPR genotype and cortisol reactivity to acute psychosocial stress by applying a meta-analytical technique based on 11 relevant data sets (total N=1686), which were identified through a systematic literature search up to October 2011.
**Results:** The present meta-analysis indicates a small ($d = 0.27$), but significant association between 5-HTTLPR genotype and HPA-axis reactivity to acute psychosocial stress with homozygous carriers of the S allele displaying increased cortisol reactivity compared to individuals with the S/L and L/L genotype. The latter association was not further moderated by participants’ age, sex or the type of stressor. Formal testing revealed no evidence for a substantial selection or publication bias.

**Conclusions:** Our meta-analytical results are consistent with a wide variety of experimental studies indicating a significant association between 5-HTTLPR genotype and intermediate phenotypes related to stress sensitivity. Future studies are needed to clarify the consistency of this effect and to further explore whether altered HPA-axis stress reactivity reflects a potential biological mechanism conveying an elevated risk for the development of stress-related disorders in S allele carriers.

**Keywords:** 5-HTTLPR; hypothalamus-pituitary-adrenal axis; stress; cortisol; saliva; meta-analysis

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**Free access to highly palatable food during adolescence and youth ameliorates depression-like behaviors of female, but not male, rats that experienced neonatal maternal separation**

**Rationale:** Neonatal maternal separation (MS) leads to a long-term dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis in the offspring. Consumption of highly palatable food (HPF) strongly activates the brain reward center and modulates the HPA response to stress. In this study, we have examined the effects of HPF free access during adolescence and youth on the adverse psycho-emotional behaviors by MS experience in rats.

**Methods:** Male and female SD rat pups were separated from dam for 3 h daily during PND 2–14 (MS) or left undisturbed (NH). Half of NH and MS pups had free choices of cookie (HPF) and chow from PND 28, the rest half received chow only. All rats (n = 8–10 in each group) were subjected to behavioral tests during young adulthood (PND 54–59), and the feeding conditions continued until the end of behavioral sessions.

**Results:** Maternal separation (MS) experience suppressed ambulatory activity both in male and female rats, and HPF access restored it only in males. Caudal grooming was reduced and rostral grooming increased by MS, and HPF access restored them both in males and females. HPF access did not alter MS-induced anxiety-like behaviors during elevated plus maze test both in male and females. Immobility duration during Porsolt swim test was increased by MS experience both in males and females, and HPF access restored it only in females, not in males.

**Conclusion:** Results demonstrate that free access to HPF during adolescence and youth may partly improve MS-induced anxiety-like behaviors both in male and female offspring, and depression-like behaviors only in females.

**Keywords:** neonatal maternal separation; palatable food; adolescence; psycho-emotional behaviors

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**MicroRNA profiling of the human stress response**

**Rationale/ statement of the problem:** The impact of psychosocial stress on a variety of negative health outcomes is well documented, with much of the current research efforts directed at possible mechanisms. For example, psychosocial stress in humans has recently been associated with DNA damage that plays a role in the etiology of negative health outcomes, and also with changes in DNA transcription to messenger Ribonucleic Acid (mRNA). We have become interested in one putative regulatory element in mRNA translation to proteins: microRNA (miRNA). In this study, we aimed to investigate the relationship between psychosocial stress and changes in gene expression changes on the miRNA level, and to further investigate whether stressful life events and personality traits moderate these relationships.

**Methods:** Using a pre-post design, 36 adults were exposed to standardized psychosocial stress in the laboratory (Trier Social Stress Test [TSST]) and completed measures on perceived and chronic stress. In addition, cortisol
levels were determined from saliva samples obtained prior to stressor and at eight time points during recovery. Before and after the TSST, subjects underwent a total of three blood draws from which peripheral blood mononuclear cells (PBMCs) were extracted in order to determine miRNA gene expression levels, using the Affymetrix Genechip 2.0 microRNA array. RNA was extracted from each sample and gene expression was measured by hybridization to the miRNA microarray. In an effort to identify a miRNA expression profile for the acute stress response, we compared miRNA expression changes at baseline (before onset of the stressor) with miRNA expression at the two time points following the stressor.

**Results:** The acute psychosocial stressor produced a higher cortisol response in a subset of the study participants (high responders). We expect these individuals to exhibit significant changes in miRNA expression from baseline to post-stress. We further hypothesize that these changes will be most significant for miRNAs that regulate expression of genes associated with the cortisol stress response.

**Conclusion:** Our study aims to identify a miRNA signature of social stress and to correlate differences in miRNA expression with psychological variables such as early life stress and resiliency, which may function to mitigate the stress response.

Keywords: stress; gene expression; microRNA

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**Effects of chronic social stress on maternal behavior, anhedonia, milk intake, pup growth, and gene expression**

**Background:** Exposure to chronic social stress is a strong predictor of postpartum depression and anxiety. Recent studies have described a chronic social stress (CSS) rodent model for postpartum depression where the repeated exposure of lactating dams to novel male intruders attenuates both the display of maternal care and growth during lactation and increases self-grooming, a measure of anxiety. Investigation of the adult female offspring of these affected dams reveals an attenuated nursing efficiency that is associated with decreases in central oxytocin, prolactin, and vasopressin gene expression.

**Methods:** The current study continued the characterization of the (CSS) model by expanding the analyses to include milk intake, saccharin intake (a measure of anhedonia), and gene expression of the stressed dams.

**Results:** CSS decreased maternal care and saccharin intake, attenuated pup milk intake by 40%, and altered gene expression in lactating dams.

**Conclusions:** It is concluded that CSS is an ethologically and translationally relevant model for postpartum depression and anxiety, as well as associated impairments in nursing.

Keywords: postpartum depression; anxiety; maternal behavior; stress; anhedonia

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**Cortisol levels differ after the low dose dexamethasone-suppression test in outpatients and inpatients with stress related disorders as compared to healthy subjects**

**Rationale/ statement of the problem:** The low-dose dexamethasone-suppression test (DST) has originally been introduced by Yehuda et al.

**Method:** We here report data on the salivary cortisol responses to awakening (CAR) to the DST in healthy subjects (N=102), as well as in outpatients (N=92) and inpatients (N=99) with stress related disorders. Patient groups
were matched for age and sex by propensity score matching. Stress pathology was assessed by the Patient Health Questionnaire (PHQ).

**Results:** We observed stepwise highly significant differences among these three populations with respect to both supersuppression (<2 nmol/l) and escape (>6 nmol/l) of cortisol levels. Amazingly, a supersuppression was most frequently observed in healthy subjects, while an escape was most prevalent in inpatients, less common in outpatients, and rare in healthy subjects. While none of the healthy subjects got a PHQ diagnosis, inpatients and outpatients showed an average of 1.8 and 1.9 diagnoses, respectively, but did not differ with respect to the type and degree of stress pathology. Thus, the DST may rather be considered an unspecific test of dysregulations of the pituitary-adrenal axis.

**Conclusion:** Many research studies observed a supersuppression of cortisol levels in hypocortisolemic subjects with stress related disorders, such as post traumatic stress disorder (PTSD), fibromyalgia, chronic pelvic pain. These subjects commonly express symptoms of fatigue, pain, and an enhanced stress sensitivity, but seem to be protected against deleterious effects of cortisol on organ functions. Such a protective effect may possibly explain our observation that hypocortisolemia and supersuppression are less common in inpatients and outpatients. However, the increasing number of escapes from healthy subjects to outpatients and inpatients was not unexpected. We discuss these findings by applying an additional analysis of endophenotypes.

Keywords: cortisol response; stress; dexamethasone suppression; stress-related disorders; inpatient; outpatient

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**Neonatal orbital frontal damage alters basal cortisol and emotional reactivity, but not stress reactive cortisol response, in adult rhesus monkeys**

**Rationale:** Rodent studies indicate that the orbital and medial prefrontal cortex have an inhibitory control on the hypothalamic–pituitary–adrenal (HPA) axis, by restraining the acute stress response and facilitating negative feedback inhibition, which can also affect its basal tone of activity. Similarly in humans, extent of damage to the medial prefrontal cortex correlates negatively with cortisol levels. However, lesions of the orbital frontal cortex (OFC) in adult monkeys resulted in no effects on HPA activity. In the present study, we assessed the effects of neonatal OFC lesions on emotional and HPA reactivity to an acute stressor.

**Methods:** Subjects received bilateral aspiration lesions of orbital frontal areas 11 and 13 (Neo-Oasp, n = 5) or sham operations (Neo-C, n = 6) between 7 and 14 days of age. Upon reaching adulthood (6–8 years), emotional responses were examined using the Human Intruder (HI) paradigm given at 7:00 hr for all animals and blood samples were collected immediately before and after the stressor to assess HPA axis reactivity. Two days prior to the HI test, two blood samples were collected at the same time of day but without the stressor. Diurnal cortisol rhythm was assessed one year later with blood samples collected at Lights-On (7:00 hr), Mid-day (13:00hr), and Lights-Off (19:00hr).

**Results:** In the presence of the HI, Neo-Oasp animals exhibited less species typical defensive freezing responses as compared to controls (Group: F[1,9] = 14.43, \( p = 0.004 \)), yet they exhibited more hostility throughout the test (Group: \( F[1,9] = 5.45, p = 0.044 \)). Groups did not differ in their neuroendocrine response to the HI, showing a significant increase in cortisol after the stressor as compared to baseline (\( F[1,9] = 22.08, p = 0.001 \)). To control for individual variability and determine that changes in hormone levels were not due to handling or sampling technique, blood samples taken without the stressor revealed that Neo-Oasp animals exhibited lower cortisol at Lights-On compared to Neo-C animals (\( F[1,9] = 6.01, p = 0.037 \)). This lower basal HPA activity was also observed when the diurnal cortisol rhythm was later investigated in the same animals (Group × Time of Day \( F[2,18] = 3.81, p = 0.042 \)).

**Conclusion:** Results indicate that OFC damage in infancy alters emotional behaviors as well as basal but not stress reactive HPA axis function.

Keywords: stress; cortisol response; orbital frontal cortex; HPA activity; emotional reactivity

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Investigating the effects of hormonal contraceptive use on mood and sexuality

Rationale: Hormonal contraception has been the subject of numerous research studies. Despite the fact pharmaceutical companies advertise the physical side effects of the medication both positive (e.g. improved acne, reduced ovarian cancer risk) and negative (e.g. increased risk of stroke, weight gain), the knowledge of the potential psychological effects are often based on Internet searches or less than credible resources. The range of empirical support for the effects of the medications on mood has been beneficial including improved mood to negative such as mental health distress. Aside from psychological research, sexual side effects including reduced libido and reduced sexual responsiveness have also been reported. The majority of the research on hormonal contraceptives has been conducted in a clinical setting. It is unclear if the preceding findings would be found with females self-selecting to use the medication as opposed to paid study participants in a clinical setting.

Methods: In order to gain a greater understanding of the relationship between hormonal contraceptive usage and affect, an Internet survey with females of childbearing age (age range: 17–48, N = 379) was conducted to examining psychological distress (stress, anxiety, depression, and negative mood), improved mood (life satisfaction, happiness, and positive mood), and sexuality (sexual frequency and sexual satisfaction).

Results: Contrary to previous findings, results from this correlational study suggest no effects of hormonal contraceptive use on psychological distress or mood. Females using hormonal contraception did, however, report higher scores for sexual satisfaction and increased sexual activity.

Conclusions: While this investigation was not experimental and, therefore, causation cannot be determined, females using hormonal contraception may be relieved that this research suggests that these drugs do not lead to psychologically harmful side effects and sexuality may be improved with usage. More research is needed to confirm these findings.

Keywords: hormonal contraception; psychological distress; sexuality; mood

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The comparative study of salivary alpha-amylase and salivary cortisol reaction to electric stimulation in avoidant personality disorder

Background: Avoidant personality disorder (AvPD) is a personality disorder recognized in the Diagnostic and Statistical Manual of Mental Disorders handbook (DSM-IV TR) in a person characterized by a pervasive pattern of social inhibition, feelings of inadequacy, extreme sensitivity to negative evaluation, and avoidance of social interaction. To this day, the causes of AvPD are not clearly defined, and may be influenced by a combination of social, genetic, and psychological factors. The disorder may be related to temperamental factors that are inherited. Moreover, the disorder may be related to the dysfunction of stress response systems. A role for hypothalamic-pituitary-adrenal (HPA)-axis activity in mediating stress responses has been intensively investigated for decades. Cortisol is an essential hormone in the regulation of stress response in the HPA axis, and salivary cortisol (sC) has been used as a simple, noninvasive index of free circulating cortisol levels. Recently, salivary alpha-amylase (sAA) has emerged as a new biomarker for responses to psychosocial stress within the sympathetic adrenomedullary (SAM) systems. To evaluate the effects of physical stress on HPA and SAM systems, we assessed the secretion of sAA and sC in AvPD patients and healthy volunteers after exposure to electric stimulation stress.

Methods: Eleven AvPD patients with no psychiatric comorbidity (7 males and 4 females, aged 25.2 ± 4.4) and 126 healthy volunteers with no history of psychiatric disorder (56 males and 70 females, aged 25.9 ± 4.5) participated in this study. All subjects were exposed to electric stimulation stress with the stimulator coil on their wrists. Subjects were stimulated in incremental steps until they reached their threshold stimulus, defined as the greatest stimulus they could tolerate. The greatest stimulus lasted 40 seconds. To examine sAA and sC stress responses, we measured sAA and sC levels three times immediately before, immediately after, and 20 min after the intervention.
We also determined State-Trait anxiety Inventory (STAI) scores and Profile of Mood State (POMS) scores of all subjects before the intervention. This study was approved by the Ethics Committee of Oita University. Written informed consent was obtained from all participants.

**Results:** A significant sAA response to electric stimulation was found with peak values registered immediately after interventions in AvPD patients. However, we found no significant sAA response to electric stimulation in healthy controls. Moreover, AvPD patients always showed significantly higher sAA levels than healthy controls immediately before, immediately after, 20 min after the intervention. However, there was no significant difference in sC reactions between AvPD patients and healthy controls, and we found no significant sC response to electric stimulation in each group. The age, the proportion of males to females and the mean strength of electric stimulation in each group were statistically equal. STAI-Trait and STAI-State scores of AvPD patients were both greater than those of healthy controls. And POMS scores also showed greater subscales of tension-anxiety, depression, fatigue, confusion in AvPD patients than those of healthy patients.

**Conclusion:** These preliminary results suggest that AvPD patients may be easily suffered from stronger feelings of tension-anxiety, depression, fatigue, and confusion compared to healthy people in stressful situation. Moreover, AvPD patients may react to stressors with SAM systems predominantly. The above indicates that the excessive acceleration of sympathetic nerves system may be related to the pathology of AvPD.

Keywords: cortisol; personality disorders; avoidant personality disorder; stress; salivary markers

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**Salivary alpha-amylase and cortisol responsiveness following electrical physical stress in bipolar disorder patients**

**Background:** Bipolar disorder (BP) is often associated with altered functioning of the hypothalamic-pituitary-adrenal (HPA) axis by chronic stress. In comparison, psychosocial stress-induced activation of salivary alpha-amylase (sAA) functions as a marker of sympathoadrenal medullary system (SAM) activity. However, in contrast to salivary cortisol, sAA has been less extensively studied in BP patients. The present study measured sAA and salivary cortisol levels in patients with BP.

**Methods:** The authors determined Profile of Mood State (POMS) and State-Trait anxiety Inventory (STAI) scores, Heart Rate Variability (HRV), and sAA and salivary cortisol levels in 25 patients with BP and 22 healthy volunteers following the application of electrical stimulation stress. Patients with bipolar disorder scored eight points or more on the Hamilton Depression Scale (HAM-D) scores.

**Results:** Tension-anxiety, depression-dejection, anger-hostility, fatigue, and confusion scores in patients with bipolar disorder were significantly increased compared to healthy controls. In contrast, Vigor scores in patients with BP were significantly decreased compared with healthy controls. There was no difference in heart rate variability measures between BP patients and healthy controls. There was no difference in the threshold of applied electrical stimulation between BP patients and healthy controls. There were significant differences in sAA levels between patients with BP and healthy controls. There were significantly higher salivary sAA levels in female patients with BP versus controls. There was a trend toward higher salivary sAA levels in male patients with BP versus controls. Finally, there were no differences in salivary cortisol levels between BP patients and controls. In the present study only three time points were explored. Furthermore, the increased secretion of sAA before and after stimulation could allude to an increased responsiveness to novel and uncontrollable situations in patients with BP.

**Conclusions:** These preliminary results suggest that sAA might be a useful biological marker of BP.

Keywords: salivary markers; bipolar disorder; cortisol response; stress; biological markers

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**Interleukin-6 reflects trait impulsivity in suicide attempters**

**Background:** High cerebrospinal fluid (CSF) and plasma interleukin-6 (IL-6) levels have been reported in suicide attempters. Features of the suicidal temperament include such personality traits as anger and aggression, impulsivity, anxiety proneness and low socialization. High levels of neuroticism and low levels of conscientiousness assessed with structured personality inventories have previously been associated to increased levels of IL-6, in population based samples. The aim of this study was to assess whether plasma levels of IL-6 were associated to specific personality traits in suicide attempters.

**Methods:** Plasma concentration of IL-6 was measured in 58 suicide attempters with a high throughput automated biochip immunoassay system. Patients were evaluated using the Karolinska Scale of Personality (KSP). A standard multiple regression analysis was performed with IL-6 as the dependent variable and KSP factors Neuroticism, Nonconformity, Psychoticism and Extraversion as independent variables adjusted for age and gender.

**Results:** The regression model was significant ($R^2 = 0.40$, $F$ ratio $= 7.3$, df $= 6$, $p < 0.0001$), and the results suggested that high scores on Extraversion were associated with high levels of IL-6 ($t$ ratio $= 4.14$, $p < 0.0001$). IL-6 levels showed a significant positive correlation with trait impulsivity ($r = 0.39$, $p = 0.003$).

**Conclusions:** In suicide attempters, IL-6 may be related to trait impulsivity, a key feature of the suicidal temperament. This study motivates further studies on cytokine activity and their involvement in behavioural development. The study adds further support on biological involvement in suicidal behaviour.

Keywords: cytokines; neuroinflammation; suicide; depression; personality; impulsivity

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attention, fine motor skills, or processing speed. In HIV+ women, cortisol levels were not correlated with most outcomes, though levels were marginally associated with working memory ($r = -0.37$, $p = 0.08$) which was likely attributable to women with high ($r = -0.55$, $p = 0.03$) not low stress.

**Conclusion:** Our findings indicate that HIV is associated with verbal memory difficulties among women and that high perceived stress may exacerbate the effect of HIV infection on poor memory performance. Longitudinal assessments are underway to determine the robustness of these associations.

**Keywords:** HIV; stress; stress hormones; cognition

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**Mitochondrial allostatic load? The combined effect of glucose intolerance and mitochondrial DNA mutations on the incidence of neurological symptoms**

**Rationale/statament of the problem:** High blood glucose levels increase individuals' susceptibility to age-related diseases and mortality. However, the molecular mechanisms by which hyperglycemia impairs cellular function is unclear. Emerging research suggests that mitochondrial dysfunction may be a potential allostatic mechanism that mediates the deleterious effects of hyperglycemia via dynamic pathways. Mitochondria are ubiquitous organelles that are the primary producer of cellular energy and, therefore, central to health and disease. In addition, mitochondria contain their own genetic material – the mitochondrial DNA (mtDNA). Importantly, mutations in mtDNA cause human neurological diseases, and hyperglycemia can impair mitochondrial DNA and function. Here, we hypothesized that in patients with inherited mtDNA mutations, those with poor glucose homeostasis or with diabetes would present with more severe neurological symptoms than those with normal glucose balance.

**Methods:** A literature review and retrospective study of 86 patients with the mtDNA 3243A > G mutation was conducted. We assessed glucose homeostasis and neurological symptoms using the Newcastle Mitochondrial Disease Assessment Scale (NMDAS), and Chi-squared statistics were used to compare the incidence of neurological symptoms in patients with or without glucose intolerance.

**Results:** In patients with pre-existing mitochondrial disease, the incidence of neurological symptoms, including cerebellar ataxia (OR: 9.52; 95% CI: 2.03-44.52) and peripheral neuropathy (OR: 3.91; 95% CI: 1.43-10.76) were greater in those with glucose intolerance than in those with no diagnosed glucose intolerance. In addition, a dose–response relationship linked the severity of glucose intolerance and incidence of cerebellar ataxia.

**Conclusions:** These preliminary results suggest that mtDNA mutations may render brain tissue more susceptible to glucose toxicity. Given that the accumulation of mtDNA damage occurs with senescence, our findings may have implications for resilience in the elderly. In addition to metabolic stress (i.e., hyperglycemia), mitochondrial functions are modulated by mediators of stress (i.e., cortisol), suggesting that integration of psychoneuroendocrine mediators can occur within mitochondria, thus contributing to the “wear and tear” of allostatic load. In this presentation, we introduce mitochrondrial allostatic load (MAL) as a biological mechanism that might contribute to explain how metabolic and psychosocial stresses synergistically influence health and disease susceptibility.

**Keywords:** mitochondria; hyperglycemia; allostatic load; mitochondrial DNA; primary effects

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**Emotions may influence the production of pro-inflammatory cytokines in HIV positive individuals**

**Rationale:** Emotions have been associated with production of pro-inflammatory cytokines such as TNF-alpha and IL-6; more precisely, negative emotions with greater cytokines level whereas positive emotions with lower level of pro-inflammatory cytokines. This may have significant repercussions on individuals’ health specifically for those
who are subjected to chronic inflammation as in the case of HIV positive persons. In fact, HIV virus itself produces greater TNF-alpha production, which in its turns might promote greater IL-6 levels. Thus, this work was conducted in order to verify whether along with HIV association with pro-inflammatory cytokines production, negative and positive emotions, as well as their “balance”, might be associated with cytokines level.

Methods: Participants to this cross-sectional study were 90 individuals with HIV diagnosis. Emotions were assessed through the Italian version of Derogatis Affects Balance Scale edited by the first two authors of this work. The biomarkers included were viral load, TNF-alpha, and IL-6. Individuals also self-reported whether they were under antiretroviral therapy.

Results: A Structural Equation Model was performed in order to test if negative and positive emotions and their balance (that consisted in the ratio of positive/negative emotions) along with viral load were associated with cytokines level. Results indicated that viral load ($\beta = 0.538$, $p < 0.001$), negative emotions ($\beta = 0.366$, $p < 0.05$) and positive/negative emotions ($\beta = -0.420$, $p < 0.05$) ratio were significantly associated with greater TNF-alpha production. No significant associations were observed with IL-6.

Conclusion: Taken together, these results may indicate that together with virus effect in producing greater inflammation, emotions may also contribute to it. Negative emotions could then promote greater inflammation whereas, when individuals experience more positive emotions than negative, inflammation might be reduced.

Keywords: HIV; cytokines; emotions; inflammation

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A study on mental development of children born after earthquake in Ningqiang County of China

Statement of the problem: Pregnant women with stress are at increased risk of adverse pregnancy outcomes. And prenatal stress (PNS) can influence newborn’s mental development. Earthquake exposure is a special stressor for pregnant women. Ningqing County is one of the worst-hit areas of the Wenchuan Earthquake (8.0 magnitude) happened in Sichuan Province, China on 12 May 2008. To explore the related influencing factors of children’s mental development whose mother exposed to the earthquake, we investigated the mental development of children born after the Wenchuan Earthquake in Ningqiang County.

Methods: A total of 86 children aged 0–3 years were recruited in this study. They were randomly selected and were screened by “the mental developmental screening test (DST)” for children aged 0–6 years compiled by Children’s Hospital of Fudan University. For ease of interpretation, children were classified in four different groups based on ages: 0-year-old; 1-years-old; 2-years-old; and 3-years-old.

Results: Among the 86 children, there were 54 boys and 32 girls. The mean Development Quotient (DQ) score was 98.59 ± 2.08. Twenty two (including 18 boys and 4 girls) children’s DQ score was <85, and they shared the percentage of 25.6. The mean Mental Development Index (MI) score was 97.35 ± 1.64. Seventeen children’s MI score was less than 85, and they shared the percentage of 19.8. The incidence of DQ <85 was significantly higher than the national urban average (14.9%) ($p = 0.006$). The incidence of DQ <85 was 33.3% among boys, which was higher than 12.5% among girls ($p = 0.032$). There was no significant difference in the incidence of MI <85 compared with the national urban average (6.0%) ($p = 0.35$). DQ and MI scores, the rate of DQ <85 and MI <85, were not significantly different between mother’s schooling years ≤9 years and more than 9 years. There was no significant difference among all groups by age in terms of DQ and MI scores.

Conclusions: Earthquake possibly contributes to the retardation of children born after Wenchuan Earthquake in Ningqiang County of China.

Keywords: children; earthquake; development quotient; mental development index

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Effects of earthquake on pregnant women in Ningqiang County of China within three years

Statement of the problem: An eight-magnitude earthquake struck Wenchuan, Sichuan Province of China on 12 May 2008. Ningqing County is one of the worst-hit areas. Earthquake exposure was a special stressor for pregnant women. But little is known about what the earthquake influence on pregnant women and the degree of the influence. Only if we understand people's mentation after a natural disaster that can we help them to get over it. To assess the impact of the earthquake on the mental health, we investigated the impact of the Wenchuan Earthquake on pregnant women who lived in Ningqiang County.

Methods: Women who had babies within 3 years after earthquake in Ningqiang County were randomly recruited in this study. Seventy five women were screened by employing Life Events Scale for Pregnant Women (LESPW) compiled by Yan Gao et al. in 2005 and 87 women were screened by employing Post-traumatic Stress Disorder Self-rating Scale (PTSD-SS) compiled by Xianchen Liu et al. in 1998.

Results: Among 75 women, the mean score of LESPW was 297.08 ± 21.95, and 30.67% women's score was equal or greater than 375. This result was significantly higher than that of Xiaomei Li’s report of general pregnant women in Weifang (223.18 ± 129.30)(p <0.001). The mean score of PTSD-SS was 38.55 ± 1.56, and 19.54% women's score was equal or greater than 50. Women who had baby at age of more than 30 got more scores and more detection at the scale of LESPW compared with those age less than 30 (p <0.05, p <0.05 respectively), and the results at PTSD-SS similarly (p <0.01, p <0.001, respectively). In both scales, the detection rates were not significantly different between mother's schooling years less than or equal to 9 years and more than 9 years.

Conclusion: The Wenchuan earthquake brings lasting adverse influences to pregnant women in Ningqiang county of China within three years.

Keywords: pregnant woman; earthquake; LESPW; PTSD-SS

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Alterations in leukocyte transcription factor activities are associated with major depressive disorder and antidepressant treatment

Rationale: Previous work in our and other laboratories has demonstrated dysregulated immune function and cellular oxidative stress responses in subjects with Major Depressive Disorder (MDD). In the current study, we determined whether there were differences in the transcriptional regulation of these pathways in leukocytes from subjects with MDD, and healthy controls.

Methods: We used genome-wide transcriptional profiling (Affymetrix U133 Plus 2 oligonucleotide arrays) and promoter-based bioinformatic strategies (TELiS) to assess transcription factor (TF) activity in leukocytes from 15 unmedicated MDD patients versus 19 age-, gender-, and ethnicity-matched healthy controls, prior to initiation of antidepressant therapy, and after 8 weeks of sertraline treatment.

Results: Bioinformatic analysis of 39,000 differentially expressed genes indicated increased transcriptional activity of cAMP Response Element-Binding (CREB) factor, Interferon Response Factors, and the oxidative stress-responsive Nuclear Factor (erythroid-derived 2)-like 2 (NRF2). Eight weeks of antidepressant therapy was associated with significant reductions in Hamilton Depression Rating Scale scores and reduced activity
of NRF2, but not CREB or interferon response factor activities. Several other transcriptionally regulated pathways previously associated with depression, including the glucocorticoid receptor (GR), nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), and early growth response proteins 1-4 (EGR1-4) pathways, showed either no significant differences as a function of disease or treatment, or activities that were opposite to those previously hypothesized in previous research. Quantitative RT-PCR analysis confirmed the expression profiling data.

**Conclusions:** These results are consistent with the hypothesis that oxidative stress and innate antiviral responses may be involved in MDD by activating immune cell transcriptional pathways, and that successful antidepressant therapy may result in reduced oxidative stress responses at the level of gene transcription.

Keywords: depression; antidepressant treatment; leukocytes; immune function; stress responses

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**Hormonal responses among normal-weight adolescents and obese teenagers undergoing laparoscopic adjustable gastric banding**

**Background:** Bariatric procedures such as laparoscopic adjustable gastric banding (LAGB) can markedly decrease body adiposity in severely obese adolescents, but relatively little is known about the short-term effects of such procedures on meal-related hormonal response.

**Methods:** Participants completed a fixed size breakfast meal and fasting concentrations of appetitive hormones (leptin, insulin/glucose, ghrelin, PYY) were measured. PYY, ghrelin, and visual analog scale (VAS) ratings of fullness, hunger, nausea, and desire to eat were assessed immediately before the meal and 15, 30, 60, and 90 minutes afterwards.

**Results:** A total of 10 normal-weight controls (age: 15.4 ± 2.0 years, BMI: 21.3 ± 1.7 kg/m²; n = 5 female) and 21 severely obese (age: 16.1 ± 1.0 years, BMI: 46.4 ± 6.6 kg/m²; n = 18 females) adolescents were studied pre-LAGB. Eleven of the obese adolescents were studied again 122.6 ± 17.8 days post-LAGB (BMI 40.9 ± 7.8 kg/m², mean change in BMI: −3.5 ± 2.5 kg/m²). In comparison to normal-weight controls, surgical candidates had significantly higher fasting insulin and leptin and lower fasting ghrelin. Fasting PYY decreased significantly post-surgery. Meal-related suppression of ghrelin, as measured by area under the curve (AUC), was significantly less in absolute value among pre-operative candidates than among normal weight controls \[t(9.65) = 2.90, p = 0.017, d = 1.29\], with a trend for a decrease in AUC for candidates pre- to post-LAGB \[t(10) = 2.07, p = 0.065, d = 0.811\]. No significant differences for AUC for PYY were found between normal-weight controls and surgical candidates, or surgical candidates pre- to post-LAGB. Normal-weight controls and surgical candidates did not differ by AUC for any VAS rating; however, post-LAGB, adolescents reported a significantly greater AUC for nausea \[t(10) = −2.58, p = 0.03\].

**Conclusions:** Despite short-term decreases in body mass index post-LAGB, few changes were observed in appetitive hormones prior to or following a standardized breakfast. In addition, subjective ratings of fullness, hunger, nausea, and desire to eat did not differ between surgical candidates and normal-weight controls, but following LAGB, adolescents reported significantly more nausea. Future studies should examine longer-term effects of LAGB on appetitive hormones.

Keywords: laparoscopic adjustable gastric banding; adolescent; eating behavior; appetitive hormones

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Dysregulated mitochondria-focused genes in US military service members with PTSD

Background: Posttraumatic Stress Disorder (PTSD) is a complex mental disorder with functional and structural changes in the brain that may result from mitochondria-centered responses to harmful stresses. PTSD is an ongoing issue in the military. However, at present, there is no biological tool for PTSD diagnosis. Diagnosis for PTSD is established on the basis of clinical history and mental status examination, using a clinically structured interview based on a symptom checklist or patient self-report. It is often under-diagnosis. The clinical assessment would benefit substantially from a more objective means to identify PTSD patients. Here, we present evidence that there are significant differences of expression profiles of mitochondria-focused gene in the blood between PTSD and non-PTSD control US military service members.

Methods: Using a mitochondria-focused gene cDNA array, we examined the expression profiles of 1170 mitochondria-focused genes across samples from subjects with (n=28) or without (n=31) probable PTSD who were active duty US Army Special Operations soldiers deployed to the Iraq and/or Afghanistan war and who were evaluated for probable current PTSD using the PTSD Checklist (PCL). Using the analytical approach of unsupervised pattern recognition with algorithmic basis of clustering, 10 clusters or pathways were revealed from the mitochondria-focused gene microarray data.

Results: Significance tests demonstrated different expression levels in 26 genes between PTSD and non-PTSD controls. A relationship analysis found that among the 26 genes, the expression levels of five genes were significantly correlated with the total PCL score in the PTSD subjects.

Conclusion: The expression of mitochondria-focused gene fingerprints and dysregulated genes in the blood of PTSD patients warrants a large size study to determine their clinical utility in military population

Keywords: PTSD; array; mitochondria; biomarker; PTSD Checklist; military

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Biological vulnerability factors for the development of PTSD, depressive, and fatigue symptoms in response to military deployment are condition specific

Rationale: Deployed military personnel are at risk for (mental) health problems, including post traumatic stress disorder (PTSD), major depressive disorder (MDD), and fatigue. We hypothesized that development of these conditions is associated with biological vulnerability factors. Therefore, we assessed whether the development of PTSD, depressive and/or fatigue symptoms in response to military deployment could be predicted by glucocorticoid (GC) signalling in leukocytes and the capacity of peripheral blood cells to produce cytokines.

Methods: We included 1,032 Dutch military personnel prior to deployment to Afghanistan. Symptom severity was assessed 6 months after return. In blood collected prior to deployment, we assessed GC signalling in leukocytes (glucocorticoid receptor [GR] number, target gene mRNA expression, and GC-sensitivity) and cytokine production upon stimulation with LPS, PHA, or IL-1β.

Results: We identified different vulnerability factors for development of a high level of PTSD, depressive, and fatigue symptoms. PTSD symptom development was predicted by high GC signalling in leukocytes. In contrast, depressive symptom development was associated with low GC signalling in T-cells and high T-cell cytokine production capacity. Finally, development of fatigue was associated with low GC signalling in monocytes prior to deployment and high reactivity of monocytes to IL-1β after deployment.

Conclusions: The identified vulnerability factors for the development of high levels of PTSD, depressive, and fatigue symptoms were condition specific. This indicates PTSD, depression, and fatigue have different underlying biological mechanisms. Moreover, the results suggest that the biological profile prior to stress/trauma exposure may not only determine if a stress-related condition will develop but also which specific stress-related condition will develop.
A decrease in perceived social support during military service is associated with a concomitant increase in baseline and decrease in stress reactivity levels of salivary $\alpha$-amylase

**Rationale/Statement of the Problem:** Stress provokes physiological alterations, which are thought to mediate the development, maintenance, and progression of several disorders. Social support is thereby thought to possess a buffer function, decreasing the physiologic effects of stress. In our previous work, we were able to show a buffering effect of perceived social support (PSS) on the stress response of salivary $\alpha$-amylase (sAA), an index of sympathetic nervous system activity. The aim of the present longitudinal study was to examine the effects of alterations in PSS on baseline and stress levels of sAA.

**Methods:** Swiss male recruits ($n=145$) participated twice in a standardized psychosocial stress test (Trier Social Stress Test for Groups, TSST-G) 10 weeks apart. Saliva was collected prior to and after the stress test to measure the activity of sAA. On both examinations, a questionnaire was distributed to determine the level of PSS (Berlin Social Support Scale, BSSS).

**Results:** The TSST-G induced a significant increase in sAA activity on both occasions, while military service resulted in an overall decrease in PSS. Changes in PSS were associated with alterations in baseline and stress responses of sAA: recruits with a decrease in PSS over the 10-week period revealed an increase in baseline activity ($r = 0.248$, $p=0.005$) and a decrease in stress reactivity of sAA ($r=0.226$, $p=0.010$) over time.

**Conclusion:** Our findings show that military service is associated with a decrease in PSS. This decrease is related to alterations of sympathetic nervous system activity, characterized by an increased tone and decreased responsiveness. This longitudinal study emphasizes the need to boost psychosocial resources during military service.

Keywords: perceived stress; Trier Social Stress Test; amylase; stress reactivity; military service

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**High dose corticosterone immediately after stress exposure prevents hippocampal cytoarchitecture and neuronal plasticity damage in an animal model of PTSD**

**Rationale:** In a previous study, we examined the effect of a single intervention with high-dose corticosterone, 1h after predator stress-exposure (PSS), and showed a significant reduction in the incidence of post traumatic stress disorder (PTSD)-like behaviors and improved resilience. The underlying mechanism of corticosterone action remains largely unclear. The goal of this study was to explore the cytoarchitecture and molecular changes in hippocampal subareas of animals “treated” with high-dose corticosterone immediately after exposure.

**Methods:** Animals were exposed to PSS and treated 1 hour later with corticosterone (25mg/kg) or saline. The outcome measures included behavior in an elevated plus-maze and acoustic startle response 7 days after the exposure. Pre-set cut-off behavioral criteria classified exposed animals according to behavioral responses as those with “extreme behavioral response”, “minimal behavioral response”, or “intermediate response”. Dendritic arborization in Golgi-impregnated neurons in hippocampal areas was evaluated. Given the importance of integrin $\beta 1$, calcium/calmodulin-dependent protein kinase II (CAMKII), phospho-glutamate receptor 1 (pGLU-R1), and postsynaptic density-95 (PSD-95) in neuronal function and dendritic spine plasticity, the expression of these factors in the hippocampus was also examined.

**Results:** Stress exposure altered the morphology of the hippocampal dendritic cells selectively in individuals whose behavior was extremely disrupted (EBR) in response to the exposure, whereas animals whose behavior was less severely affected displayed no significant changes in hippocampi morphology. Extreme responders clearly
demonstrated significantly reduced dendritic arbor and spine density along hippocampal dendrites 8 days after exposure. The results showed that EBR animals displayed significantly lower levels of integrin 1β, CAMKII and higher expression of pGLU-R1 and PSD-95 than vehicle-treated animals. In contrast, steroid-treated stressed animals displayed significantly increased dendritic arbor and spine density, with increased levels of integrin 1β, pCAMKII, and obtunded pGLU-R1 and PSD-95 levels.

**Conclusions:** The data provide initial evidence that a single dose of corticosterone administered in the acute aftermath of stress promotes recovery while promoting enhanced neuronal and synaptic plasticity and connectivity in the secondary prevention of PTSD.

Keywords: PTSD; stress; corticosterone; neuronal plasticity; hippocampus

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**Sex differences in fear conditioning in posttraumatic stress disorder**

*Rationale/statement of the problem:* Women are twice as likely as men to develop Posttraumatic stress disorder (PTSD). Abnormal acquisition of conditioned fear has been suggested as a mechanism for the development of PTSD. While some studies of healthy humans suggest that women are either no different or express less conditioned fear responses during conditioning relative to men, differences in the acquisition of conditioned fear between men and women diagnosed with PTSD has not been examined.

**Methods:** Thirty-one participants (18 men, 13 women) with full or subsyndromal PTSD completed a fear-conditioning task. Participants were shown computer-generated colored circles that were paired (CS+/CS-) or unpaired (CS —) with an aversive electrical stimulus, and skin conductance levels were assessed throughout the task.

**Results:** Repeated measures ANOVA analyses indicated a significant sex by stimulus interaction during acquisition, $F(1, 232) = 5.16, p < 0.05$. Women had greater differential conditioned skin conductance responses (CS+ trials compared to CS — trials) than did men, suggesting greater acquisition of conditioned fear in women with PTSD.

**Conclusion:** In contrast to studies of healthy individuals, we found enhanced acquisition of conditioned fear in women with PTSD. Greater fear conditioning in women may either be a pre-existing vulnerability trait or an acquired phenomenon that emerges in a sex-dependent manner after the development of PTSD. Characterization the underlying mechanisms of these differences is needed to clarify sex-related differences in the pathophysiology of PTSD.

Keywords: sex differences; learning; conditioning; fear; posttraumatic stress disorder; galvanic skin response

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**A non-verbal, quantitative measure of emotion dysregulation in veterans: is affective startle a potential biomarker for suicide?**

*Rationale:* In healthy individuals, the magnitude of the startle-eyeblink reflex to a brief, acoustic probe is modulated by the valence (goodness/badness) of a photographic picture and this modulation shows a linear, stepwise pattern. Startle amplitude is smallest during pleasant, largest during unpleasant, and intermediate during neutral pictures. Animal work shows that startle modulation is mediated by the brain's fear/defensive circuit which is centered on the amygdala—a region important in valence and emotion regulation. We previously reported (Hazlett et al., 2007) exaggerated affective startle modulation during processing of unpleasant (e.g., “suicidal”) but
not neutral words in individuals with borderline personality—a disorder characterized by emotion dysregulation and suicidal behavior.

**Methods:** In light of this work, we present preliminary data from an ongoing Department of Defense (DoD)-sponsored study examining whether suicidal behavior confers defensive hyperreactivity measured as increased affective startle modulation during emotional pictures, irrespective of diagnosis. We examined 40 age- and gender-matched veterans with varying levels of suicidal behavior: ideators (I): \( n = 9 \); single suicide attempters (SA): \( n = 10 \); and multiple suicide attempters (MA): \( n = 21 \). Principal disorders included post traumatic stress disorder (PTSD) and major depression. Participants viewed a series of intermixed standardized unpleasant, neutral, and pleasant social pictures (each presented for 6 sec and a subset containing acoustic probes) and were instructed to think about the meaning of the pictures for them personally while eyeblink responses were assessed.

**Results:** Compared with the I and SA groups, the MA group showed startle hyperreactivity during unpleasant pictures (MA > I: \( p = 0.03 \); MA > SA: \( p = 0.06 \) [trend]; Fisher’s LSD). In contrast, there were no group differences during pleasant or neutral pictures (Group \( \times \) Picture type interaction was non-significant, \( p = 0.30 \)).

**Conclusion:** These findings indicate a spectrum of hyperreactivity during unpleasant picture viewing that parallels the severity of suicidal behavior: Startle amplitude during unpleasant pictures progressively increased from Is at the minimum, to SAs, and finally MAs at the extreme. Affective startle may provide a useful non-verbal, psychophysiological biomarker for suicidal behavior. Correlations between affective startle, symptom severity, and emotion regulation will also be presented.

Keywords: emotion; emotion dysregulation; fear/defensive brain circuitry; affective startle eyeblink modulation; suicide ideation; suicidal behavior

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**Exaggerated autonomic responding to acoustic stimuli in Gulf War Veterans with current versus remitted post-traumatic stress disorder**

**Rationale:** Post-traumatic stress disorder (PTSD) is associated with exaggerated autonomic responses to sudden, loud acoustic stimuli, particularly under conditions characterized by ambiguous threat. However, it is not clear if such exaggerated responses are a stable vulnerability factor for developing PTSD or a feature of current PTSD that resolves with symptom resolution. We investigated this issue by comparing autonomic startle responses to acoustic stimuli under low, medium, and high threat conditions in Gulf War Veterans with and without current and past PTSD.

**Methods:** Our sample included three groups: no PTSD (\( n = 151 \)), PTSD in remission (\( n = 51 \)), and current PTSD (\( n = 54 \)) (M age = 44.3, SD = 9.6; 11.6% female). Current and past PTSD symptoms were assessed with the clinician-administered PTSD scale. All participants were exposed to an acoustic stimulus in three conditions: 1) low threat, in which participants experienced no threat of shock; 2) medium threat, in which participants wore a finger electrode but were told that they would not get shocked; and 3) high threat, in which participants wore a finger electrode and were told that they would get shocked. Independent sample \( t \)-tests were used to compare group differences in startle responding.

**Results:** Individuals with current PTSD had significantly higher heart rate responses compared with the no PTSD group in the low, \( t(196) = 2.52, p = 0.011 \), and medium threat conditions, \( t(66.7) = 2.40, p = 0.022 \), and compared with the PTSD in remission group in the low, \( t(87) = 1.957, p = 0.05 \), and medium threat conditions, \( t(77.81) = 2.50, p = 0.02 \). In analyses, including only patients with current or past PTSD who had current clinician administered PTSD scale (CAPS) across the entire range from 0 to 108 (M = 41.0, SD = 25.4), we found that higher severity of current PTSD symptoms was not only associated with higher startle responses, particularly in the medium threat condition \( r = 0.22, p = 0.04 \), but also with trend level in the low \( r = 0.18, p = 0.09 \) and high \( r = 0.18, p = 0.09 \) threat conditions.

**Conclusion:** These results suggest that exaggerated autonomic startle responses under conditions of low and medium threat vary as a function of current PTSD severity and are not a marker of PTSD vulnerability. Moreover,
the data suggest that this startle paradigm with varying threat levels may be a useful index of hyperarousal of fear-related neurocircuitry in PTSD.

Keywords: veterans; Gulf War; PTSD; autonomic response

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Neuroimaging biomarkers in veterans with blast-mild traumatic brain injury with or without comorbid PTSD

Rationale/statement of the problem: Because posttraumatic stress disorder (PTSD) and blast-mild traumatic brain injury (mTBI) commonly are comorbid in veterans of the wars in Iraq and Afghanistan, attributing persistent behavioral or other symptoms to one or the other entity remains controversial. Here, we asked if multimodal neuroimaging would reveal persistent functional or structural abnormalities in veterans who had experienced blast-mTBIs in Iraq and/or Afghanistan and, if so, could any such abnormalities be attributed to comorbid PTSD.

Methods: Thirty-four blast-mTBI veterans (26 with PTSD and 8 without PTSD) and 16 Iraq and/or Afghanistan-deployed veterans without blast or blunt impact mTBI or PTSD were studied. Each veteran underwent magnetic resonance diffusion tensor (DTI) and magnetization transfer/cross-relaxation imaging (MT-CRI), as well as fluorodeoxyglucose positron emission tomography (FDG-PET); structured clinical assessments of blast and combat exposure, psychiatric diagnoses, and posttraumatic stress disorder symptoms; neurologic evaluations; and self-report scales of postconcussive symptoms (PCS), combat exposure, depression, sleep quality, and alcohol use.

Results: Blast-mTBI veterans exhibited reduced fractional anisotropy in the genu and splenium of the corpus callosum on DTI; reduced macromolecular-bound proton fraction (a brain putative measure of myelin integrity) in white and gray matter and multiple regions of interest on MT-CRI; and parietal, somatosensory, and visual cortex hypometabolism on FDG-PET. The presence of PTSD in mTBI veterans had no effect on DTI or MT-CRI structural brain biomarkers. The only effect of PTSD on FDG-PET functional biomarkers was lower glucose metabolism in visual cortices bilaterally.

Conclusions: Iraq and Afghanistan combat veterans with blast-mTBI exhibit abnormalities of brain white matter structural integrity and macromolecular organization and regional cortical glucose metabolism years after blast exposure. Although comorbid PTSD was associated with lower visual cortex metabolism, it had no effect on structural biomarkers. These findings are consistent with recent neuropathologic evidence of cortical tauopathy and neuronal degeneration in a small sample of Veterans with blast-mTBI.

Keywords: mild traumatic brain injury; neuroimaging; biomarkers; PTSD; magnetic resonance imaging; FDG-PET

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Regional cerebral volumes in veterans with current versus remitted posttraumatic stress disorder: a study at 4 Tesla

Rationale/statement of the problem: We previously reported that hippocampal volume was associated with current, but not lifetime post traumatic stress disorder (PTSD) symptom severity. In this study, we further...
investigated the role of current versus remitted PTSD on the volumes of other brain regions previously implicated in PTSD.

**Methods:** Magnetic resonance imaging data from a 4 Tesla scanner of 191 veterans (75 trauma unexposed, 43 trauma exposed without PTSD, 39 trauma exposed with PTSD, 34 trauma exposed recovered from PTSD) were analyzed with FreeSurfer software program (version 4.5).

**Results:** Veterans with current PTSD had smaller hippocampal, caudal anterior cingulate, insula, and corpus callosum volumes than trauma unexposed veterans \( (p \leq 0.01) \), trauma-exposed veterans who had recovered from PTSD \( (p \leq 0.02) \) and trauma-exposed veterans who never developed PTSD \( (p \leq 0.05) \).

**Conclusions:** The finding that current but not lifetime PTSD accounted for the volumes of multiple brain regions suggests either that smaller brain volume is a vulnerability factor that either impedes recovery from PTSD; or less likely, that recovery is accompanied by a wide-spread restoration of brain tissue.

Keywords: veterans; PTSD; brain volume

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**Glucocorticoid receptor polymorphisms predict response to treatment in PTSD**

**Rational:** Increased GR sensitivity has been associated with PTSD severity in several studies, and in a recent report, was found to predict the extent of improvement in severity of PTSD symptoms from pre- to post-treatment. These findings provided the rationale for an investigation of two GR genotype polymorphisms known to affect GR sensitivity in relation to PTSD severity and treatment response. The BclI (rs41423247) single nucleotide polymorphism (SNP) is an intronic restriction fragment length polymorphism located 646 bp downstream from GR exon 2. SNP 9β (rs6198) is located on exon 9β of the GR. It is believed to increase the stability of splice variant GRβ, an inhibitor of the wild-type GRα. Carriers of the BclI minor allele have been associated with an increased sensitivity to glucocorticoids (GCs), whereas 9β carriers have been linked to relatively diminished sensitivity. We studied these polymorphisms in the context of a treatment study in which participants were evaluated prior to and following treatment.

**Methods:** For the treatment study, subjects were randomized into two treatment conditions, weekly prolonged exposure therapy and a minimal attention, in which participants received a weekly phone call to evaluate symptom severity and monitor for safety. Clinical outcome was assessed using pre- and post-treatment Clinician Administered PTSD Scale (CAPS) total scores. Pre-treatment genotype data were available for 27 of 36 receiving prolonged exposure and for 9 or 13 who received the minimal attention condition. DNA was isolated from lymphocytes using Ficoll-Paque Plus (Amersham Pharmacia Biotech) and extracted (using FlexGene DNA Kit, Qiagen); genotyping of SNPs BclI and 9β was performed using the allelic discrimination technique with custom designed probes and primers according to the published genomic sequences, with results that did not differ from Hardy–Weinberg equilibrium.

**Results:** The presence of the G allele in the BclI SNP was inversely associated with lifetime, but not current, total CAPS score for treatment completers \( (t = 2.94, df = 29, p = 0.006) \), indicating a less severe lifetime course of PTSD. Polymorphisms at the Snp9Beta locus were not related to lifetime PTSD severity. The same polymorphism at BclI predicted the absence of a PTSD diagnosis following treatment \( (\chi^2(1) = 7.30, p = 0.007) \). A similar relationship for Snp9Beta was not apparent. In order to test the relative strength of BclI genotype in the prediction of PTSD outcome, a logistic regression was performed with age, ethnicity, treatment type, and pre-treatment CAPS total score as covariates. In this model, only BclI genotype was a significant predictor \( (B = -2.59, p = 0.022, OR = 0.074) \). Without BclI genotype in the model, there was a trend for pre-treatment CAPS total score to predict PTSD at post-treatment \( (B = 0.062, p = 0.080, OR = 1.05) \).

**Conclusion:** The BclI polymorphism is related to a less severe lifetime course of PTSD, and is a substantial predictor of positive outcome in response to short-term psychotherapy. The relation of this genotype to recovery from PTSD was even stronger than pre-treatment clinical severity or type of treatment. The result suggests that BclI genotype may be a useful biomarker in the selection of potential treatment candidates. This work should be repeated in additional, and larger samples for verification.
Clinical features of military veterans with or without a history of suicide attempt

**Background:** Suicidal behavior is a critical problem among military veterans. Therefore, it is important to identify psychological suicide risk factors that are unique for veterans of military service. We compared clinical features of 55 veteran suicide attempters with 55 veterans without a history of suicide attempts.

**Methods:** Demographic and clinical characteristics of suicide attempters and non-attempters were assessed and recorded. Based on the Scale for Suicide Ideation (SSI) all patients were divided into two groups: patients who do not report any suicidal ideation at all (non-ideators) and people who do (ideators).

**Results:** There was no difference between the groups with regard to age ($t = -0.71$, $df = 108$, $p = 0.48$), gender ($X^2 = 1.50$, $df = 1$, $p = 0.36$), and race ($X^2 = 4.84$, $df = 5$, $p = 0.44$). There were more subjects with a lifetime history of bipolar disorder, substance dependence, or psychotic disorder among suicide attempters compared to non-attempters ($X^2 = 6.67$, $df = 1$, $p = 0.01$, $X^2 = 4.71$, $df = 1$, $p = 0.04$, and $X^2 = 9.83$, $df = 1$, $p = 0.002$, respectively). There were 34% of current suicide ideators among suicide attempters and 9.3% of suicide ideators among non-attempters ($X^2 = 9.67$, $df = 1$, $p = 0.002$). There was no difference with regard to the proportion of patients with major depression or posttraumatic stress disorder between suicide attempters and non-attempters ($X^2 = 0.10$, $df = 1$, $p = 0.83$ and $X^2 = 0.41$, $df = 1$, $p = 0.54$, respectively).

**Conclusion:** A history of suicide attempt in military veterans is associated with a lifetime history of bipolar disorder, substance dependence, psychotic disorder, or current suicidal ideation but not with a lifetime history of major depression or posttraumatic stress disorder.

Keywords: suicide; veterans; substance dependence; psychosis; bipolar disorder

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Using bio- and neurofeedback to enhance psychological recuperation in Afghanistan veterans

**Rationale/Statement of the problem:** Both bio- and neurofeedback (training) protocols are hypothesized to be beneficial in the management of arousal states and psychological recuperation after aversive and potentially traumatic experiences. As military deployments in theatres like Iraq or Afghanistan imply a significant risk for potentially traumatic experiences and stress-related outcomes, the present research explored the potency of both bio- and neurofeedback protocols during the recuperation period after the deployment of Dutch soldiers in Afghanistan.

**Methods:** Within half a year after re-deployment, 38 Afghanistan veterans (Dutch 200 Logistic Battalion) participated in the present study. Of these, 14 conducted 10 sessions of alpha power–based neurofeedback, 10 randomized beta (mock) neurofeedback, and 14 participants conducted 10 sessions of biofeedback gaming. Previously to and immediately after these sessions baseline heart rate variability (HRV), the cortisol awakening response (CAR), quantitative electroencephalography (QEEG), and cognitive performance and psychological parameters (like quality of sleep and stress-related symptoms) were assessed.

**Results:** In all conditions, HRV significantly increased ($F(1,24) = 18.7$, $p < .05$), though no differences were found between conditions ($F(3,25) = .90$, n.s.). No significant results were found in CAR or in any EEG component or derivative. However, stress-related symptoms appeared to decrease significantly, though only in the bio- and neurofeedback alpha conditions ($F(3,43) = 2.85$, $p < .05$). Working memory was significantly increased in the neurofeedback alpha condition only ($F(3,37) = 2.78$, $p < .05$).
Discussion: Although the number of participants in the present study is yet quite small, and no posttreatment assessment after some weeks or months could be conducted, the present findings do support the hypothesis that both bio- and neurofeedback may contribute to psycho(physio)logical recuperation after (professional) challenging periods. Initial effects may be expected on self-reported psychological well-being and working memory performance.

Keywords: biofeedback; veterans; working memory; psychophysiology; cortisol; EEG

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