Psychoneuroendocrinology 106 (2019) 1–8

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

# Hypothalamic-pituitary-adrenal axis responsiveness, startle response, and sensorimotor gating in late pregnancy

Julia Breedh[a], Erika Comasco[a,*], Charlotte Hellgren[b], Fotios C. Papadopoulos[c], Alkistis Skalkidou[b], Inger Sundström Poromaa[b]

[a] Department of Neuroscience, Science for Life Laboratory, Uppsala University, Uppsala, Sweden
[b] Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden
[c] Department of Neuroscience, Psychiatry, Uppsala University Hospital, Uppsala University, Uppsala, Sweden

ARTICLE INFO

*Keywords:*
AUC
CAR
Cortisol
Pregnancy
Sensorimotor gating
Startle response

ABSTRACT

During pregnancy, the hypothalamic-pituitary-adrenal (HPA) axis, the main regulator of the stress response, undergoes dramatic changes. The acoustic startle response (ASR) and the prepulse inhibition (PPI) of the startle response are neurophysiological research tools and objective measures of an individual's response to an emotional context or stressor. The ASR and PPI are influenced by psychiatric diseases characterized by anxiety symptoms and are sensitive to cortisol. Hence, the ASR and the PPI can be used to investigate the effects of pregnancy-induced endocrine changes and their contribution to affective disorders. The present study sought to investigate the association between measures of HPA-axis responsiveness, startle reactivity and sensorimotor gating during pregnancy that to date remains unknown. The eye-blink component of the ASR, and its prepulse inhibition, were measured in 107 late third trimester pregnant women. Saliva samples were collected to assess the cortisol awakening response (CAR), a measure of HPA-axis activity. Blood was sampled to measure serum levels of cortisol, cortisone and the cortisone to cortisol ratio. Ongoing anxiety disorders, sleep duration, smoking, and age were considered as potential confounders in the statistical analyses. CAR reactivity, measured as area under the curve (AUC) increase and above baseline, was positively associated with baseline startle magnitude [Cohen's $d = 0.27$; $F(1, 105) = 4.99$; $p = 0.028$, and Cohen's $d = 0.30$; $F(1, 105) = 6.25$; $p = 0.014$, respectively] as well as PPI at 86 dB [Cohen's $d = 0.29$; $F(1, 105) = 5.93$; $p = 0.017$; and Cohen's $d = 0.34$; $F(1, 105) = 8.38$; $p = 0.005$, respectively]. The observed positive correlation between startle magnitude in pregnant women and greater increase in cortisol during the awakening response may be interpreted as heightened neurophysiological reactivity, likely associated with dysregulation of the stress system.

## 1. Introduction

The hypothalamic-pituitary-adrenal (HPA) axis, a key regulator of the stress response, undergoes considerable changes during human pregnancy (Chrousos et al., 1998). Throughout the second and the third trimester of pregnancy, the maternal cortisol levels increase approximately two to three times compared to non-pregnant levels, followed by a decrease to normal baseline levels a few days after parturition (Jung et al., 2011).

The circadian rhythm of cortisol secretion includes a distinct increase in cortisol levels within 30–60 minutes after awakening in the morning, denoted as the cortisol awakening response (CAR) (Clow et al., 2004). The CAR, a measure of HPA-axis activity and basal cortisol physiology, remains present in the third trimester of pregnancy, although the absolute value of free saliva cortisol concentration increases during pregnancy (de Weerth and Buitelaar, 2005). However, decreased CAR at gestational week 31, compared to week 17, suggests a relationship between length of pregnancy and HPA-axis reactivity (Buss et al., 2009). It has also been noted that elevated levels of adrenocorticotropic hormone (ACTH) and cortisol during late pregnancy result in reduced HPA axis responsiveness to stress, since the axis is already activated by extremely high levels of placental corticotrophin releasing hormone (CRH) (Sasaki et al., 1989). Dysregulation of HPA-axis responsiveness has been associated with psychiatric disorders in non-pregnant populations (Jolley et al., 2007; Kudielka and Kirschbaum, 2003), whereas findings in pregnant populations are less conclusive (Hellgren et al., 2013; Iliadis et al., 2015).

The interconversion between cortisol and its inactive metabolite

* Corresponding author at: Department of Neuroscience, Science for Life Laboratory, Uppsala University, BMC, Pub 593, 75124 Uppsala, Sweden.
*E-mail address:* erika.comasco@neuro.uu.se (E. Comasco).

https://doi.org/10.1016/j.psyneuen.2019.03.008
Received 19 November 2018; Received in revised form 15 February 2019; Accepted 12 March 2019

cortisone is catalyzed by 11 β-hydroxysteroid dehydrogenase (11β-HSD) isoenzymes, type I (11β-HSD1) responsible for the reversible conversion of cortisone to cortisol and type 2 (11β-HSD2) that catalyzes the irreversible conversion of cortisol to cortisone. Hence, the ratio between cortisol and cortisone is dependent on 11β-HSD isoenzymes activity (Ricketts 1998, Smith 1998). When the maternal cortisol levels increase during the course of pregnancy, the placental 11β-HSD protect the fetus from adverse effects of maternal glucocorticoids (Murphy, 1981). Higher levels of anxiety in late pregnancy have been associated with downregulation of placental 11β-HSD (O´Donnell 2011) and peripartum depression has been associated with polymorphisms in the gene *HSD11B1* (Skalkidou et al., 2019). However, the possible correlation between serum cortisone levels during pregnancy and HPA-axis reactivity is largely unstudied.

The effects of cortisol are mediated by two types of nuclear receptors in the brain, with a widespread distribution; the glucocorticoid receptor and to some extent the mineralocorticoid receptor, both being ligand-driven transcription factors. These receptors are present abundantly in limbic neurons such as the medial and central nucleus of the amygdala and the hippocampus, thus capable to influence cognitive as well as emotional networks (Joels et al., 2008; Quax et al., 2013; Wang et al., 2014).

The startle response is a reflexive response elicited by a sudden aversive stimulus. It has been described as a defense mechanism protecting the organism against adverse or potentially harmful influences in the surrounding environment (Grillon and Baas, 2003). The startle response consists of a fast contraction of facial (eye-lid closure) and body muscles, as well as acceleration of the heart rate, after exposure to a sudden intense tactile, visual, or acoustic stimulus (Koch, 1999). The auditory stimulus-elicited startle response is often referred to as the acoustic startle response (ASR) and the primary ASR in humans is thought to be mediated by a relatively simple neuronal circuit, which substantially involves three central synapses (Davis et al., 1982; Koch, 1999; Lee et al., 1996). In addition, higher brain functions play a role in the ASR; lesion studies indicate the importance of the central nucleus of amygdala in the potentiated startle (Hitchcock and Davis, 1986). The magnitude of ASR can indeed be modulated by a variety of endogenous and exogenous variables, such as pathological conditions or experimental manipulations (e.g. classical conditioning, fear conditioned response, motivational states, habituation, prepulse inhibition, and drugs) (Koch, 1999). Consequently, the baseline ASR magnitude is not constant and can be both enhanced and attenuated, with inter-individual variation that may be influenced by the activity of brain structures involved in the neuronal circuit of the ASR. Based on these characteristics, the ASR can be considered as an index of neurophysiological reactivity; that is an objective measure of neural function. Furthermore, increased startle response modulation has been demonstrated in anxiety disorders characterized by physical hyper-arousal (Butler et al., 1990; Grillon and Baas, 2003).

Sensorimotor gating is a neurophysiological process important for filtering and processing information in higher brain areas and hence to inhibit or suppress the response to incoming irrelevant sensory input (Cromwell et al., 2008). The measurement of the prepulse inhibition (PPI) of the startle response allows investigating the neural basis of sensorimotor gating and information processing. PPI of the startle is a semi-automatic process consisting of reduced responsiveness to a startle eliciting stimulus if a weaker stimulus is presented shortly (e.g. 30–500 milliseconds) before the targeted stimuli (Braff et al., 2001).

Moreover, as measurement of the ASR and PPI of the startle is non-invasive, they are ideal neurophysiological research tools to study the effects of endocrine changes during pregnancy (Hantsoo et al., 2018). Indeed, we previously demonstrated that women in late pregnancy display greater ASR than non-pregnant controls (Comasco et al., 2015). Further, it has long been known that direct intracerebroventricular administration of CRH produces a dose-dependent increase of the ASR magnitude in rats (Liang et al., 1992; Swerdlow et al., 1986). Additionally, administration of exogenous cortisol has been found to exert a dose dependent biphasic effect on the ASR magnitude in humans (Buchanan et al., 2001). Consequently, these results indicate that hormones of the HPA-axis may influence the ASR magnitude. Furthermore, reduced sensorimotor gating after intravenous administration of cortisol, which is comparable to the physiological response to a mild or moderate stressor, has been demonstrated in non-pregnant populations (Richter et al., 2011) and experimental stress has been associated with reduced PPI (De la Casa et al., 2016). Previously, we demonstrated that women with antenatal anxiety disorders display lower PPI than healthy pregnant controls (Comasco et al., 2015), and that pregnant women exhibit lower levels of PPI compared to late postpartum women (Kask et al., 2008b). Furthermore, higher antenatal anxiety levels have been associated with increased HPA-axis activity (Kane et al., 2014). However, the association between ASR, PPI and measures of HPA axis responsiveness in pregnancy has not yet been studied.

The aim of the present study was to investigate the association between ASR and PPI of the startle response and the cortisol awakening response (CAR), as well as with serum levels of cortisol and cortisone in pregnant women in gestational week 35–39. While we expected a positive correlation of HPA-axis reactivity and levels of serum cortisol and cortisone with ASR, analyses on PPI were hypothesis-free.

## 2. Materials and methods

### 2.1. Study procedure

Pregnant women in gestational week 35–39 (according to the ultrasound-estimated date of delivery) were recruited to the present study and were assessed at the research laboratory of the Department of Women's and Children's Health, Uppsala University between January 2010 and May 2013 (Comasco et al., 2015; Hellgren et al., 2013). The present study is a sub-study to the pregnancy cohort "Biology, affect, stress, imaging and cognition in pregnancy and the puerperium" (BASIC), which in turn, is a longitudinal study investigating the biological correlates of mood and anxiety disorders during pregnancy and in the postpartum period. All pregnant women in Uppsala County are invited to participate at the time of their routine ultrasound screening in gestational week 16-18. After providing informed written consent, the women are sent a web-based questionnaire, including the Swedish version of the Edinburgh postnatal depression scale (EPDS) (Cox et al., 1987). For this sub-study, women with EPDS score $\geq 13$ at gestational week 32 and a random sample of women with EPDS scores $< 13$ at gestational week 32 were invited with the intent of oversample women with antenatal depressive and anxiety symptoms. This has been demonstrated as the optimal cut-off score on EPDS for detecting depression in pregnancy (Rubertsson et al., 2011). Women with twin pregnancies and women with serious pregnancy-related conditions such as gestational diabetes, preeclampsia, and intrauterine growth restriction were excluded. Antidepressant drug use was not an exclusion criterion.

On the test session day, the participants were screened for any ongoing psychiatric disorder according to the Mini International Neuropsychiatric Interview (MINI), version 5.0.0. MINI is a short diagnostic interview that includes the criteria for the most common psychiatric diseases in accordance with the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and ICD-10 (Sheehan et al., 1998). Women with ongoing anxiety and depressive disorders were not excluded from participation. On the test session day, the participants were also asked to fill in the Swedish version of the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) and the Spielberger State-Trait Anxiety Inventory (STAI-S) (Hodgues and Spielberger, 1969). Furthermore, the participants were asked about obstetric history, alcohol use and medication in the previous three months. Moreover, the women were asked about the number of hours of sleep the night preceding the test session. Information about EPDS scores in gestational week 32, educational level, ethnicity and smoking habits during

pregnancy were available from self-reports in the BASIC web-questionnaires. Blood samples were collected at the end of the test session and the women were instructed to perform the CAR saliva sampling as soon as possible after the test session day. The study procedure was in accordance with ethical standards for human experimentation and has been approved by the Regional Ethical Review Board at Uppsala University (nr 2009/171).

### 2.2. Acoustic startle response and prepulse inhibition

The acoustic startle response was assessed by electromyographic (EMG) measurement of the orbicularis oculi muscle of the right eye. For recording of the acoustic startle reflex and generation of the startle eliciting stimulus a commercial startle system (SR-HLAB, San Diego Instruments, San Diego, CA, USA), designed for human clinical research, was used. The startle eliciting stimulus was delivered binaurally by circumaural telephonic headphones (TDH-39-P, Maico, Minneapolis, USA). The frequency of the sound was carefully calibrated with a Quest Electronics meter (model 210 Quest Technologies, Oconomov, WI, USA). For measurement of the blink response two EMG recording electrodes were used. After skin preparation, the EMG recording electrodes were filled with a small amount of high-conductivity electrode gel (Sigma gel, In Vivo Meteric, CA, USA) before they were attached to the skin with double-sided adhesive collars. One electrode was positioned below the lower eyelid in line with the pupil of the right eye and the second was placed 1–2 cm laterally to the first (White et al., 2012). Additionally, an isolated ground electrode was attached in the center of the forehead (electrically inactive site). Electrode impendence was less than 5 kOhm. The EMG signal was filtered between 100–1000 Hz and digitized at 1 kHz and analyzed by the EMG startle response software.

The participants were placed in a comfortable chair in an undisturbed, quiet room with the headphones on. The test session started with an acclimation period of five minutes, during this time a background 70 dB white noise was delivered through the headphones. The acclimation period was followed by a series of trial with a continuous background 70 dB white noise in between. The test session consisted of four blocks. Block 1 included five pulse alone trials (115 dB 40 ms broad-band white noise), measuring the baseline startle response. Block 2 and 3 consisted of 25 trials, comprised of 5 pulses–alone and 20 prepulse trials presented in pseudo-random order. The pulse stimuli consisted of a 115 dB 40 ms noise burst preceded at a 100 ms interval by prepulses (20 ms noise bursts) that were 2, 4, 8, 16 dB above the 70-dB background noise (72 dB; 74 dB; 78 dB; 86 dB). The last block consisted of five pulse-alone trials, which allowed measurement of within-test habituation. The inter-trial interval was pseudo-randomly variable, averaging 30 s.

Peak startle amplitudes were measured automatically within 20–150 ms following the onset of the startle stimulus. Zero response trials were considered invalid and not used in startle magnitude and PPI calculations if (1) the peak startle response occurred outside the 20–150 ms time frame (2) a baseline shift exceeded 40 arbitrary units, or (3) the startle response was 25 arbitrary amplitude units or less. Patients with negligible baseline startle responses (mean amplitude < 10 V), and more than 50% zero responses were considered as non-responders and were consequently excluded from further analyses. An arbitrary unit corresponded to 0.076 mV.

### 2.3. Hormonal analyses

Venous blood samples were collected at the end of the 90-minutes test session. Sample preparation was done using a slightly modified method of steroid extraction (Liu et al., 2011). Separation of steroids were performed using ultra-performance convergence chromatography ($UPC^2$) and identification of serum cortisol and cortisone was done by tandem mass spectrometry (Xevo TQ-S), as previously described (Hellgren et al., 2016).

The participating women collected saliva samples for cortisol analyses at home. All women were carefully instructed how to perform the saliva sampling using Salivette tubes (Sarstedt, Sweden). The first saliva sample was to be taken immediately after awakening, the second 15 min later, the third 30 min later and the fourth and last one 45 min after awakening. The women were instructed to report time of awakening and the four-sampling time points on a report sheet. No food, drink, smoking or tooth brushing was allowed within one hour before or between the samples, and women who provided the first sample more than 5 min after awakening were excluded. After completed sampling, the Salivette tubes and the report sheet were sent back to the research laboratory by mail. The saliva samples were analyzed using a Cobas 8000 e602 instrument with the Cobas Elecsys cortisol reagent kit (Roche Diagnostics, Bromma, Sweden).

### 2.4. Statistical analyses

For participants with valid ASR, PPI and cortisol levels at all four time-points (n = 107), the area under the curve of cortisol levels (nmol/ (l min)) following awaking was calculated with respect to the ground (AUCg), the increase (AUCi), and above baseline (AUCab) (Fekedulegn et al., 2007). The different formulas for the area under the curve can be derived from the trapezoid formula. The information needed in order to calculate the formula consists of (a) the measurements themselves and (b) the time distance between the measurements (Pruessner et al., 2003). AUCg as calculated includes both the time differences between the single measurement and the difference for each of those measurements from the ground (zero). Thus, AUCg can be considered a measure of total cortisol release during the awakening response as it represents the total area under the curve, based on the four salivary cortisol measurements with respect to the ground (zero). On the other hand, unlike AUCg, AUCi and AUCab are calculated with respect to the first value (baseline) measured instead of the ground (zero). AUCi measures the increase in salivary cortisol from the baseline value without respect to the ground. AUCab is variant of AUCi but only considers the measures above baseline. Consequently, if subsequent measures are less than the baseline salivary cortisol measure AUCab will always be zero (Fekedulegn et al., 2007). Hence, AUCi and AUCab emphasize the change over time and can be considered as measures of reactivity.

Prepulse inhibition (PPI) was computed as the percentage reduction in peak magnitude of startle on pulse-alone (PA) trials by the formula; $PPI = 100 \times (M_{PA} - M_{PP})/ M_{PA}$, where $M_{PA}$ is the mean magnitude of pulse-alone in block 2 and 3, and MPP is the magnitude of prepulse–pulse trials.

The ASR and PPI (78 dB and 86 dB) values followed a normal distribution, assessed using the Shapiro-Wilk test (Shapiro- Wilk > 0.95). However, among the PPI values at the four prepulse levels, the first two (72 dB and 74 dB) were found to be non-normally distributed (Shapiro-Wilk = 0.899 and 0.908). PPI at 72 dB approached, but did not statistically reach, normal distribution (Shapiro-Wilk = 0.938), whilst PPI at 74 dB deviated even more from normal distribution after natural logarithm transformation (Shapiro- Wilk = 0.888). Hence, the natural logarithm transformed ratio was used for PPI at 72 dB but not for the PPIs following 74, 78 and 86 dB prepulses in the final regression model.

Confounders of the association between ASR, PPI of the startle response, and measures of the HPA-axis were evaluated by Pearson's correlation test and independent t-tests with both exposure and outcome. The confounders in the final model were selected based on significant findings in these analyses, or on previous findings in the literature and included any ongoing anxiety disorder, EPDS-score, sleep duration the night before the test session, smoking during pregnancy, and maternal age (Comasco et al., 2016; Duncan et al., 2001; Ludewig et al., 2002; Petrovsky et al., 2014; Poli and Angrilli, 2015). Use of antidepressant medication was discarded as a confounder due to strong collinearity with ongoing anxiety disorder.

**Table 1**
Participants´characteristics.

| | n | Mean ± SD or n (%) | Minimum | Maximum |
|---|---|---|---|---|
| Age, years | 107 | 31.4 ± 4.8 | 19.0 | 44.0 |
| BMI (first trimester) | 105 | 24.4 ± 4.2 | 17.4 | 37.4 |
| Caucasian ethnicity | 107 | 106 (99.1) | | |
| Smoking during pregnancy | 107 | 2 (1.9) | | |
| Previous children | 107 | 57 (53.3) | | |
| Singleton pregnancies | 107 | 107 (100) | | |
| Pre-term delivery | 107 | 0 | | |
| Sleep duration, h | 106 | 7.1 ± 1.4 | 2.5 | 10.0 |
| EPDS | 107 | 5.1 ± 4.8 | 0.0 | 22.0 |
| Baseline startle, AU | 107 | 3009 ± 1766 | 355 | 7512 |
| Prepulse inhibition (72 dB), % | 107 | −0.62 ± 29.1 | −160.1 | 67.4 |
| Prepulse inhibition (76 dB), % | 107 | 29.2 ± 28.9 | −103.8 | 70.4 |
| Prepulse inhibition (78 dB), % | 107 | 42.4 ± 27.7 | −44.2 | 92.8 |
| Prepulse inhibition (86 dB), % | 107 | 51.4 ± 27.7 | −51.1 | 97.5 |
| Salivary cortisol 0 min after awakening, nmol/l | 107 | 18.2 ± 5.2 | 8.3 | 39.0 |
| Salivary cortisol 15 min after awakening, nmol/l | 107 | 18.4 ± 5.0 | 7.2 | 40.0 |
| Salivary cortisol 30 min after awakening, nmol/l | 107 | 20.5 ± 5.3 | 9.1 | 40.0 |
| Salivary cortisol 45 min after awakening, nmol/l | 107 | 19.7 ± 5.9 | 9.1 | 47.0 |
| AUCg, nmol/(1 min) | 107 | 868 ± 208 | 413.3 | 1635 |
| AUCi, nmol/(l min) | 107 | 50.1 ± 161 | −455.3 | 540.0 |
| AUCab, nmol/(l min) | 107 | 374 ± 322 | 0.0 | 1268.0 |
| Cortisol, nmol/l | 99 | 201 ± 140 | 47.3 | 765.2 |
| Cortisone, nmol/l | 99 | 166 ± 186 | 32.5 | 970.9 |
| Cortisone to cortisol ratio | 99 | 1.9 ± 1.2 | 0.3 | 6.2 |

AU = Arbitrary units, AUCab = Area under the Curve above baseline, AUCg = Area under the Curve with respect to the ground, AUCi = Area under the Curve with respect to the increase, BMI = Body Mass Index, EPDS = Edinburgh Postnatal Depression Scale.

All values in the text and tables are displayed as mean ± standard deviation, unless otherwise stated. All statistical analyses in the present study were performed with IBM SPSS Statistics, version 21. P-values less than 0.05 were considered statistically significant.

## 3. Results

### 3.1. Sample characteristics

Two hundred and thirty-four pregnant women were recruited for the study, among whom data on all variables of interest was available for 107 women (Supplementary material). As presented in Table 1, the included women had a mean age of 31.4 ± 4.8 years and 57 (53.3%) had previously given birth. Only two women reported regular smoking during pregnancy, none of the women reported use of systemic corticosteroid steroid therapy or alcohol during pregnancy; however, six women reported antidepressant drug use. The anxiety subtypes presented in this sample include: social anxiety disorder (n = 7), panic disorder (PD) (n = 1), obsessive compulsive disorder (OCD) (n = 7), posttraumatic stress disorder (PTSD) (n = 1) and generalized anxiety disorder (GAD) (n = 3), according to the MINI and based on the DSM-IV and ICD-10 classification system. In addition, two women had PTSD symptoms ("subthreshold-PTSD") according to the MINI. The startle response test sessions and blood sampling took place on average 19.0 ± 9.0 days before delivery in gestational week 37.7 ± 0.7, and the CAR saliva sampling took place approximately 4.4 ± 3.8 days after the test session.

### 3.2. ASR, prepulse inhibition, CAR, and confounders

The relationships between the ASR magnitude, PPI, CAR and potential confounders are presented in Table 2. As previously shown in this population, pregnant women who had any ongoing anxiety disorder had significantly lower PPI than women without anxiety disorders. Also, women with antidepressant drugs use had significantly higher CAR AUCi and AUCab compared to women with no antidepressant drug use. No association between age, BMI, parity, smoking, sleep duration, or depressive symptoms and any of the primary outcomes was noted (Table 2). Moreover, no correlation could be found between symptoms of anxiety, assessed by STAI-S, and CAR, cortisol, cortisone, and ASR. Nevertheless, in addition to any ongoing anxiety disorder, EPDS-score, age, smoking, and sleep duration were included in the subsequent regression models due to previously described associations.

### 3.3. ASR and HPA axis measures

In concordance with the hypothesis of the present study and as presented in Table 3, the CAR measured as AUCi, AUCab and AUCg significantly predicted the ASR (Fig. 1). Women with higher CAR displayed a higher baseline startle magnitude, whereas women with lower

**Table 2**
Relationships between the acoustic startle response, prepulse inhibition, cortisol awakening response and potential confounders.

| | | Baseline startle magnitude *r* | Prepulse inhibition (86 dB) *r* | AUCg *r* | AUCi *r* | **AUCab *r*** |
|---|---|---|---|---|---|---|
| EPDS, score | | 0.02 | −0.16 | −0.08 | 0.03 | −0.05 |
| Sleep duration | | −0.19 | −0.04 | −0.17 | −0.07 | −0.10 |
| Age, years | | −0.12 | 0.05 | −0.09 | −0.07 | −0.09 |
| First trimester BMI, kg/m$^2$ | | 0.07 | 0.03 | −0.11 | 0.06 | −0.01 |
| Gestational length, weeks | | 0.29 | 0.26 | 0.12 | 0.16 | 0.16 |
| | ***n*** | **mean ± SD** | **mean ± SD** | **mean ± SD** | **mean ± SD** | **mean ± SD** |
| Smoker | 2 | 3940 ± 13.2 | 66.9 ± 15.4 | 1003 ± 81 | 139 ± 196 | 594 ± 361 |
| Non-smoker | 105 | 2992 ± 1779 | 51.1 ± 27.8 | 866 ± 209 | 48 ± 161 | 370 ± 322 |
| Anxiety disorder | 16 | 3069 ± 1717 | 36.5 ± 24.7 [a] | 875 ± 229 | 99 ± 170 | 435 ± 347 |
| No anxiety disorder | 90 | 3007 ± 1792 | 53.9 ± 27.6 | 867 ± 206 | 43 ± 158 | 367 ± 318 |
| Antidepressant drug use | 6 | 4085 ± 2506 | 52.9 ± 21.8 | 958 ± 251 | 246 ± 181[b] | 724 ± 310[b] |
| No antidepressant drug use | 101 | 2945 ± 1709 | 51.3 ± 28.1 | 863 ± 205 | 39 ± 153 | 353 ± 312 |
| Previous children | 57 | 3054 ± 1781 | 50.8 ± 27.4 | 862 ± 228 | 35 ± 174 | 312 ± 329 |
| No previous children | 50 | 2958 ± 1767 | 52.1 ± 28.3 | 876 ± 184 | 68 ± 143 | 443 ± 302 |

[a] Significantly lower than women with no anxiety disorder, $p < 0.05$.
[b] Significantly higher than women with no antidepressant drug use, $p < 0.05$.

**Table 3**
Linear regression analyses of the acoustic startle response and prepulse inhibition in relation to the cortisol awakening response.

| Variable | Unstandardized B | β | *p* |
|---|---|---|---|
| **Acoustic startle response** | | | |
| AUCg | 2.33 | 0.273 | 0.004 |
| AUCi | 2.34 | 0.213 | 0.028 |
| AUCab | 1.30 | 0.237 | 0.014 |
| **Prepulse inhibition (72 dB)** | | | |
| AUCg | −0.001 | −0.168 | 0.216 |
| AUCi | −0.001 | −0.119 | 0.381 |
| AUCab | 0.000 | −0.074 | 0.586 |
| **Prepulse inhibition (76 dB)** | | | |
| AUCg | −0.004 | −0.031 | 0.747 |
| AUCi | 0.008 | 0.044 | 0.653 |
| AUCab | 0.008 | 0.085 | 0.387 |
| **Prepulse inhibition (78 dB)** | | | |
| AUCg | −0.003 | −0.023 | 0.811 |
| AUCi | 0.028 | 0.160 | 0.100 |
| AUCab | 0.014 | 0.165 | 0.089 |
| **Prepulse inhibition (86 dB)** | | | |
| AUCg | 0.020 | 0.147 | 0.130 |
| AUCi | 0.040 | 0.231 | 0.017 |
| AUCab | 0.023 | 0.272 | 0.005 |

**Table 4**
Linear regression analyses of the acoustic startle response magnitude and prepulse inhibition in relation to serum levels of cortisol and cortisone, and the cortisol to cortisone ratio.

| Variable | Unstandardized B | β | p |
|---|---|---|---|
| **Acoustic Startle response** | | | |
| Cortisol | −0.26 | −0.02 | 0.84 |
| Cortisone | −0.47 | −0.05 | 0.62 |
| Cortisol: Cortisone ratio | 143.0 | 0.09 | 0.35 |
| **Prepulse inhibition (72 dB)** | | | |
| Cortisol | −0.000108 | −0.013 | 0.928 |
| Cortisone | 0.002 | 0.235 | 0.090 |
| Cortisol: Cortisone ratio | −0.231 | −0.235 | 0.090 |
| **Prepulse inhibition (74 dB)** | | | |
| Cortisol | 0.009 | 0.050 | 0.626 |
| Cortisone | −0.007 | −0.047 | 0.641 |
| Cortisol: Cortisone ratio | 1.807 | 0.080 | 0.431 |
| **Prepulse inhibition (78 dB)** | | | |
| Cortisol | −0.001 | −0.007 | 0.946 |
| Cortisone | 0.009 | 0.060 | 0.557 |
| Cortisol: Cortisone ratio | −1.024 | −0.044 | 0.669 |
| **Prepulse inhibition (86 dB)** | | | |
| Cortisol | −0.01 | −0.52 | 0.61 |
| Cortisone | −0.01 | −0.07 | 0.48 |
| Cortisol: Cortisone ratio | 1.67 | 0.07 | 0.49 |

CAR had lower startle magnitude (AUCg B = 2.33, β = 0.27, p = 0.004; AUCi B = 2.34, β = 0.21, p = 0.028; AUCab B = 1.30, β = 0.24, p = 0.014). The relationship remained significant for AUCg and AUCab when adjusting for any ongoing anxiety disorder, EPDS-score, sleep duration, smoking and age (AUCg B = 1.98, β = 0.23, p = 0.022; AUCab B = 1.13, β = 0.21, p = 0.04). However, for the AUCi the relationship was borderline significant (AUCi B = 2.10, β = 0.19, p = 0.055). As presented in Table 4, no significant association was found between ASR magnitude and serum cortisol, cortisone and cortisone to cortisol ratio.

### *3.4. Prepulse inhibition and HPA axis measures*

A significant association between AUCi and AUCab and PPI at 86 dB prepulses was observed, Table 3. Women with higher HPA-axis reactivity measured as AUCi and AUCab had higher PPI (AUCi B = 0.04, β = 0.23, p = 0.017; AUCab B = 0.02, β = 0.27, p = 0.005, Fig. 2. These findings remained following adjustment for any ongoing anxiety disorder, EPDS-score, sleep duration, smoking and age (AUCi B = 0.05, β = 0.27, p = 0.005; AUCab B = 0.03, β = 0.31, p = 0.002). No association was noted between PPI (86 dB) and AUCg, nor between PPI (with 72 dB, 76 dB, and 78 dB prepulses) and the CAR indices, Table 3. Furthermore, PPI across all prepulse intensities was not associated with levels of cortisol, cortisone or the cortisone to cortisol ratio, as presented in Table 4.

## 4. Discussion

The present study investigated the association between the baseline acoustic startle response (ASR) and prepulse inhibition (PPI) of the startle response with the cortisol awakening response (CAR) in saliva samples, as well as serum levels of cortisol, cortisone and the cortisone to cortisol ratio in women in their late pregnancy. The main findings were that pregnant women with higher CAR (measured as AUCg, AUCi and AUCab) displayed higher ASR magnitude and higher PPI compared to women with lower CAR. However, no association was found between serum levels of cortisol or cortisone and the ASR and PPI of the startle response.

To our knowledge, this is the first study demonstrating a positive association between the CAR and the ASR magnitude in late pregnancy, a period when plasma cortisol levels are tripled (Jung et al., 2011), but a distinct rise in cortisol following awakening (CAR) is still present (de Weerth and Buitelaar, 2005). However, it has previously been demonstrated that the CAR physiologically decreases with gestational length, indicating altered HPA-axis responsiveness (Buss et al., 2009). Thus, it is plausible to speculate that a smaller attenuation of the CAR in late gestation may represent a marker of stress system dysregulation. Cortisol released from the adrenal gland during pregnancy stimulates the placental CRH synthesis and release, rather than providing negative feedback, a phenomenon that is in contrast to the non-pregnant cortisol suppression of CRH secretion from the hypothalamus (Chrousos et al., 1998; Jung et al., 2011; Robinson et al., 1988). Furthermore, hormones of the HPA-axis have previously been demonstrated to affect the ASR magnitude (Buchanan et al., 2001; Liang et al., 1992; Swerdlow et al., 1986). Altogether, these findings support the result of the present study of increased startle magnitude in association with higher CAR in late pregnancy and may be interpreted as a link between HPA-axis

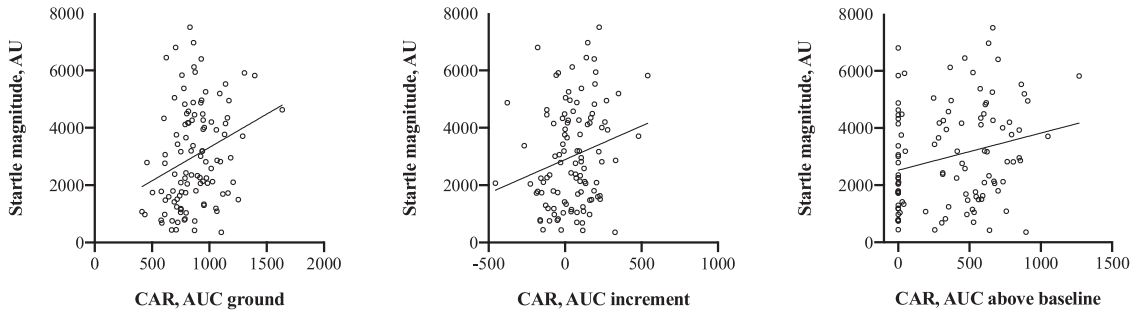


**Fig. 1.** Linear association between the baseline acoustic startle response magnitude and cortisol awakening response measured as AUCg, AUCi and AUCab.

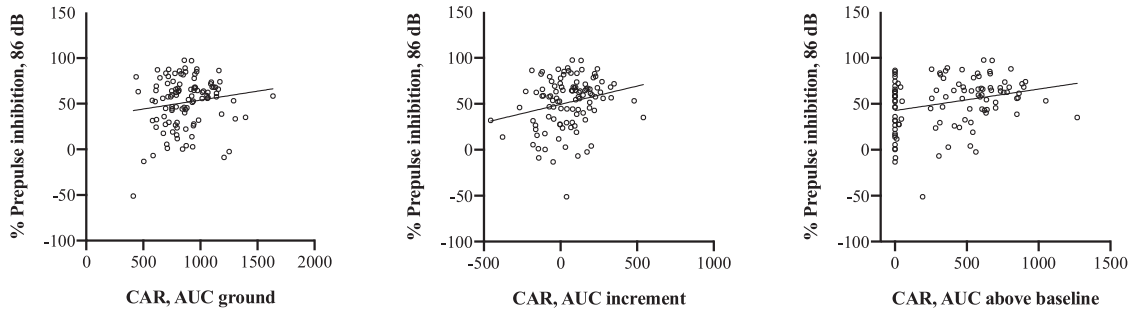


**Fig. 2.** Linear association between the prepulse inhibition at 86 dB and cortisol awakening response measured as AUCg, AUCi and AUCab.

reactivity and neurophysiological reactivity measured as the ASR. The measurement of CRH levels, that was not performed in the present study, would further explore the relation between the HPA-axis and the baseline ASR magnitude.

Another finding of the present study was that third trimester pregnant women with increased HPA-axis reactivity measured as the CAR (AUCi and AUCab, but not AUCg) displayed greater PPI (86 dB). Contrary to AUCi and AUCab, that measure the changes in salivary cortisol over time and hence are considered as measures of reactivity, AUCg is a measure of the total hormonal output and a state indicator of the salivary cortisol released during the awakening response (Fekedulegn et al., 2007). Vreeburg et al. previously investigated the association between anxiety disorders (social anxiety disorder, PD and GAD) and HPA-axis activity in a non-pregnant population and demonstrated higher CAR, measured as AUCi and AUCg, in participants with current anxiety disorders compared to controls, indicating that both the dynamic measure of the CAR, as well as the total cortisol output is increased in anxiety disorders (Vreeburg et al., 2010). However, cautious interpretation of the results regarding PPI is needed as this is the first study demonstrating an association of PPI of the startle with HPA-axis reactivity in pregnant women, and study findings are in contrast to results in non-pregnant participants. For instance, De la Casa et al. demonstrated that induced stress reduces both the ASR magnitude and PPI of the startle (De la Casa et al., 2016). But as pregnancy represents a supraphysiological hormonal state, the HPA influence on the PPI of the startle response may not be as straight-forward as in non-pregnant individuals. For instance, progesterone levels are increased by approximately 10 times during pregnancy compared to normally cycling women, and high progesterone levels may, hypothetically, counteract or have a greater impact than the HPA axis on sensorimotor gating (Hantsoo et al., 2018). In fact, sex differences in PPI have been associated with changes in progesterone levels (Swerdlow et al., 1997). Moreover, lower PPI has been found during the luteal phase of the menstrual cycle (Kumari, 2011), and in women of childbearing ages, as well as healthy pregnant women, compared with postmenopausal women (Bannbers et al., 2010; Kask et al., 2008a).

Further, no association was found between serum levels of cortisol and cortisone, nor cortisone to cortisol ratio, with neither the ASR nor PPI of the startle. The most straight-forward interpretation is that HPA reactivity, such as the CAR, rather than static measures of HPA hormone levels, are the major driver for arousal and sensorimotor gating at this stage of pregnancy. Another explanation could be that salivary cortisol better assesses the hypothalamic–pituitary–adrenal (HPA) function than serum cortisol, since cortisol in saliva is present only in the unbound form. Binding proteins in plasma increase markedly during pregnancy, hence cortisol present in saliva likely provides a more accurate measure of the biologically active hormone (Kirschbaum and Hellhammer, 1994).

Strengths of the present study include the relatively large population-based sample size and that the participating women included in the study were in a narrow gestational age-range that should have minimized variation caused by the dampening of cortisol reactivity with gestational age (Buss et al., 2009). Limitations include the home-based saliva sampling that was performed at a different day than the test session. However, the latter was based on previous findings suggesting that CAR shows moderate to high intra-individual stability across days (Wust et al., 2000). The participating women were instructed to document the four time points when the saliva samples were taken to enable better control over the participants' adherence to the salivary cortisol sampling protocol. Participants who did not collect the first wake-up sample of salivary cortisol within five minutes after awakening were excluded from the present study. In addition, Kudielka et al. demonstrated a strong correlation between the magnitude of the CAR and the time of awakening; individuals who wake up early in the morning showed higher increase in the CAR magnitude compared to the ones that wake up later (Kudielka and Kirschbaum, 2003). This factor was not considered in the present study and will therefore form the basis for further investigations.

Several factors have been suggested to influence the ASR, and in this context it is important to consider the variation in ASR magnitude that exists between individuals but also intra-individual variations that possibly can be explained by the organism's internal and emotional state (Koch, 1999). Furthermore, it is known that factors affecting startle reactivity may also influence the PPI. Nicotine use is a factor known to influence both the ASR and PPI of the startle, resulting in a decreased ASR and an increased PPI (Baschnagel and Hawk, 2008; Duncan et al., 2001). Even though only a few women in the present study self-reported nicotine use, this factor was included in the final regression model. Furthermore, another important confounding factor is sleep. Sleep has important homeostatic functions and sleep deprivation is a stressor (McEwen, 2006). Sleep deprivation enhances CRH neuronal activity in the limbic areas of the brain (Fadda and Fratta, 1997), including the amygdala (Davis and Whalen, 2001). Interestingly, sleep deprivation has been associated with increased baseline startle response magnitude in rats (Frau et al., 2008) and reduced sensorimotor gating in healthy subjects (Petrovsky et al., 2014) and in post-partum women (Comasco et al., 2016). However, no such association between ASR, PPI or sleep was found in the present study of third trimester pregnant women. The absence of association could be explained by the degree of impact on the sleep. While sleep disturbances are prevalent throughout pregnancy (Mindell et al., 2015), the post-partum period usually affects the number of hours of sleep to a greater extent than during pregnancy, resulting in sleep deprivation rather than sleep disturbances (Mindell et al., 2015).

Affective as well as cognitive dysregulation are indeed key characteristics of many psychiatric disorders and the relationship between measures of the HPA-axis and affective disorders, such as depression, has been repeatedly demonstrated (Nemeroff and Vale, 2005). However, present knowledge of the mechanisms behind HPA-axis hormone influence on the human brain and how these hormones contribute to the development of affective disorders such as anxiety is scarce. Comorbidity of depression and anxiety disorders is highly prevalent, and depression is often preceded by anxiety disorder (Lamers et al., 2011). Noteworthy, in this study population, no association between

depressive symptoms and any of the primary outcomes was noted, although pregnant women who had an ongoing anxiety disorder had significantly lower PPI than women without anxiety disorders. This result is in line with previous studies demonstrating reduced PPI in several psychiatric disorders, including schizophrenia and a number of anxiety disorders, such as obsessive-compulsive disorder, panic disorder, and post-traumatic stress disorder (Braff et al., 2001 Kohl et al., 2013). In contrast, a study of Perry and colleagues demonstrates that MDD patients did not have PPI deficits when compared to schizophrenic and control subjects (Perry et al., 2003). Symptoms of anxiety disorders include difficulty with concentration and inattention, symptoms that possibly can be associated with impaired sensorimotor gating (Braff et al., 2001).However, it is unclear how many of those symptoms can be attributed to anxiety disorders alone. Hence, the discrepancies found may partly be explained by cognitive bias associated with personality traits of anxiety rather than coexisting symptomatology between anxiety and depression disorders.

Pregnancy is characterized by dramatic alterations of the woman´s hormonal status, including a continuous increase in the plasma concentrations of CRH and cortisol (Skalkidou et al., 2012). These hormones play a modulatory role in cognitive-affective processing via their actions on receptors that are expressed in brain regions involved in emotional processing and cognitive regulation (Joels et al., 2008; Quax et al., 2013). However, the low PPI consistently associated with schizophrenia (Swerdlow et al., 2014) has not yet been related to HPA-axis malfunction.

The clinical application of the startle response measurement can provide important insights to improve our understanding of psychiatric disorders such as anxiety and form the basis for further examination of other psychiatric disorders occurring during pregnancy. Importantly, progesterone levels during pregnancy dramatically increase in comparison to non-pregnant normally cycling women. Consequently, it is inevitable not to take account of this hormone´s potential impact on the outcome variables of this study. Furthermore, Epperson et al., demonstrated that women suffering from premenstrual dysphoric disorder show an increase in baseline startle magnitude in the luteal phase compared to the follicular phase (Epperson et al., 2007). Clearly, further studies are needed to investigate the role of changes in progesterone during pregnancy in relation to the neurophysiological changes associated with the pregnancy period.

## 5. Conclusion

In conclusion, the findings of the present study demonstrate that enhanced startle reactivity and high prepulse inhibition of the startle response (a neurophysiological correlate of improved sensorimotor gating) in late pregnancy are associated with enhanced HPA-axis reactivity (AUCi and AUCab) respectively. These findings suggest that hypothalamic-pituitary-adrenal axis responsiveness, rather than state-indicators, may be related to neurophysiological reactivity and sensorimotor gating in women in late pregnancy.

## Conflict of interest

Sundström-Poromaa I., M.D., Ph.D., serves occasionally on advisory boards or act as invited speaker at scientific meetings for Gedeon Richter, MSD, Novo Nordisk, Bayer Health Care, and Lundbeck A/S. Skalkidou A, M.D., Ph.D., has occasionally been invited as a speaker at scientific meetings for Biotekna, Ferring and Merck. The other authors report no financial relationships with commercial interests. All authors have no conflict of interest related to this work.

## Role of the funding source

The funding source had no role in the study design, in the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the article for publication.

## Acknowledgments

The authors would like to sincerely thank all the women who participated in this study. The study was partially supported by the Swedish Research Council (VR: 521-2013-2339), the Marianne and Marcus Wallenberg Foundation (MMW2011.0115), the Swedish Medical Association (SLS-250581), the Uppsala University Hospital (2012-Skalkidou) to A.S.; the Swedish Research Council to I.SP. (VR: 521-2013-2339); and Märta Lundqvist foundation and Swedish Society of Medicine (SLS-331991) to E.C. E.C. is a Marie Skłodowska Curie fellow and receives funds from the Swedish Research Council (VR: 2015-00495) and EU FP7-People-Cofund (INCA 600398), as well as from SciLifeLab.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2019.03.008.

## References

Bannbers, E., Kask, K., Wikstrom, J., Sundstrom Poromaa, I., 2010. Lower levels of prepulse inhibition in luteal phase cycling women in comparison with postmenopausal women. Psychoneuroendocrinology 35, 422–429.
Baschnagel, J.S., Hawk Jr, L.W., 2008. The effects of nicotine on the attentional modification of the acoustic startle response in nonsmokers. Psychopharmacology 198, 93–101.
Braff, D.L., Geyer, M.A., Swerdlow, N.R., 2001. Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. Psychopharmacology 156, 234–258.
Buchanan, T.W., Brechtel, A., Sollers, J.J., Lovallo, W.R., 2001. Exogenous cortisol exerts effects on the startle reflex independent of emotional modulation. Pharmacol. Biochem. Behav. 68, 203–210.
Buss, C., Entringer, S., Reyes, J.F., Chicz-DeMet, A., Sandman, C.A., Waffarn, F., Wadhwa, P.D., 2009. The maternal cortisol awakening response in human pregnancy is associated with the length of gestation. Am. J. Obstet. Gynecol. 201 (398) e391-398.
Butler, R.W., Braff, D.L., Rausch, J.L., Jenkins, M.A., Sprock, J., Geyer, M.A., 1990. Physiological evidence of exaggerated startle response in a subgroup of Vietnam veterans with combat-related PTSD. Am. J. Psychiatry 147, 1308–1312.
Chrousos, G.P., Torpy, D.J., Gold, P.W., 1998. Interactions between the hypothalamic-pituitary-adrenal axis and the female reproductive system: clinical implications. Ann. Intern. Med. 129, 229–240.
Clow, A., Thorn, L., Evans, P., Hucklebridge, F., 2004. The awakening cortisol response: methodological issues and significance. Stress 7, 29–37.
Comasco, E., Hellgren, C., Olivier, J., Skalkidou, A., Sundstrom Poromaa, I., 2015. Supraphysiological hormonal status, anxiety disorders, and COMT Val/Val genotype are associated with reduced sensorimotor gating in women. Psychoneuroendocrinology 60, 217–223.
Comasco, E., Gulinello, M., Hellgren, C., Skalkidou, A., Sylven, S., Sundstrom-Poromaa, I., 2016. Sleep duration, depression, and oxytocinergic genotype influence prepulse inhibition of the startle reflex in postpartum women. Eur. Neuropsychopharmacol. 26, 767–776.
Cox, J.L., Holden, J.M., Sagovsky, R., 1987. Detection of postnatal depression. Development of the 10-item edinburgh postnatal depression scale. Br. J. Psychiatry 150, 782–786.
Cromwell, H.C., Mears, R.P., Wan, L., Boutros, N.N., 2008. Sensory gating: a translational effort from basic to clinical science. Clin. EEG Neurosci. 39, 69–72.
Davis, M., Whalen, P.J., 2001. The amygdala: vigilance and emotion. Mol. Psychiatry 6, 13–34.
Davis, M., Gendelman, D.S., Tischler, M.D., Gendelman, P.M., 1982. A primary acoustic startle circuit: lesion and stimulation studies. J. Neurosci. 2, 791–805.
De la Casa, L.G., Mena, A., Ruiz-Salas, J.C., 2016. Effect of stress and attention on startle response and prepulse inhibition. Physiol. Behav. 165, 179–186.
de Weerth, C., Buitelaar, J.K., 2005. Cortisol awakening response in pregnant women. Psychoneuroendocrinology 30, 902–907.
Duncan, E., Madonick, S., Chakravorty, S., Parwani, A., Szilagyi, S., Efferen, T., Gonzenbach, S., Angrist, B., Rotrosen, J., 2001. Effects of smoking on acoustic startle and prepulse inhibition in humans. Psychopharmacology 156, 266–272.
Fadda, P., Fratta, W., 1997. Stress-induced sleep deprivation modifies corticotropin releasing factor (CRF) levels and CRF binding in rat brain and pituitary. Pharmacol. Res. 35, 443–446.
Fekedulegn, D.B., Andrew, M.E., Burchfiel, C.M., Violanti, J.M., Hartley, T.A., Charles, L.E., Miller, D.B., 2007. Area under the curve and other summary indicators of repeated waking cortisol measurements. Psychosom. Med. 69, 651–659.
Frau, R., Orru, M., Puligheddu, M., Gessa, G.L., Mereu, G., Marrosu, F., Bortolato, M.,

2008. Sleep deprivation disrupts prepulse inhibition of the startle reflex: reversal by antipsychotic drugs. Int. J. Neuropsychopharmacol. 11, 947–955.
Grillon, C., Baas, J., 2003. A review of the modulation of the startle reflex by affective states and its application in psychiatry. Clin. Neurophysiol. 114, 1557–1579.
Hantsoo, L., Golden, C.E.M., Kornfield, S., Grillon, C., Epperson, C.N., 2018. Startling differences: using the acoustic startle response to study sex differences and neurosteroids in affective disorders. Curr. Psychiatry Rep. 20, 40.
Hellgren, C., Akerud, H., Skalkidou, A., Sundstrom-Poromaa, I., 2013. Cortisol awakening response in late pregnancy in women with previous or ongoing depression. Psychoneuroendocrinology 38, 3150–3154.
Hellgren, C., Edvinsson, A., Olivier, J.D., Fornes, R., Stener-Victorin, E., Ubhayasekera, S.J., Skalkidou, A., Bergquist, J., Sundstrom-Poromaa, I., 2016. Tandem mass spectrometry determined maternal cortisone to cortisol ratio and psychiatric morbidity during pregnancy-interaction with birth weight. Psychoneuroendocrinology 69, 142–149.
Hitchcock, J., Davis, M., 1986. Lesions of the amygdala, but not of the cerebellum or red nucleus, block conditioned fear as measured with the potentiated startle paradigm. Behav. Neurosci. 100, 11–22.
Hodgues, W.F., Spielberger, C.D., 1969. An indicant of trait or state anxiety? J. Consult. Clin. Psychol. 33, 430–434.
Iliadis, S.I., Comasco, E., Sylven, S., Hellgren, C., Sundstrom Poromaa, I., Skalkidou, A., 2015. Prenatal and postpartum evening salivary cortisol levels in association with peripartum depressive symptoms. PLoS One 10, e0135471.
Joels, M., Karst, H., DeRijk, R., de Kloet, E.R., 2008. The coming out of the brain mineralocorticoid receptor. Trends Neurosci. 31, 1–7.
Jolley, S.N., Elmore, S., Barnard, K.E., Carr, D.B., 2007. Dysregulation of the hypothalamic-pituitary-adrenal axis in postpartum depression. Biol. Res. Nurs. 8, 210–222.
Jung, C., Ho, J.T., Torpy, D.J., Rogers, A., Doogue, M., Lewis, J.G., Czajko, R.J., Inder, W.J., 2011. A longitudinal study of plasma and urinary cortisol in pregnancy and postpartum. J. Clin. Endocrinol. Metab. 96, 1533–1540.
Kane, H.S., Dunkel Schetter, C., Glynn, L.M., Hobel, C.J., Sandman, C.A., 2014. Pregnancy anxiety and prenatal cortisol trajectories. Biol. Psychol. 100, 13–19.
Kask, K., Backstrom, T., Gulinello, M., Sundstrom-Poromaa, I., 2008a. Lower levels of prepulse inhibition of startle response in pregnant women compared to postpartum women. Psychoneuroendocrinology 33, 100–107.
Kask, K., Backstrom, T., Gulinello, M., Sundstrom-Poromaa, I., 2008b. Lower levels of prepulse inhibition of startle response in pregnant women compared to postpartum women. Psychoneuroendocrinology 33, 100–107.
Kirschbaum, C., Hellhammer, D.H., 1994. Salivary cortisol in psychoneuroendocrine research: recent developments and applications. Psychoneuroendocrinology 19, 313–333.
Koch, M., 1999. The neurobiology of startle. Prog. Neurobiol. 59, 107–128.
Kudielka, B.M., Kirschbaum, C., 2003. Awakening cortisol responses are influenced by health status and awakening time but not by menstrual cycle phase. Psychoneuroendocrinology 28, 35–47.
Kumari, V., 2011. Sex differences and hormonal influences in human sensorimotor gating: implications for schizophrenia. Curr. Top. Behav. Neurosci. 8, 141–154.
Lamers, F., van Oppen, P., Comijs, H.C., Smit, J.H., Spinhoven, P., van Balkom, A.J., Nolen, W.A., Zitman, F.G., Beekman, A.T., Penninx, B.W., 2011. Comorbidity patterns of anxiety and depressive disorders in a large cohort study: the Netherlands Study of Depression and Anxiety (NESDA). J. Clin. Psychiatry 72, 341–348.
Lee, Y., Lopez, D.E., Meloni, E.G., Davis, M., 1996. A primary acoustic startle pathway: obligatory role of cochlear root neurons and the nucleus reticularis pontis caudalis. J. Neurosci. 16, 3775–3789.
Liang, K.C., Melia, K.R., Miserendino, M.J., Falls, W.A., Campeau, S., Davis, M., 1992. Corticotropin-releasing factor: long-lasting facilitation of the acoustic startle reflex. J. Neurosci. 12, 2303–2312.
Liu, Y., Uboh, C.E., Soma, L.R., Li, X., Guan, F., You, Y., Rudy, J.A., Chen, J.W., 2011. Detection and confirmation of 60 anabolic and androgenic steroids in equine plasma by liquid chromatography-tandem mass spectrometry with instant library searching. Drug Test. Anal. 3, 54–67.
Ludewig, S., Ludewig, K., Geyer, M.A., Hell, D., Vollenweider, F.X., 2002. Prepulse inhibition deficits in patients with panic disorder. Depress. Anxiety 15, 55–60.
McEwen, B.S., 2006. Sleep deprivation as a neurobiologic and physiologic stressor: allostasis and allostatic load. Metab.: Clin. Exp. 55, S20–23.
Mindell, J.A., Cook, R.A., Nikolovski, J., 2015. Sleep patterns and sleep disturbances across pregnancy. Sleep Med. 16, 483–488.
Nemeroff, C.B., Vale, W.W., 2005. The neurobiology of depression: inroads to treatment and new drug discovery. J. Clin. Psychiatry 66 (Suppl 7), 5–13.
Petrovsky, N., Ettinger, U., Hill, A., Frenzel, L., Meyhofer, I., Wagner, M., Backhaus, J., Kumari, V., 2014. Sleep deprivation disrupts prepulse inhibition and induces psychosis-like symptoms in healthy humans. J. Neurosci. 34, 9134–9140.
Poli, E., Angrilli, A., 2015. Greater general startle reflex is associated with greater anxiety levels: a correlational study on 111 young women. Front. Behav. Neurosci. 9, 10.
Quax, R.A., Manenschijn, L., Koper, J.W., Hazes, J.M., Lamberts, S.W., van Rossum, E.F., Feelders, R.A., 2013. Glucocorticoid sensitivity in health and disease. Nat. Rev. Endocrinol. 9, 670–686.
Richter, S., Schulz, A., Zech, C.M., Oitzl, M.S., Daskalakis, N.P., Blumenthal, T.D., Schachinger, H., 2011. Cortisol rapidly disrupts prepulse inhibition in healthy men. Psychoneuroendocrinology 36, 109–114.
Robinson, B.G., Emanuel, R.L., Frim, D.M., Majzoub, J.A., 1988. Glucocorticoid stimulates expression of corticotropin-releasing hormone gene in human placenta. Proc. Natl. Acad. Sci. U. S. A. 85, 5244–5248.
Rubertsson, C., Borjesson, K., Berglund, A., Josefsson, A., Sydsjo, G., 2011. The Swedish validation of Edinburgh Postnatal Depression Scale (EPDS) during pregnancy. Nord. J. Psychiatry 65, 414–418.
Sasaki, A., Shinkawa, O., Yoshinaga, K., 1989. Placental corticotropin-releasing hormone may be a stimulator of maternal pituitary adrenocorticotropic hormone secretion in humans. J. Clin. Invest. 84, 1997–2001.
Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (Suppl 20), 22–33 quiz 34-57.
Skalkidou, A., Hellgren, C., Comasco, E., Sylven, S., Sundstrom Poromaa, I., 2012. Biological aspects of postpartum depression. Women's Health 8, 659–672.
Skalkidou, A., Poromaa, I.S., Iliadis, S.I., Huizink, A.C., Hellgren, C., Freyhult, E., Comasco, E., 2019. Stress-related genetic polymorphisms in association with peripartum depression symptoms and stress hormones: a longitudinal population-based study. Psychoneuroendocrinology 103 (February), 296–305. https://doi.org/10.1016/j.psyneuen.2019.02.002. [Epub ahead of print] PMID: 30776573.
Swerdlow, N.R., Geyer, M.A., Vale, W.W., Koob, G.F., 1986. Corticotropin-releasing factor potentiates acoustic startle in rats: blockade by chlordiazepoxide. Psychopharmacology 88, 147–152.
Swerdlow, N.R., Hartman, P.L., Auerbach, P.P., 1997. Changes in sensorimotor inhibition across the menstrual cycle: implications for neuropsychiatric disorders. Biol. Psychiatry 41, 452–460.
Swerdlow, N.R., Light, G.A., Sprock, J., Calkins, M.E., Green, M.F., Greenwood, T.A., Gur, R.E., Gur, R.C., Lazzeroni, L.C., Nuechterlein, K.H., Radant, A.D., Ray, A., Seidman, L.J., Siever, L.J., Silverman, J.M., Stone, W.S., Sugar, C.A., Tsuang, D.W., Tsuang, M.T., Turetsky, B.I., Braff, D.L., 2014. Deficient prepulse inhibition in schizophrenia detected by the multi-site COGS. Schizophr. Res. 152, 503–512.
Vreeburg, S.A., Zitman, F.G., van Pelt, J., Derijk, R.H., Verhagen, J.C., van Dyck, R., Hoogendijk, W.J., Smit, J.H., Penninx, B.W., 2010. Salivary cortisol levels in persons with and without different anxiety disorders. Psychosom. Med. 72, 340–347.
Wang, Q., Verweij, E.W., Krugers, H.J., Joels, M., Swaab, D.F., Lucassen, P.J., 2014. Distribution of the glucocorticoid receptor in the human amygdala; changes in mood disorder patients. Brain Struct. Funct. 219, 1615–1626.
White, M.G., Bogdan, R., Fisher, P.M., Munoz, K.E., Williamson, D.E., Hariri, A.R., 2012. FKBP5 and emotional neglect interact to predict individual differences in amygdala reactivity. Genes Brain Behav. 11, 869–878.
Wust, S., Wolf, J., Hellhammer, D.H., Federenko, I., Schommer, N., Kirschbaum, C., 2000. The cortisol awakening response - normal values and confounds. Noise Health 2, 79–88.