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Supraphysiological hormonal status, anxiety disorders, and COMT Val/Val genotype are associated with reduced sensorimotor gating in women

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ABSTRACT

Pregnancy is a period characterized by a supraphysiological hormonal status, and greater anxiety proneness, which can lead to peripartum affective symptoms with dramatic consequences not only for the woman but also for the child. Clinical psychiatry is heavily hampered by the paucity of objective and biology-based intermediate phenotypes. Prepulse inhibition (PPI) of the startle response, a neurophysiological measure of sensorimotor gating, has been poorly investigated in relation to anxiety and in pregnant women.

In the present study, the PPI of healthy non-pregnant women ($n = 82$) and late pregnant women ($n = 217$) was investigated. Age, BMI, depression and anxiety symptoms, tobacco use, and antidepressant medication were considered. We investigated and provided evidence of lower PPI: (i) in healthy pregnant women compared to healthy non-pregnant controls, (ii) in pregnant women with anxiety disorders compared to healthy pregnant women, (iii) in pregnant women with anxiety disorders using SSRI compared to un-medicated pregnant women with anxiety disorders, and (iv) in healthy pregnant women carrying the COMT Val158Met Val/Val genotype compared to Met carriers.

Altogether, a reduced sensorimotor gating as an effect of supraphysiological hormonal status, anxiety disorders, SSRIs, and catecholaminergic genotype, implicate the putative relevance of lower PPI as an objective biological correlate of anxiety proneness in pregnant women. These findings call for prospective studies to dissect the multifactorial influences on PPI in relation to mental health of pregnant women.

1. Introduction

Pregnancy is one of the most extreme endocrine circumstance women could face throughout their lives. In comparison with non-pregnant women, estradiol levels at term are increased by approximately 50 times, and progesterone levels by 10 times, while additional hormone changes also involve the hypothalamus–pituitary–adrenal axis, thyroid hormones, prolactin as well as placenta-specific hormones (Skalkidou et al., 2012). Additionally, while the prevalence of anxiety disorders is similar to non-pregnant women (Goodman et al., 2014; Vesga-Lopez et al., 2008), anxiety symptoms may be more common than depressive symptoms during pregnancy (Andersson et al., 2003; Lee et al., 2007), and may result in adverse consequences not only for the mother but also for the offspring (Olivier et al., 2014). Yet, few studies have addressed the pathophysiology of antenatal anxiety from a more biological perspective (Goodman et al., 2014).

Prepulse inhibition (PPI) of the startle response is a neurobiological measure used to investigate sensorimotor gating and information processing (Braff et al., 1992). While it is an important endophenotype for schizophrenia (Swerdlow et al., 2014), accumulating evidence also suggests lower PPI in a range of anxiety disorders such as obsessive compulsive disorder, panic disorder, and post-traumatic stress disorder (Kohl et al., 2013). Moreover, PPI is a sexually dimorphic measure (Swerdlow et al., 1993), typified by lower PPI in healthy women of childbearing ages than in similar-aged men (Kumari, 2011), and lower PPI in female than in male schizophrenia patients (Kumari et al., 2004; Swerdlow et al., 2014). The sex difference is absent before puberty (Ornitz et al., 1991) and

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also disappears following menopause (Kumari et al., 2008). Variations in circulating levels of estradiol and progesterone have been held responsible for the sex-related differences (Swerdlow et al., 1997), and lower PPI is typically found at times when estradiol and progesterone levels are high, such as during the luteal phase of the menstrual cycle (Kumari, 2011). In addition, women of childbearing ages, as well as healthy pregnant women have lower PPI than postmenopausal women (Bannbers et al., 2010; Kask et al., 2008). However, it remains to be determined if the PPI in pregnant women in fact differs from normally cycling women. To this end, a lower PPI is expected in pregnant women. Furthermore, the relation between affective symptoms during pregnancy and PPI remains uninvestigated (Kohl et al., 2013; Takahashi et al., 2011). To dispose of an objective measure of sensorimotor gating in pregnancy would further our understanding of sensorimotor and cognitive-affective functioning in the presence of supraphysiological hormonal levels which likely trigger the onset of psychiatric symptoms in pregnant women.

Neurochemical regulation of PPI involves among others the catecholaminergic corticolimbic circuitry (Koch, 1999; Swerdlow et al., 1992, 2001; Takahashi et al., 2011), which is impaired in anxiety disorders. Catechol-*O*-methyltransferase (COMT) is a ubiquitous enzyme which inactivates cathecolaminergic neurotransmitters, i.e. dopamine, adrenaline, noradrenaline as well as catechol estrogens and exogenous catechols. The G (Valine (Val)) allele of the functional single nucleotide polymorphism of the *COMT* gene (rs4680), leading to a three- to four-fold higher enzyme activity compared to the methionine (Met) allele (Chen et al., 2004), has been associated with anxiety traits, neural correlates of anxiety, and deficient PPI (Aleman et al., 2008; Goldman et al., 2009; Takahashi et al., 2011). Additionally, a somewhat complex COMT by sex and sex hormones interaction in relation to psychiatric phenotypes has been indicated (Tunbridge and Harrison, 2011). The *COMT* gene hosts estrogen-like response elements (Jiang et al., 2003; Xie et al., 1999), and the startle response has been found to be lower in Val/Val carrier females in the presence of low estradiol levels (Armbruster et al., 2011; Montag et al., 2008a) but higher in pregnant women having higher estradiol level (Comasco et al., 2013). However, no previous attempts exist to investigate the effect of *COMT* Val158Met genotype on PPI in pregnant women.

To test the hypothesis that sensorimotor gating is reduced as an effect of supraphysiological hormonal status, anxiety, and catecholaminergic genotype, the present study assessed the PPI of the startle response in non-pregnant women as well as pregnant women with or without anxiety disorders, and considered the *COMT* Val158Met genotype as a proxy of catecholaminergic function. The present study addressed the following questions: (i) does PPI differs between third-trimester pregnant women and non-pregnant luteal phase women? (ii) do pregnant women with an anxiety disorder differ in regards to PPI from non-anxious pregnant women? and (iii) are *COMT* gene variations associated with differences in PPI in pregnant women?

2. Material and methods

Pregnant women were recruited as a sub-study to the cohort 'biology, affect, stress, imaging, and cognition in pregnancy and the puerperium' (BASIC). BASIC is a longitudinal study investigating 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.

For this sub-study, women with EPDS score ≥13 and a random sample of women with Edinburgh postnatal depression scale (EPDS) (Cox et al., 1987) scores <13 at gestational week 32 were invited to oversample women with antenatal depressive and anxiety symptoms (Rubertsson et al., 2011). Exclusion criteria were serious pregnancy-related conditions such as preeclampsia, intrauterine growth restriction, gestational diabetes or twin pregnancies. Treatment with antidepressant drugs was not an exclusion criterion, but records were kept on any ongoing medication. Totally, 234 pregnant women visited the research laboratory at the Department of Women's and Children's Health, Uppsala University in gestational week 35–39 between January 2010 and May 2013. Presence of ongoing primary anxiety and depressive disorders was established by use of the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). In women who were on treatment with SSRI but where the diagnostic interview failed to indicate the reason for treatment, no attempts were made to ascertain the reason for treatment initiation.

All pregnant women filled out the Montgomery-Åsberg Depression Rating Scale (MADRS-S) (Montgomery and Asberg, 1979) and the Spielberger State-Trait Anxiety Inventory (STAI) (Hodgues and Spielberger, 1969). Among the 234 pregnant women who participated in the study, nine women opted out of the PPI assessment, most commonly due to time restraints; three discontinued during the experiment as it was considered too aversive; two recordings could not be used due to technical problems; and three women were considered as non-responders and were thus excluded from further analyses. Hence, the study population consisted of 217 pregnant women, among whom 51 were suffering from an anxiety disorder. The remaining 166 pregnant women were used as controls, even though some of them were diagnosed with ongoing depressive disorders (none with bipolar disorder) (Table 1). However, as depression has not been shown to influence PPI we considered it a conservative approach to keep these women in the statistical analyses.

Healthy non-pregnant women ($n = 82$) were recruited by advertisement. They had regular menstrual cycles and had not used any hormonal compounds or contraceptives during three months prior to inclusion. Exclusion criteria for healthy non-pregnant subjects included pregnancy or breastfeeding within the last three months, and treatment with psychotropic drugs. The MINI interview confirmed absence of ongoing mood or anxiety disorders, and all women filled out the MADRS-S. Measurements in the non-pregnant women were made during the luteal phase, day −1 to −7 before onset of menstruation, as confirmed by records of next onset of menstrual bleeding and from progesterone levels sampled on the testing day. All women were interviewed about medical and obstetric history, alcohol use, smoking, and medication in the preceding three months.

2.1. Startle response

Each subject sat in a comfortable chair in a quiet room. The eyeblink component of the acoustic startle response was assessed using electromyographic (EMG) measurements of musculus Orbicularis Oculi. Delivery of the acoustic startle stimuli and recording of the eyeblink response were controlled by a commercial startle system (SR-HLAB, San Diego Instruments, San Diego, CA). Acoustic startle stimuli were delivered binaurally by telephonic headphones (TDH-39-P, Maico, Minneapolis, USA). The sound was calibrated with a Quest electronics meter (model 210 Quest Technologies, Oconomov, WI). After the skin was cleaned, two miniature silver/silver chloride electrodes (In Vivo Metric, Healdsburg, CA, USA), with a small amount of electrode gel (Sigma gel, In Vivo Metric, Healdsburg, CA, USA) were positioned below the subject's right eye, over the Orbicularis Oculi muscle. A ground electrode was placed in the centre of the forehead. Electrode impedances was less than 5 kOhm. The EMG signal was filtered (100–1000 Hz), digitized at 1 kHz and analysed by the EMG startle response software,

Table 1
Demographic variables in the pregnant population.

	Pregnant women with any anxiety disorder ($n = 51$)	Pregnant controls($n = 166$)	p
Age, years (mean ± SD)	30.8 ± 5.7	31.6 ± 4.1	0.3
Caucasian ethnicity, *n* (%)	51 (100)	164 (98.8)	1.0
Married/cohabiting, *n* (%)	51 (100)	164 (98.8)	1.0
University education, *n* (%)	31 (60.8)	141 (82.0)	0.001
Employed, *n* (%)	36 (70.6)	143 (86.1)	0.05
Parous, *n* (%)	27 (47.1)	92 (44.6)	0.8
Smokers, *n* (%)	3 (5.9)	5 (3.0)	0.4
Sleep duration night before assessment			0.01
More than 8 h, *n* (%)	10 (19.6)	25 (15.1)	
6 –8 h, n (%)	24 (47.1)	116 (69.9)	
Less than 6 h, *n* (%)	17 (33.3)	25 (15.1)	
BMI, kg/m^2(mean ± SD)	23.5 ± 3.8	22.6 ± 3.5	0.2
STAI-*t* score (mean ± SD)	45.8 ± 11.4	33.8 ± 8.0	0.001
STAI-*s* score (mean ± SD)	38.5 ± 9.4	30.2 ± 6.8	0.001
Comorbid depressive disorder, *n* (%)	21 (41.2)	8 (4.8)	0.001
SSRI treatment	8 (15.7)	12 (7.2)	0.07

which rectified and smoothed the EMG response with a 10 ms time constant.

The acoustic startle reflex test session began with a five-minute acclimation period, with a background 70 dB white noise delivered by the headphones. A series of trials was then administered and the startle responses recorded. Throughout the session, a background 70 dB white noise continued in between the trials. The test session included four blocks. Block 1 consisted of five pulse-alone trials (115 dB 40 ms broad-band white noise), measuring the baseline startle response. Blocks 2 and 3 each consisted of 25 trials, containing 5 pulse-alone and 20 prepulse–pulse trials presented in pseudorandom 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 a measure 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 valid and 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. Less than 7.5% of responses were scored as zero-responses, and more than 80% of these occurred during PPI trials. Patients with negligible baseline startle responses (mean amplitude <10 μV), and more than 50% zero responses were considered as non-responders. An arbitrary unit corresponded to 0.076 mV.

Mean startle magnitude was defined as the total amplitude of all valid trials/total number of trials. Habituation of startle response (HAB) was calculated as the percent reduction in startle amplitude between the first and last block of pulse-alone trials. 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 blocks 2 and 3, and M_{PP} is the magnitude of prepulse–pulse trials.

2.1.1. Biological analyses

Before the test session, blood samples for progesterone serum concentrations were taken in cycling women. Progesterone was analysed on Immulite 1000 (DPC, Los Angeles, CA, USA), and intra assay coefficient of variation was 16% at 2.9 nmol/l and 6.3% at 25.1 nmol/l. Because of previous failure to correlate PPI or startle response with progesterone and estradiol in pregnancy (Kask et al., 2008), these hormones were not analysed in pregnant women.

DNA was extracted from blood using the silica-based Kleargene DNA extraction method. Genotyping analysis of *COMT* Val158Met (rs4680) SNP was performed using the KBioscience Allele-Specific Polymorphism assay (KASP) based on competitive allele-specific PCR and bi-allelic scoring of the SNP. No-template control samples were included to enable the detection of contamination or non-specific amplification. Genotype frequencies were: GG: 16.0%, GA: 50.6%, and AA: 33.3%; and the allele frequency of the G allele was 0.41. Genotypes were in Hardy–Weinberg equilibrium ($\chi^2 = 0.3$; $p = 0.58$).

2.1.2. Statistical analyses

Startle magnitude and PPI were compared between groups by use of two-way ANCOVA with repeated measures. As there was no indication of PPI habituation across blocks 2 and 3, data were collapsed across these blocks for PPI analyses.

Within subjects factors in the ANCOVA, analyses were prepulse intensity (2, 4, 8 and 16 dB above background noise), whereas group (non-pregnant vs. pregnant or non-anxious pregnant vs. anxious pregnant) was used as the between-groups factor. In the comparisons between non-pregnant and pregnant women age, tobacco use and baseline startle magnitude were entered as covariates. For remaining analyses in pregnant women, tobacco use, sleep duration, and baseline startle magnitude were always adjusted for in the ANCOVA. Where appropriate, Tukey's HSD was used as post hoc analysis. Statistical analyses were performed with IBM SPSS Statistics, version 20.

3. Results

3.1. Differences between non-pregnant and healthy pregnant women

Non-pregnant women were slightly younger than the healthy pregnant women, but did not differ in BMI or depression rating scores (Table S1). Not surprisingly, smoking was more common in non-pregnant women than in the pregnant ones. Also, pregnant women had a greater baseline startle magnitude than non-pregnant controls, but did not differ in habituation rate across the experimental session, Fig. 1. Thus, subsequent statistical analyses on PPI included baseline startle magnitude, age, and tobacco use, as covariates.

The ANCOVA revealed a significant main effect of prepulse intensity $F(1,236) = 5.34$; $p < 0.05$, and a significant prepulse intensity by group interaction $F(1,236) = 8.75$; $p < 0.01$, Fig. 1. As seen in Fig. 1, this interaction was manifested as lower PPI with 86 dB prepulses in pregnant women, $F(1,236) = 8.68$; $p < 0.01$, whereas

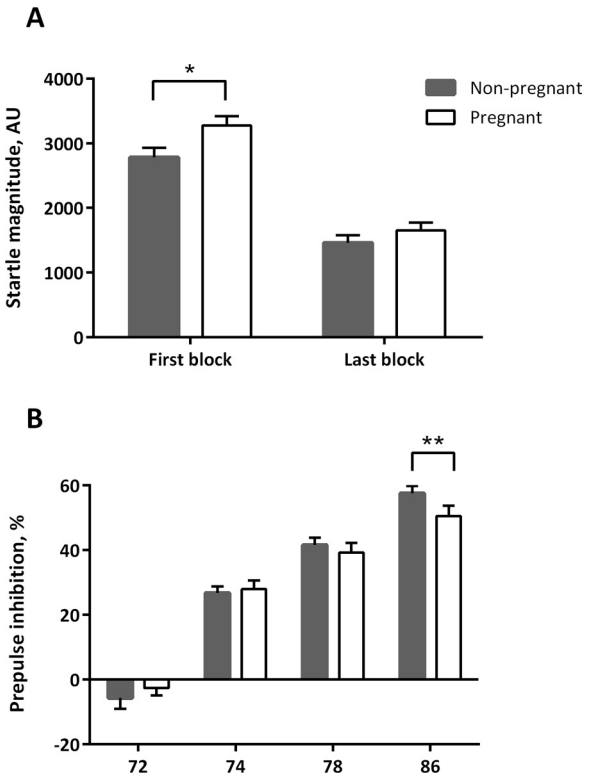

Fig. 1. Mean ± SEM startle magnitude during the first and last block of the test sessions (A) and percent prepulse inhibition by trial type (B) in 82 healthy non-pregnant luteal phase women and 158 healthy pregnant women. Baseline startle magnitude, i.e. during the first block, was significantly greater in pregnant women, $p < 0.05$. (B) Pregnant women exhibited lower levels of PPI with 86 dB prepulses compared to non-pregnant luteal phase women, $p < 0.01$. $^{*}p < 0.05$, $^{**}p < 0.01$. AU = arbitrary units.

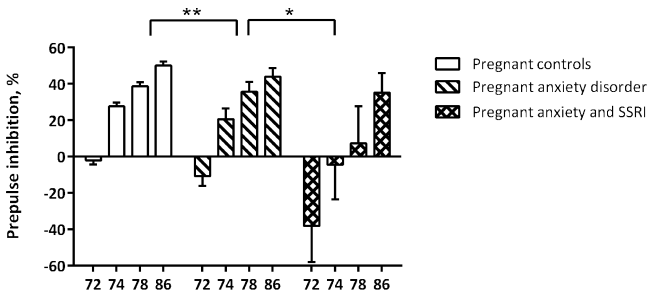

Fig. 2. Mean ± SEM percent prepulse inhibition by trial type in 166 non-anxious pregnant women and 51 pregnant women with anxiety disorder. Following adjustment for tobacco use and baseline startle response, pregnant women with anxiety disorders had overall lower PPI in comparison with the non-anxious pregnant control group, $p < 0.01$. Women with anxiety disorder who also continued SSRI treatment during pregnancy had ever further diminished PPI; anxiety × SSRI treatment interaction $F(1,211) = 7.51$; $p < 0.01$. $^{*}p < 0.05$, $^{**}p < 0.01$.

no differences at other prepulse intensities were found between groups.

3.2. Differences between non-anxious pregnant women and pregnant women with anxiety disorders

Distribution of anxiety disorders is displayed in Table S2. Demographic data of the pregnant women with and without anxiety disorders are displayed in Table 1. The pregnant women who were diagnosed with any anxiety disorder were more often unemployed, and had less often obtained a university degree. The grand majority had a pre-pregnancy history of mental health problems ($n = 40$, 78.4%), and co-morbid depression was common. However, while 15.7% of women with anxiety disorders were on treatment with SSRIs at the time of assessment, yet another 7.2% of the pregnant controls were also using SSRI. None of the latter no longer fulfilled diagnostic criteria for any anxiety or depressive disorder, but as it cannot be ruled out that anxiety disorder had been the reason for initiation of treatment, SSRI treatment was included as a separate variable in the ANCOVA. The baseline startle magnitude did not differ between the two groups of pregnant women (anxiety group 2991 ± 1754 AU vs. non-anxious 3239 ± 1856 AU), and similarly, no difference in habituation across the experiment was found (anxiety group 57.2 ± 24.4% vs. non-anxious 51.7 ± 27.6%).

After controlling for tobacco use, sleep duration, and baseline startle magnitude, pregnant women with anxiety disorders were shown to have an overall lower PPI in comparison with the non-anxious pregnant women, main effect of group: $F(1,210) = 7.98$; $p < 0.01$, Fig. 2. SSRI treatment was also associated with lower PPI in pregnant women, main effect of treatment $F(1,210) = 5.51$; $p < 0.05$, and a significant anxiety × SSRI treatment interaction was noted: $F(1,210) = 7.08$; $p < 0.01$, where women who suffered from anxiety disorders and also used SSRI ($n = 8$) were found to have a significantly lower PPI than both non-anxious pregnant controls and those who were diagnosed with anxiety disorders, Fig. 2. The inclusion of baseline startle magnitude in the model only marginally influenced the parameter estimates. Without adjustment for baseline startle magnitude, the main effect of group, the main effect of treatment and the group by treatment interaction were $F(1,211) = 8.42$; $p < 0.01$, $F(1,211) = 4.02$; $p < 0.05$, and $F(1,211) = 6.72$; $p = 0.01$, respectively.

Comorbid depressive disorder did not influence PPI, $F(1,210) = 0.89$, and similarly, depressive disorder on its own ($n = 29$) had also no effect on PPI, $F(1,210) = 0.071$. Because of low numbers and the relatively high frequency of comorbid anxiety disorders, no attempt was made to distinguish which anxiety disorder had the greatest influence on PPI during pregnancy. Finally, the baseline startle response or PPI were not influenced by gestational length, measured as number of weeks left to actual delivery, $F(4,211) = 1.09$ and $F(4,210) = 0.98$, respectively, data not shown.

3.3. Differences according to catecholaminergic genotype in non-anxious pregnant women

We also wanted to establish if a candidate genetic variant would influence PPI in the high-hormone setting of pregnancy. Blood samples were available for 156 non-anxious pregnant women and genotyping for the functional *COMT* Val158Metpolymorphism was completed in all. Two were, however, excluded because of non-Caucasian background. No differences between genotype groups were present regarding neither demographic variables nor baseline startle or habituation (Table S3). The ANCOVA model, adjusted for baseline startle and tobacco use, revealed a significant prepulse intensity by genotype interaction $F(1,150) = 3.96$; $p < 0.05$. Post hoc tests revealed that the *COMT* Val158Met genotype dose dependent interaction was mainly driven by significantly higher PPI at 72 and 74 dB prepulses in the Met/Met carriers compared to the Val/Val carriers, and Val/Met carriers being intermediate, Fig. 3A.

COMT Val158Met genotype frequencies in women with anxiety disorders ($n = 46$) were A/A 8 (17.4%), G/A 26 (56.5%), and G/G 12 (26.1%). The Val158Met A/A (Met/Met) genotype was significantly less common in women with anxiety disorders, $p < 0.05$. While numbers were too small to yield any significant differences, a similar pattern of *COMT* Val158Met genotype by PPI interaction as in healthy controls was found, (main effect of genotype $F(1,42) = 1.14$, genotype by PPI interaction $F(1,42) = 0.47$), Fig. 3B.

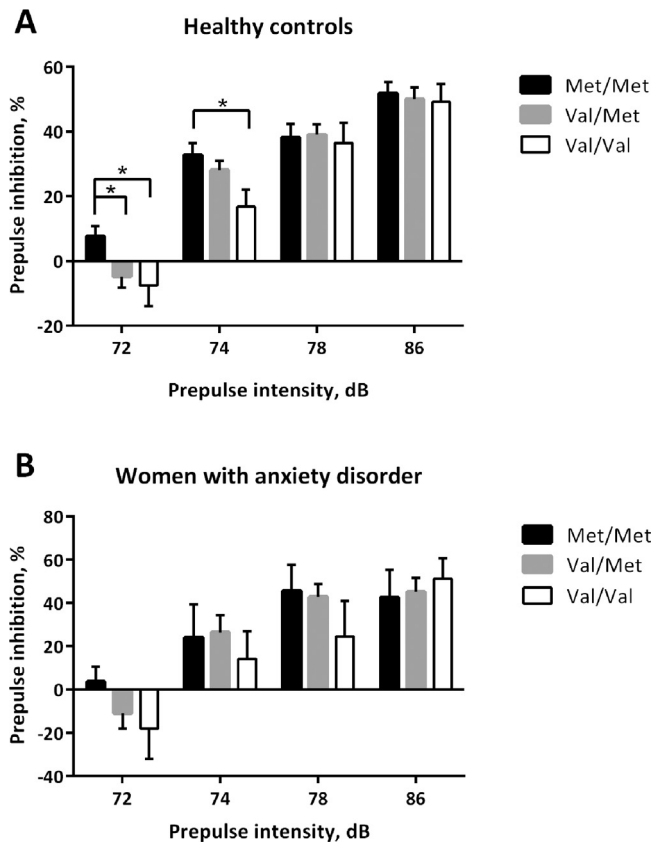

Fig. 3. Mean ± SEM percent prepulse inhibition by trial type in 154 healthy pregnant women (A) and 46 pregnant women with anxiety disorders (B) genotyped for *COMT*Val158Met. Significant prepulse intensity by genotype interactions were found for the COMT Val158Met ($F(1,152) = 3.73$; $p < 0.05$) in healthy controls. No significant genotype interaction emerged in the pregnant women with anxiety disorders, but a similar pattern was noted. Post hoc Tukey HSD results are displayed in the figure, $^{*}p < 0.05$.

4. Discussion

In this study, reduced sensorimotor gating, as measured by prepulse inhibition, was found in pregnant women compared to non-pregnant women. Reduced PPI was also observed in association with anxiety, SSRI treatment, and catecholaminergic genotype, providing a pattern of association which is consistent with previous findings in humans and rodents.

4.1. Lower PPI in pregnant women compared to healthy non-pregnant controls

Pregnancy is characterized by a constellation of hormonal changes, including a 50-fold increase in estradiol levels at term (Skalkidou et al., 2012). Among the ovarian steroid influences on PPI, estradiol has gained most interest, due to higher PPI in the follicular, relative to the luteal, phase (Kumari, 2011). In addition, estrogen induces a dose-dependent increase in PPI in ovariectomized rats (Charitidi et al., 2012; Van den Buuse and Eikelis, 2001), and prevents 5-HT_{1A}-, dopamine-, and NMDA receptor-induced disruptions of PPI (Gogos et al., 2010, 2012, 2006; Gogos and Van den Buuse, 2004; Thwaites et al., 2014). While a role for progesterone in PPI has been suggested (Kumari et al., 2010), this effect is presumably not mediated by GABA-active progesterone metabolites (Kask et al., 2009).

Moreover, hypothalamus–pituitary–adrenal axis hormones increase throughout pregnancy, and of greatest relevance for the startle response and PPI is presumably the 10–100-fold increase in placental corticotropin releasing hormone (CRH) (Skalkidou et al., 2012). It is well known that CRH mediates acute startle response changes during stress, but also chronic CRH activation may influence startle magnitude (Flandreau et al., 2014). It is thus plausible to speculate on a supraphysiological hormone-driven reduction of PPI in pregnant women, with possible relevance to the occurrence of affective symptoms in concomitance with the peripartum.

4.2. Lower PPI in pregnant women with anxiety compared to healthy pregnant women and in pregnant women with anxiety using SSRI compared to un-medicated pregnant women with anxiety

PPI of the startle response is a first-choice endophenotypic marker of schizophrenia, a sex dimorphic mental disorder, and a putative one for PTSD. However, PPI has been poorly investigated in relation to anxiety disorders (Braff et al., 2001; Kohl et al., 2013). Considering the high test–retest stability of PPI (Cadenhead et al., 1999; Schwarzkopf et al., 1993), and that in the current study the diagnosis of any anxiety disorders was antecedent to pregnancy for the majority of women, a reduced sensorimotor gating in the presence of anxiety disorders, possibly exaggerated by the supraphysiological hormonal levels, further implicates the relevance of lower PPI as an objective and biological correlate of anxiety proneness.

In common with other neuropsychiatric disorders, as well as with the common subjective complaint of distressed and troubled cognitive functioning reported by pregnant women (Henry and Sherwin, 2012), symptoms of anxiety disorders comprise inattention, difficulties with concentrating, and altered cognitive performance, which could plausibly be associated with reduced gating of possibly irrelevant stimuli (Braff et al., 2001; Robinson et al., 2013). Ideally, a control group of non-pregnant women with a diagnosis of anxiety disorder could have assisted in unravelling the potential effect of the supraphysiological state from the disorder on PPI. Furthermore, cognitive bias associated with anxiety traits of personality should be investigated by means of PPI assessment in healthy subjects.

Many factors have been suggested to influence PPI, such as tobacco and sleep deprivation, both of which were considered as confounding factors in the present study. Beside psychiatric status, the effect of antidepressant medication was tested and shown to influence the PPI in a virtually similar pattern, but even more marked in those who still fulfilled criteria for anxiety disorders despite ongoing treatment. To disentangle the effect of SSRI on PPI, longitudinal prospective observations would be needed. Though a normalized PPI as a consequence of treatment would be expected, a more marked reduction of PPI in women with anxiety disorders using SSRI might rather indicate greater severity of symptoms or suboptimal dosages. Yet no effect of SSRI on PPI has been demonstrated (e.g. (Jensen et al., 2007; Phillips et al., 2000)), thus, interpretation of the present finding should be cautious and call for further studies on chronic serotonergic modulation of PPI.

4.3. Lower PPI in healthy pregnant women carrying the COMT Val158Met Val/Val genotype compared to Met carriers

A candidate genetic proxy of the corticolimbic monoaminergic neuroanatomical and neurochemical substrate of PPI (Swerdlow et al., 1992) is the functional polymorphism *COMT* Val158Met (Koch, 1999). The present finding suggested a linear relationship between *COMT* Val158Met and PPI, providing corroborating

evidence of an impact of *COMT* on measures of anxiety (Aleman et al., 2008; Goldman et al., 2009; Takahashi et al., 2011). The Val/Val genotype has been associated with lower PPI in healthy men (Quednow et al., 2009; Roussos et al., 2008) but not in women (Montag et al., 2008b; Quednow et al., 2009). The most likely reason for this is menstrual cycle-related variability in PPI of healthy women (Kumari, 2011). For instance, we previously provided evidence of the highest startle response in Val/Val carriers at term pregnancy, especially in pregnant women having higher estradiol level (Comasco et al., 2013). The present results add to our understanding of the complex interactions between reproductive hormones and neurotransmitters underlying genetic influences on sensorimotor gating and anxiety in women in the presence of physiologically elevated levels of estradiol and other hormones. In fact, a tight interrelationship between COMT and estrogens has been supported not only regarding transcriptional regulation, and incontestably COMT by sex differences have been shown in psychiatry (Tunbridge and Harrison, 2011). Recently, humanized COMT Val/Val mice showed a higher PPI if they were females (Risbrough et al., 2014), however, oestrus cycle phase was not considered, and the complexity of comparing effects of oestrogenic state and *COMT* modulation of PPI across species is high.

COMT is broadly distributed in the brain, and pharmacological challenges suggest the involvement of dopaminergic transmission in *COMT* genotype-dependent changes in PPI throughout the cortico–striato–pallido–pontine circuit (Braff et al., 2001). The temporal window for the prepulse stimulus to inhibit the startle response peaks at 120 ms, which is a lead interval involving attentional, conscious, and voluntary processes (Braff et al., 2001; Risbrough et al., 2014; Swerdlow et al., 1992, 2001), and presumably more prefrontal mechanisms, than at shorter lead intervals. In the present study, a 100 ms prepulse-to-pulse interval was used, providing further support for an involvement of COMT which is the main actor in dopamine clearance in the prefrontal cortex. Finally, pregnant women with anxiety disorders displayed a more marked but non-significant effect of *COMT* genotype on PPI, presumably indicating a further reduced sensorimotor gating which is likely to be a feature of anxiety, and calling for independent replication in larger samples.

5. Conclusions

Pregnancy is characterized by a supraphysiological hormonal status, subjective cognitive complaints, and high anxiety proneness, which can lead to peripartum affective symptoms with dramatic consequences not only for the woman but also for the child. Prepulse inhibition of the startle, a neurophysiological measure of sensorimotor gating, has been poorly investigated in relation to anxiety and in pregnant women.

In the present study, pregnancy, anxiety disorders, and the *COMT* Val/Val genotype were associated with lower prepulse inhibition of the startle response in women. These findings contribute to advancing the neurophysiological and genetic dissection of women's mental health, and call for further studies to extricate multifactorial influences on PPI in healthy as well as psychiatric patients.

Conflict of interests

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

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2015.06.019

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