Mood and the pill

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Summary

Chapter 1 Introduction

Background

During their fertile years, women are twice as likely to develop a clinical depression as men. Some women may experience mood shifts towards depression during usage of contraceptives containing synthetic female hormones, which may even lead to the diagnosis of a clinical depression. Especially young women seem to be prone to these depressogenic effects of OC (Skovlund et al., 2017). Since hormonal contraceptives still are one of the safest ways for birth control, further research after specific determinants underlying this vulnerability to the negative mood effects of OC is needed.

Rationale

In this PhD project we investigated whether OC use and menstrual cycle phase influence emotional information processes associated with depression in healthy pre-menopausal women. We aimed at detecting subtle biases which might not be noticed in daily life. In addition, we explored whether any effects of the female hormonal status would be influenced by genetic variation in one particular component of cortisol feedback regulation in the stress response system – the mineralocorticoid receptor (MR) (De Kloet et al., 2005; Boron & Boulpaep, 2012).[32] The focus is on the MR because previous research showed that genetic variation in this receptor predicted stress-coping and resilience (Klok et al. 2011; Vinkers et al 2015). In pre-menopausal women carriers of MR haplotype 2 were less vulnerable to mood disorders following of childhood trauma than carriers MR haplotype 1/3, suggesting an interaction between the female hormonal status and genetic variation in the MR (Klok et al., 2011; Vinkers et al., 2015). In the next sections the content of Chapters 2 – 7 is summarized and followed by the general conclusion.

Chapter 2 Oral contraceptives may alter the detection of emotions in facial expressions

Background

This PhD project started with a first-of-its-kind study in which we investigated the potential antidepressant effects of the potent synthetic mineralocorticoid fludrocortisone (FC) in a neuropsychological model of drug action. In this model (emotional) information processing indices serve as a proxy for a potential therapeutic response. The model has been validated using a number of registered antidepressants in various designs, ranging from the effect of a single dose

[32] See for specificity of the MR Chapter 1, figure 4.

in healthy volunteers to repeated administration in depressed or remitted depressed patients. The findings depend on antidepressant drug, dosage and target population, but have in common that subtle antidepressant effects have subtle effects on emotional information processing are noted which cannot easily be detected by self-report. It remains to be demonstrated that the (size of the) effects are related to subsequent clinical response to antidepressants, but the immediate effects of single doses in healthy volunteers have been repeatedly demonstrated and may be a fast way to assess the antidepressant potential of new substances (see a.o. Harmer et al., 2009; Warren et al., 2019). 11

We used FC in this model because it is a potent mineralocorticoid agonist with some glucocorticoid activity. Hence, FC can also suppress HPA axis activity by synergy of its central MR- and pituitary GR-mediated actions, which may be of pharmacological interest in the treatment of disorders like depression (Lembke et al., 2013; Buckley et al., 2007). For instance, FC accelerated the antidepressant effects of the SSRI escitalopram (Otte et al., 2010), while spironolactone, a MR antagonist, decreased the efficacy of the antidepressant amitriptyline in depressed patients (Holsboer et al., 1999). We considered but decided not to exclude participants who used OC and registered OC use instead. The reason is that we expected a relatively high dose of FC to override possible confounding effects of oral contraceptives.

Procedure

We studied 40 healthy female volunteers in a randomized, double-blind, parallel-group, placebo-controlled design. Healthy pre-menopausal volunteers were included after physical examination and being screened for psychiatric present and past. In order to ensure relatively stable levels on cortisol, two hours after a standardized lunch 0,5 mg FC or placebo was administered. Subsequently participants spent two hours in sedentary activities between the intervention and assessment of the facial expression recognition test (FERT) and the emotional categorization and memory task. Participants and researchers were blind for their condition and MR-haplotypes.

Results

Contrary to expectations, we found no effect of FC administration on the accuracy in the FERT and the emotional categorization and memory task. Except for happiness trials, FC administration was associated with decreased reaction times in the FERT. Unexpectedly, users of OC detected significantly fewer facial expressions of sadness, anger and disgust than naturally cycling (NC) women in the FERT. This was true for all trial participants as well as those individuals who were randomized to the placebo condition.

Exploratory analyses in the NC group (n = 14) revealed that the administration of one dose of FC (0.5 mg) was associated with better and quicker recognition of facial expressions

of fear and happiness in carriers of MR-haplotype 1/3. They also remembered more positive characteristics after FC administration. This effect was not observed in MR-haplotype 2 carriers (homo- and heterozygotes).

Conclusion

Clearly, FC did not override the OC effects, thus confounding effects of OC may underlie the lack of effect of FC administration in general. Exploratory analyses in the NC group revealed that only in MR-haplotype 1/3 carriers a single dose of FC was associated with improved emotional information processing. The effect of OC on emotion recognition is a chance finding and if replicated, could either be an effect of OC use or a pre-existing difference between OC-users and NC women. Future studies on the effect of neuropsychiatric interventions should control for the effects of oral contraceptives on emotional and cognitive outcomes.

Chapter 3 Mineralocorticoid receptor haplotype, oral contraceptives and emotional information processing

Background

In experimental research OC-users failed to report positive affect after positive mood induction (Jarva & Oinonen, 2007). Depressogenic effects remain one of the main reasons for discontinuation of OC (Oinonen & Mazmanian, 2002). The goal of the current study was to further investigate the effects of OC use on information processing (Hamstra et al., 2014), considering potential moderating effects of MR- haplotypes. Firstly, OC-users were compared with NC women on indices of emotional information processing. Secondly, we hypothesized that performance on these tasks would be moderated by MR-haplotype. Specifically, we hypothesized that the effects of OC on emotional information processes would be more pronounced in carriers of MR haplotype 1/3 than in MR haplotype 2.

Procedure

This exploratory study had a cross-sectional, parallel-group design. Healthy pre-menopausal volunteers completed a test battery in a psychology laboratory. NC women (n = 41; mean age = 20.2) were tested between day 6 and 26 of their menstrual cycle. OC users (n = 44; mean age = 20.4) were tested outside their pill-free week. OC brand name and chemical compound, duration of OC use and in case of NC women first day of last menses were registered. Participants were genotyped at assessment.

Results

In line with the previous study, OC-users recognized fewer facial expressions of disgust, happiness, sadness and anger (only anger became significant). Further, OC-users made fewer

risky decisions in a gambling paradigm. A significant interaction effect between OC (yes/no) and MR-haplotype revealed that OC-users carrying MR-haplotype 1/3 recognized more sad and fearful faces and remembered more negative characteristics. OC-use did not affect MR-haplotype 2 carriers (homo- and heterozygotes).

Conclusion

Although the effects became less pronounced, we replicated that OC-users recognize fewer expressions of anger, disgust and sadness. Decreased sensitivity for facial expressions together with risk-avoidant behavior may reflect a blunting effect of OC on affect. Furthermore, only OC-users carrying MR-haplotype 1/3 displayed a depressogenic bias on emotional information processing. This study may shed light on why some, but not all women experience negative effects of OC on mood.

Chapter 4 Mineralocorticoid receptor haplotype moderates the effects of oral contraceptives and menstrual cycle on emotional information processing

Background

Emotional information processing is influenced during the menstrual cycle phase. The effects of OC may be due to the suppression of cyclical changes in ovarian hormones (Jones, 2012). OC decrease the HPA axis response to stress and salivary free cortisol responses to stress. The MR mediates the effect of cortisol on initial stress reactions (De Kloet et al., 2005). These rapid effects are especially mediated by the MR sited in limbic structures, regions in which early life stress, chronic stress and depression were found to downregulate MR-expression. In this exploratory study we investigated the influence of OC and menstrual cycle phase on emotional information processing in MR-genotyped healthy volunteers. We assessed tasks which have shown earlier to be sensitive to the influence of OC (chapter 2 and 3) and new tasks in order to cover more stages of emotional information processing.

Procedure

This study had a cross-sectional, parallel-group design. Tasks were assessed in a fixed order and the duration per task was 5 – 15 minutes. NC women with a regular cycle (25 – 35 days) were tested in the early follicular (day 2 – 5; n = 21) or mid luteal (day 18 – 25; n = 23) phase of their menstrual cycle. Only women using second generation OC (Ethinyl estradiol .03 mg; Levonorgestrel .15 mg) for more than three months were included and were tested outside their pill-free week (n = 49). Participants were genotyped at assessment.

Results

The female hormonal status affected the recognition of facial expressions of emotion in general, an effect that was driven by differences in the MR-haplotype 1/3 group. Only in MR-haplotype 1/3 carriers OC-users recognized significantly fewer facial expressions than mid luteal women. No effects on specific emotions were observed, however.

OC-users carrying MR-haplotype 1/3 reported more depressive cognitions following sad mood, than other groups. Regardless their hormonal status, MR-haplotype 1/3 carriers had higher scores on implicit anger and sadness than MR-haplotype 2 carriers (homo- and heterozygotes).

In general, women in the ML phase gambled more than women in the early follicular phase. Mid luteal women carrying MR-haplotype 2 took more risky-decisions in general, while mid luteal women carrying MR-haplotype 1/3 gambled more only in conditions with a low risk to lose. Performance on the reading the mind in the eye task was affected neither by hormonal status nor by MR-haplotype.

Conclusion

We observed higher negative implicit affect and more depressive cognitions following sad mood in OC-users carrying MR-haplotype 1/3, which may reflect subliminal depressive affect and is in line with our previous study (chapter 2). Furthermore, we also observed a possibly increased sensitivity to the female hormonal status in MR-haplotype 1/3 carriers in the emotion recognition paradigm. In line with earlier studies we observed that women in the mid luteal phase gambled more than in the early follicular phase (Bayer et al., 2013). This effect became pronounced in mid luteal MR-haplotype 2 carriers in all trials, while mid luteal MR 1/3 carriers only gambled more in low-risk conditions. This risky-decision making behavior of MR-haplotype 2 carriers may reflect an optimistic expectation about the outcomes of one's decisions. Signs of dispositional optimism in MR-haplotype 2-carriers have been observed earlier in a naturalistic cohort study (Klok et al., 2011).

Chapter 5 Mineralocorticoid receptor haplotype, estradiol, progesterone and emotional information processing

Background

Female hormones modulate the impact of stress on mood. The observed effects of OC and female hormones on emotional information processing may be mediated by estrogen and progesterone receptors, which are abundantly expressed in limbic brain structures (Handa and Weiser, 2014). In these limbic areas the sex steroids may modulate the function of the MR. Progesterone (P4) binds to the MR with nearly the same affinity as aldosterone and cortisol, and acts as a competitive antagonist (Quinkler et al., 2002; Carey et al., 1995). Estradiol (E2) suppresses the

synthesis and transactivation of the MR in brain and vascular endothelial cells (Barrett Mueller et al., 2014; Carey et al., 1995). Consequently, the MR is of relevance in candidate gene studies investigating the influence of female hormones on emotional information processes associated with depression (De Kloet et al., 2008).

The aim of this study was to investigate the effect of menstrual cycle phases and OC use on emotional information processing in healthy women and the possible moderation of this effect by the MR-genotype. Contrary to most previous studies, we used a longitudinal, within-person design. We measured E2 and P4 concentrations in saliva. We hypothesized that variations in female sex steroid levels affect emotional information processing more strongly in MR-haplotype 1/3 carriers than in MR-haplotype 2 carriers.

Procedure

This study had a counterbalanced within-subject design. OC-users (Ethinylestradiol .03 mg; Levonorgestrel .15 mg; n = 57) were tested in a counterbalanced entry-order: once in the second week of active OC-use (day 8 – 14) and once during inactive OC-use (day 4 – 7 of the pill-free week). Naturally cycling (NC) participants (n = 39) were tested at two counterbalanced time-points that are characterized by relatively stable hormone levels of E2 and P4. Once in the early follicular phase (day 2–6), when both hormones are low, and once in the middle of the luteal phase (3–10 days before the onset of the new cycle) when the concentration of P4 is at its maximum and E2 reaches a second peak (Bayer et al., 2014; Jones, 2012). At intake the average cycle duration of the NC participants was registered. After confirmation of the start of the new cycle, test data were scheduled and adjusted to the individual cycle-duration, reasoning that the luteal phase always lasts two weeks (Jones, 2012). Participation ended after confirmation of the start of the new cycle. This cycle onset information was used to confirm whether participants had been tested on the right moment. Participants were MR-genotyped at assessment (amount of MR-haplotype 2 alleles: 0, 1 or 2).

Results

We replicated partially a blunting effect of OC-use on the recognition of facial expressions of emotions, as OC-users recognized fewer but quicker expressions of happiness and sadness. OC-users had also fewer attentional blinks, thus performed better at the attentional blink task (all $p < .05$). These effects were no longer significant after correction for multiple comparisons ($p < .005$), however. In the second session – thus after habituation – lower levels on E2 and P4 were significantly ($p < .001$) associated with fewer attentional blinks. Finally, in contrast with our previous study (chapter 4), OC-users recognized significantly more positive characteristics in the reading the mind in the eye task ($p = .001$). Furthermore, in the first session of our study P4 was associated with an increase in implicit anxiety ($sr = 0.25$; $p = 0.015$).

We observed the following main effects on the MR-genotype, regardless their hormonal status. MR-haplotype 2 homozygotes had significantly higher scores on implicit happiness than MR-haplotype 1/3 carriers ($p < .001$). We also observed a linear relationship: the more MR-haplotype 2 alleles, the higher the scores on implicit happiness. They also reacted slower to correctly recognized happy faces ($p = .001$). Furthermore, MR-haplotype 2 homozygotes gambled more than MR-haplotype 1/3 carriers in trials with low expected losses ($p < .01$). Although this effect did not remain after corrections for multiple comparisons, the pattern was in line with our previous study (chapter 4). We also observed a linear relationship: the more MR-haplotype 2 alleles, the more risky decisions.

Finally, exploratory analyses revealed that the MR-haplotype may moderate the impact of E2 and P4 on emotional information processing. In the first session – thus in a situation of novelty – P4 was associated with an increase in implicit anxiety ($sr = 0.25$; $p = 0.015$). A significant interaction effect revealed that only in MR-haplotype 2 homozygotes higher levels of P4 were associated with reduced implicit anxiety ($sr = -.61$; $p = .012$). In the second session – thus after habituation – higher levels on E2 were associated with better happiness recognition, but only in MR-haplotype 1/3 carriers ($sr = .39$; $p = .008$).

Conclusion

We replicated that OC-users recognize fewer facial expressions of happiness and sadness. In addition, performance on the attentional blink task may be influenced by OC-use, an effect which may be explained by the suppressive effects of OC on natural estrogen and progesterone levels and has been reported earlier (Hollander et al., 2005).

Higher implicit happiness scores, slower reaction times in happiness trials and increased risky-decision making in MR-haplotype 2 homozygotes are in line with previous reports (Bogdan et al., 2010; Klok et al. 2011; chapter 3 and 4) and may be summated by the term 'dispositional optimism'. Interestingly, this study revealed a linear relationship: the more MR-haplotype 2 alleles, the more dispositional optimism was displayed. The fact that MR-haplotype 2 carriers gambled more, but only in low-risk trials may reflect a more rational attitude, too.

In this study we found indications that the MR-haplotype may moderate the influence of E2 and P4 on emotional information processing. Regardless the MR-haplotype P4 was weakly associated with an increase in implicit anxiety, but in MR-haplotype 2 homozygotes P4 was strongly associated with reduced implicit anxiety in a novel situation. These observations may reflect the controversial role of P4 in anxiety.

After habituation to the research paradigm, only in MR-haplotype 1/3 carriers E2 was positively correlated with the recognition of happy expressions. Better happiness recognition may reflect a subtle shift towards a more positive information processing bias, which has also been

observed in healthy volunteers after single doses of an antidepressant (Harmer et al., 2003, 2009). We previously found effects of OC-use on information processing in the opposite direction in MR- haplotype 1/3 carriers (chapter 3 and 4). Although we did not measure hormone levels in these studies, the observed effects may have been caused by OC's suppressing E2 or by an intrinsic effect of the synthetic estrogens.

Against expectation, important practice effects were observed and the pattern of correlations differed between the sessions. Future studies in NC women should take care to verify cycle-phase by confirmation of the next cycle onset. We had to exclude 15 cases because their cur- rent cycle was shorter or longer than expected (mean age = 20.7) and menstrual irregularities are more frequently observed in young women (Boron and Boulpaep, 2012).

Chapter 6 Oral contraceptives positively affect mood in healthy PMS-free women: a longitudinal study

Background

The term reproductive depression refers to a heightened sensitivity to hormonal shifts, which may be characterized by increased irritability and interpersonal sensitivity, depressed mood and cognitive dysfunction (Deecher et al., 2008; Harald & Gordon, 2012).

The mood effects of OC and the menstrual cycle phase may be induced by an interaction of (synthetic) hormones on the hypothalamic-pituitary-adrenal axis (Jones, 2012; Handa and Weiser, 2014). Endogenous estrogen may suppress the expression of the MR in the limbic brain (Carey et al., 1995). Progesterone binds to the MR with nearly the same affinity as cortisol and aldosterone, but acts as an antagonist (Carey et al., 1995). The MR-genotype moderates the effect of the female hormonal status on the appraisal and processing of emotionally relevant information (chapter 3, 4 and 5). Following this we hypothesized that hormonal changes during the cycle may trigger mood changes in a MR-genotype dependent manner. In this study we tested the hypothesis that NC women had higher scores on measures associated with reproductive depression than OC-users. We further hypothesized that NC women with MR-haplotype 1/3 had higher scores on these measures than MR-haplotype 2 carriers. We carefully masked our research objective to prevent artefacts caused by expectations concerning menstrual cycle symptoms (Aubuchon & Calhoun, 1985).

Procedure

This study had a prospective longitudinal design. All data were collected using an online survey tool (Qualtrics, Provo, UT) in which we assessed in consecutive order chronotype and quality of sleep (outcomes not reported), positive and negative affect (Watson et al., 1998), interpersonal

sensitivity (Boyce & Parker, 1989), affect lability (Oliver & Simons, 2004) and cognitive reactivity following sad mood (Van der Does et al, 2002). Naturally cycling (NC) participants (n = 35) filled out questionnaires on four time-points of two consecutive menstrual cycles. Care was taken to adjust the time-points to the individual cycle-duration. OC users using OC (.03 mg Ethinylestradiol; .15 mg Levonorgestrel; N = 57) for at least three months, were assessed at four equivalent time-points during two consecutive months. Their actual participation started with a new pill strip. We controlled for cycle phase and pregnancy by levels of E2, P4 and estriol in saliva at two sessions in our lab.

We masked our research objective by informing participants that we investigated the impact of chronotype and sleep on mood during two months in healthy MR-genotyped women. After completion of the eighth assessment, we asked participants to guess the underlying research question (open-ended question), to check whether the masking was successful. Subsequently they completed a questionnaire screening for premenstrual syndrome, after which they were debriefed.

Results

Masking of the research question was successful. Both OC-users and NC women reported shifts in anger in the first cycle week ($p < .001$), thus at menses or in the pill-free week. OC-users reported fewer mood-shifts between depression and elation than NC women in the ML phase ($p = .002$), when natural hormones (E2 and P4) peak. Compared to NC women, OC-users also reported also fewer ruminating thoughts in all phases ($p = .001$). These effects remained after we controlled for committed relationship status.

Conclusion

Although we observed moderating effects of the MR- genotype on the influence of the hormonal status on mood, these effects were not significant anymore after correction for multiple comparisons. Not only rumination, but also interpersonal sensitivity, affect lability and depressive cognitions associated with anger and risk avoidance tended to be reduced in OC-users. Hence, OC-users scored overall more favorably on measures associated with reproductive depression. Importantly, OC-users did not differ significantly from NC women in personal characteristics (e.g. neuroticism), mental and physical health and positive and negative affect at the time of assessment. Hence, OC-users showed decreased affect variability which is in line with previous reports on affect-stabilizing effects of OC.

Chapter 7 Mineralocorticoid receptor haplotype, not oral contraceptives use, influences resting state EEG theta/ beta ratio in healthy women

Background

The MR-haplotype may moderate the influence of the menstrual cycle phase, OC-use, estrogen and progesterone on emotional information processing associated with depression as assessed with both behavioral and self-reports (chapter, 3, 4, 5 and 6). Psychophysical studies however, show effects related to cortical arousal and may reveal subtle changes in information processing that remain unnoticed in behavioral studies.

Estrogen and progesterone enhance cortical-subcortical communication, which may contribute to improved emotion regulation (Peper et al., 2011). Resting-state electro-encephalography (rsEEG) theta/beta ratio (TBR) is a biomarker of cognitive control over the affective system. Theta power may be associated with prefrontal cortex (PFC) mediated goal-directed behavior and beta power with arousal. The aim of this study was to examine rsEEG TBR in healthy OC-users and NC women. We also investigated whether any effect of OC-use and levels on E2 and P4 was moderated by MR-haplotype.

Procedure

This study had the same counter-balanced within subject design as applied as in chapter 5.

Results

OC-users (N = 44) and NC women (N = 44) did not differ in rsEEG TBR. TBR was different between MR-haplotypes: MR-haplotype 2 homozygotes had lower TBR scores than MR-haplotype 2 heterozygotes, indicating more cognitive control.

Conclusion

Variation in the MR gene modulates cognitive control of arousal in healthy females, irrespective of OC-use. In particular, MR-haplotype 2 homozygotes have improved cognitive control which decreases the odds on developing mood-disorders.

Chapter 8 General Discussion

This PhD project revealed that the female hormonal status – including OC use – and stress vulnerability – as defined by the MR-haplotype – have practical implications in experimental psychological research. Furthermore, incorporation of these variables in models of emotional information processing may be of help in understanding and treating mood disorders in women. Namely, even small biases may affect information processing and may contribute to the resilience or proneness to mood-disorders.

Our research was among the first to show that the genetic makeup of healthy women may play a role in the influence of the female hormonal status on emotional information processing. Healthy female MR-haplotype 1/3 carriers may be more prone to distress, and may also be more sensitive to (pharmacological) changes which may counteract or sustain their vulnerability. Consistently, we observed subtle markers of depressogenic side-effects of OC only in MR-haplotype 1/3 carriers. Our findings regarding the MR-haplotypes 2 carriers are generally in line with earlier observations. We observed that MR-haplotype 2 carriers – especially homozygotes – are the less susceptible, more optimistic and more rational individuals, also in 'unstressed' conditions. However, stress-related psychopathology is very heterogeneous by nature and proteins from multiple genes are likely to interact in the stress-susceptibility phenotype. Last but not least, we should not ignore that the increased vulnerability of women to mood disorders is the result of a plethora of biological, psychological and sociological factors.

OC-users had lower affect variability and reduced sensitivity to interpersonal emotional cues. This may be experienced as either a stabilizing or a blunting effect of OC, perhaps depending on the individual's appraisal. The lower depression scores of OC-users in our longitudinal study suggests a protective effect of monophasic OC on symptoms of reproductive depression. Future studies should investigate (former) OC-users in larger cohorts including novel users, satisfied users and 'brand-switchers' in order to control for the survivor effect.