Mood and the pill

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Chapter 2

Oral contraceptives may alter the detection of emotions in facial expressions

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Abstract

A possible effect of oral contraceptives on emotion recognition was observed in the context of a clinical trial with a corticosteroid. Users of oral contraceptives detected significantly fewer facial expressions of sadness, anger and disgust than non-users. This was true for trial participants overall as well as for those randomized to placebo. Although it is uncertain whether this is an effect of oral contraceptives or a pre-existing difference, future studies on the effect of interventions should control for the effects of oral contraceptives on emotional and cognitive outcomes.

Introduction

In many women oral contraceptives (OC) reduce the variability of affect across the menstrual cycle and reduce negative affect during menstruation. However, some women experience a worsening of mood during OC use (Oinonen & Mazmanian, 2002). It is less well-known that OC may also have more subtle but important psychological effects in women who do not experience subjective mood changes. For instance, OC use induced a preference for less masculine faces (Little et al., 2013). Furthermore, partnered women who used OC reported significantly higher levels of jealousy than naturally cycling partnered women in their non-fertile cycle phase (Cobey et al., 2012).

Here we report on a coincidental finding concerning possible effects of OC use on emotion perception. The effect was observed in the context of a clinical trial investigating the between-subject effects of the mineralocorticoid receptor (MR)-agonist fludrocortison on emotional information processing in healthy women.

Experimental procedures

Participants

Forty physically and mentally healthy, non-smoking female volunteers of north-western European origin (age: 18-35) took part in this study. Participants were tested outside their pill-free week or menstrual period (two days before until five days after the start of their period). All participants provided written informed consent before the start of the study and received financial compensation for their participation. The study was approved by the medical ethics committee (METC) of Leiden University Medical Center (LUMC).

Instruments and procedure

This single-centre study had a randomized, placebo-controlled, double-blind, between-subject design. Randomization on fludrocortisone or placebo was carried out by the pharmacy of LUMC. Use of oral contraceptives was registered, since endogenous (menstrual cycle) and exogenous (oral contraceptives) hormonal changes moderate activity of the hypothalamus-pituitary-adrenal axis (Kirschbaum et al., 1999). Forty non-smoking, mentally and physically healthy participants were recruited at various sites at Leiden University. All were physically examined at Leiden University Medical Center and screened for psychiatric past by the Mini International Neuropsychiatric Interview (Sheehan et al., 1998).

After the administration of a single dose of fludrocortisone (0.5 mg) or placebo, participants rested in a neutral research room for two hours. Subsequently the facial expression recognition task

(FERT) was assessed. The FERT displays five basic emotions (happiness, sadness, fear, anger and disgust) taken from the Pictures of Facial Affect Series (Ekman and Friesen, 1976). Male and female examples of these pictures were morphed between each prototype and neutral in 10% steps. Four trials of each emotion were presented at each intensity level. Each face was also given in a neutral expression, resulting in a total of 204 stimuli that were presented in a randomized order for 500 ms and replaced by a blank screen. Participants were asked to respond as quickly and accurately as possible by pressing the corresponding buttons of a response box (happiness, sadness, fear, anger and disgust and neutral). Personality was measured with the NEO-FFI, which assesses five dimensions: Neuroticism, Extraversion, Openness to experience, Agreeableness and Conscientiousness (Hoekstra et al, 1996). The state version of the Positive Affect Negative Affect Schedule (PANAS) was administered to assess mood at intake (Watson et al., 1988). Depression vulnerability was measured with the Leiden Index of Depression Sensitivity - Revised (LEIDS-R; Van der Does, 2002).

Statistical analyses

There were no outliers (defined as > |3 SD| from the mean), multivariate influential cases (Cooks' distances > 1) or missing data. Mean scores on personality dimensions in both conditions (FC and placebo) were compared with t-tests. To analyze overall effects on the FERT we calculated sum scores (accuracy rates) and means (reaction times) for each emotion and entered these in multivariate analyses of variance, with both condition (FC/ placebo) and OC use (yes/no) as between-subject factors. When data were not normally distributed, we followed-up the findings of parametric tests with equivalent non-parametric tests.

Results

Participant characteristics

Users and non-users of OC did not differ significantly on age, BMI and personality scores, except for Agreeableness (t = - 2.91, df = 38, p = .006; see table 1).

Facial expression recognition

Multivariate tests of the multivariate ANOVA (MANOVA) revealed a significant main effect of OC use [F (5,32) = 3.78; p = .008; η_p^2= .371; power = .89]. Tests of between-subjects effects indicated that OC influence the accuracy of emotion recognition: OC users recognized fewer expressions of anger [F(1,36) = 13.09, p = .001; η_p^2= .267; power = .94], sadness [F(1,36) = 5.09, p = .030; η_p^2 = .371 ; power = .89] and disgust [F(1,36) = 5.56, p = .024; η_p^2 = .134 ; power = .63]. OC-users also had faster RTs on correctly recognized sadness [F(1,36) = 5.78, p = .022; η_p^2 = .138; power = .65];] and disgust trials [trend; F(1,36) = 3.28; p = 0.079; η_p^2 = .083; power =.42].

Table 1. Demographic and clinical characteristics.

	Non-users (n = 14)	**OC-users (n = 26)**
Age in years	22.2 (0.7)|	20.6 (0.5)
Body mass index	21.9 (0.7)	21.8 (0.6)
Neuroticism	31.6 (2.2)	30.4 (1.4)
Extraversion	41.9 (1.3)	45.0 (1.3)
Openness to experience	33.3 (0.6)	33.7 (0.6)
Agreeableness	32.6 (0.7)*	35.2 (0.7)*
Conscientiousness	40.9 (0.7)	41.3 (0.9)
LEIDS-R Total	33.6 (4.2)	32.4 (2.7)
PANAS Positive affect	23.9 (1.23)	25.7 (1.1)
PANAS Negative affect	11.9 (.74)	10.8 (.27)

Abbreviations: OC = oral contraceptives; LEIDS-R = Leiden Index of Depression Sensitivity – Revised.
Notes: Means, standard errors in parentheses; * $p < .05$.

In order to exclude the possible influence of the administration of fludrocortisone on the outcomes of FERT, we analysed the placebo condition (n = 20; 14 OC-users) separately in a MANOVA with OC as between-subjects factor. Multivariate tests for OC were significant [$F(5,14) = 5,55$; $p = .005$; $\eta_p^2 = .665$; power = .938]. Tests of between-subjects confirmed main effects for OC-use on correct recognition of anger [$F(1,18) = 15.36$, $p = .001$; $\eta_p^2 = .460$; power = .96]; sadness [$F(1,18) = 4.53$, $p = .047$; $\eta_p^2 = .201$; power = .521] and disgust [$F(1,18) = 4.75$, $p = .043$; $\eta_p^2 = .209$; power = .541]. (see figure 1). The effect of OC-use on the speed of recognition of sadness became a trend ([$F(1,18) = 3.38$, $p = .083$; $\eta_p^2 = .158$; power = .413]. The same analyses with non-parametric Kruskal-Wallis ANOVAs largely confirmed these findings. The effects of OC on the recognition of anger ($p = .002$) remained significant, whereas the effects for disgust and sadness became trends ($p = .051$).

To control for the significant difference on Agreeableness between users and non-users of OC, we added this score as a covariate in the multivariate analysis of variance of the placebo-treated participants. The effect of OC on accuracy rates of anger remained significant [$F(1,17) = 14.19$, $p = .002$; $\eta_p^2 = .455$; power = .944], whereas the effects on disgust ($p = .096$) and sadness (accuracy, $p = .093$) became trends.

Since the FERT contains both female and male pictures as stimuli, we further explored the effect of gender of stimulus picture in a repeated measures MANOVA with gender as within-subjects factor, the five emotions as measures and OC-use as between-subjects factor. This revealed significant multivariate main effects of OC [$F(5,14) = 5.55$; $p = .005$; $\eta_p^2 = .665$; power=.938] and gender [$F(5,14) = 5.22$; $p = .007$; $\eta_p^2 = .651$; power = .922];]. In univariate tests the influence of gender on the recognition of happy was significant [$F(1,18) = 21.06$; p =

.001; η_p^2 = .539; power=.991], while the effect of disgust was a trend [F(1,18) = 3.16; p = .092; η_p^2 = .149; power = .391]. Furthermore, an interaction effect between OC-use and gender appeared for the recognition of disgust [F(1,18) = 4.85; p = .041; η_p^2 = .212; power = .550]. In non-parametric tests, happiness was recognised better on a male face than on a female face by both OC-users (trend; p = .058) and non-users (p = .002). A disgusted expression, however, was recognized better in female faces by participants who were not using OC (p = .039).

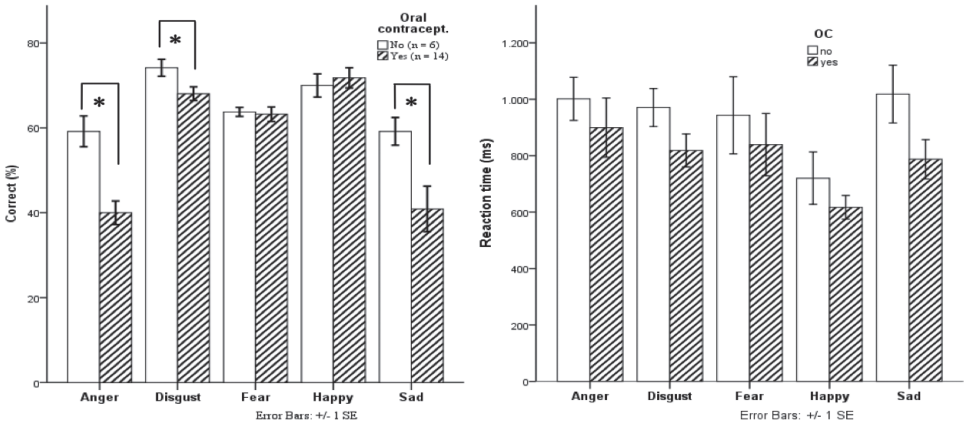

Figure 1a and 1b. Emotion recognition accuracy (left panel) and reaction time (right panel) scores of OC-users and non-users randomized to placebo. *Notes:* OC = oral contraceptives; * p < 0.05.

Discussion

We observed a possible effect of oral contraceptives use on emotion recognition: OC-users detected significantly fewer facial expressions of sadness, anger and disgust, but no effects were seen on the detection of happy or fearful facial expressions. An explorative analysis of the placebo condition confirmed these findings. Furthermore, the influence of OC use on the recognition of disgust was moderated by the gender of the poser of the facial expression.

It is uncertain whether these observed differences can be ascribed to OC use or were pre-existing. For instance, differences in personality traits may influence performance on facial expression recognition. In our study (non-)users of OC did not differ significantly from each other in terms of cognitive vulnerability to depression, positive and negative affect and personality traits, except for Agreeableness. High scorers on Agreeableness in NEO-FFI tend to be compassionate and cooperative rather than suspicious and hostile (Hoekstra et al, 1996). This positive attitude towards our fellow man may result that one is also less likely to recognize antagonistic facial expressions. However, after controlling for Agreeableness (which may actually

be overcorrection, if OC have an effect on both Agreeableness and emotion recognition), OC-users still recognized significantly fewer expressions of anger.

Hormonal contraceptive pills are used by approximately 40% of the Dutch women between 18 and 45 years. In the present sample of university students, the rate was 66%. Given the fact that students frequently serve as participants in psychological research, these subtle psychological consequences may act as confounders in many studies on social behavior and cognition. Although oral contraceptives have been studied quite extensively, little of this research has been directed towards the potential psychological consequences resulting from use (Cobey & Buunk, 2012). In view of the extensive research on the influence of fluctuations of ovarian hormones across the menstrual cycle on social behavior and cognition, the paucity of research on similar effects of OC is surprising. For instance, young naturally cycling women recognize facial expressions of emotion better during their follicular than the luteal phase (Derntl et al., 2008). Recently it was found that the partners of women who started using OC at relationship formation have less masculine faces than the partners of women who did not start using OC (Little et al., 2013).

The most frequently used OC contain a synthetic progestin and an estrogen. These synthetic hormones inhibit the rise of estrogen and maturation of the ovarian follicle that occurs during the follicular phase of the menstrual cycle by altering the hypothalamic-pituary-ovarian feedback loop (Rivera et al., 1999). Furthermore, the rise of the progesterone level after ovulation is mainly caused by the empty follicle. Hence, in pill-taking women the endogenous levels on both estrogen and progesterone are lower compared with naturally cycling women (Fleischmann et al, 2010). Possibly, the suppressing effect of OC on endogenous female hormones mimics a condition in which the higher social sensitivity that females experience during their follicular phase is not needed, since users of OC recognized fewer facial expressions of disgust, fear and anger. In the follicular phase, social interaction needs to be facilitated which may favorably influence mating behavior as well (Derntl et al., 2008). Since we neither registered menstrual cycle phase nor collected hormonal measures, we were not able to explore the association between endogenous female hormones on our findings.

We also observed a possible effect of OC on the speed of recognition of sadness. Although the effect was non-significant in non-parametric testing, similar effects have been found in naturally cycling women: women in their luteal phase recognized sadness faster in a working memory task for emotional facial expressions (Gasbarri et al, 2008). The luteal phase is characterized by a lower level of estrogen. Estrogens mediate signaling cascades in individual hippocampal neurons (Wu et al., 2011), which suggests functional consequences of estrogen levels for these central limbic structures. A multimodal, translational study in female humans and rodents revealed that both endogenous and exogenous estrogens improve the ability to retain extinguished fear memories by modulating neuronal activity and synaptic plasticity in the ventromedial prefrontal

cortex and amygdala - regions involved in fear expression and extinction in both species (Zeidan et al., 2011). These effects were not found in a study on the effects of progesterone on fear extinction or its recall (Milad et al, 2010). Furthermore, a placebo-controlled fMRI study in women with previous OC-induced mood deterioration who reinitiated OC-use revealed that OC affected amygdala habituation in an emotion processing task (Gingnell, 2013). Hormonal contraceptives may also affect brain structure, including areas involved in face processing and emotional memory (Pletzer et al., 2010; De Bondt et al., 2013).

As our study was not aimed primarily at assessing the influence of OC on emotional information processing, we ask for replication of our findings. Future studies should not only investigate bigger sample sizes, but should also register menstrual cycle phase, OC-type and duration of use. Last but not least, interpersonal differences in sensitivity to side-effects of OC need closer investigation.