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Oral contraceptive use changes brain activity and mood in women with previous negative affect on the pill—A double-blinded, placebo-controlled randomized trial of a levonorgestrel-containing combined oral contraceptive

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Summary
Objective: Most women on combined oral contraceptives (COC) report high levels of satisfaction, but 4—10% complain of adverse mood effects. The aim of this randomized, double-blinded, placebo-controlled trial was to investigate if COC use would induce more pronounced mood symptoms than placebo in women with previous history of COC-induced adverse mood. A second aim was to determine if COC use is associated with changes in brain reactivity in regions previously associated with emotion processing.
Methods: Thirty-four women with previous experience of mood deterioration during COC use were randomized to one treatment cycle with a levonorgestrel-containing COC or placebo. An emotional face matching task (vs. geometrical shapes) was administered during functional magnetic resonance imaging (fMRI) prior to and during the COC treatment cycle. Throughout the trial, women recorded daily symptom ratings on the Cyclicity Diagnoser (CD) scale.
Results: During the last week of the treatment cycle COC users had higher scores of depressed mood, mood swings, and fatigue than placebo users. COC users also had lower emotion-induced reactivity in the left insula, left middle frontal gyrus, and bilateral inferior frontal gyri as compared to placebo users. In comparison with their pretreatment cycle, the COC group had

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decreased emotion-induced reactivity in the bilateral inferior frontal gyri, whereas placebo users had decreased reactivity in the right amygdala.
Conclusion: COC use in women who previously had experienced emotional side effects resulted in mood deterioration, and COC use was also accompanied by changes in emotional brain reactivity. These findings are of relevance for the understanding of how combined oral contraceptives may influence mood. Placebo-controlled fMRI studies in COC sensitive women could be of relevance for future testing of adverse mood effects in new oral contraceptives.
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Introduction

Most women on combined oral contraceptives (COC) are satisfied with their contraceptive method (Skouby, 2010). However, 4–10% of COC users experience mood side effects, which typically include depressive symptoms, irritability, and mood swings (Ernst et al., 2002; Kelly et al., 2010). Mood-related side effects are a major reason for discontinuing COC use (Lindh et al., 2009), and in doing so, women turn to less safe contraceptive alternatives (Skouby, 2010), thus increasing their risk of unplanned pregnancies (Segebladh et al., 2009).

To improve tolerability (and safety) of COCs, new progestagens have been developed over the years. Indeed, COCs with anti-androgenic progestagens such as drospirenone and desogestrel appear more favorable in terms of mood symptoms than progestagens with a more androgenic profile such as levonorgestrel (Poromaa and Segebladh, 2012). However, even though COCs have been available for more than 50 years, surprisingly little is known about the underlying biological mechanisms involved in the mood and affect changes that some women experience. Previous depression predisposes to COC-induced mood deterioration (Joffe et al., 2003), but until relevant placebo-controlled trials have been performed, drug-related causality cannot be established. Thus far, three placebo-controlled COC trials have been performed in healthy women, but as these studies only included sterilized women or dysmenorrhea patients, the results may not be valid for typical users (Leeton et al., 1978; Graham et al., 1995; O'Connell et al., 2007). Cross-sectional studies of COC users have indicated that they have increased cortisol levels (Maes et al., 1992; Ansseau et al., 1993), reduced cortisol responsivity (Kirschbaum et al., 1995; Bouma et al., 2009) and lower levels of neurosteroids (Paoletti et al., 2004; Rapkin et al., 2006). Peripheral markers of the serotonin system also appear to be altered in COC users (Weizman et al., 1988; Maes et al., 1992), although a recent PET study found no difference in cortical $5HT_{2A}$ binding between COC users and non-users (Frokjaer et al., 2009). Finally, we have previously reported that women who experience adverse mood while on COC have deficient prepulse inhibition, a measure of sensorimotor gating with relevance for many anxiety disorders (Braff et al., 2001), in comparison with COC users who reported unchanged emotional well-being (Borgstrom et al., 2008). To date, no studies using functional magnetic resonance imaging (fMRI) have been performed in COC users, why potential emotion-induced brain reactivity effects of COCs remain unexplored.

Stimulus-induced emotional processing typically involves activation of the amygdala, anterior cingulate cortex (ACC) and insula, forming a hypothesized emotion-processing network (Davidson et al., 2000). In addition to these regions, areas in the ventromedial and orbitofrontal cortex have been proposed to have important roles for emotion processing (Fusar-Poli et al., 2009; Pessoa and Adolphs, 2010; Diekhof et al., 2011; Etkin et al., 2011). Of importance for the context of the present study, all of these regions are responsive to ovarian hormones changes or treatments (Amin et al., 2006; Dreher et al., 2007; Andreano and Cahill, 2010; van Wingen et al., 2011; Gingnell et al., 2012; Shafir et al., 2012). Generally, hormonal variations in estradiol and progesterone seem to have opposing effects on reactivity in areas generating and controlling emotions (van Wingen et al., 2011) but findings are not uniform. For example, luteal phase amygdala reactivity has been reported to be both increased (Gingnell et al., 2012; Ossewaarde et al., 2010; Andreano and Cahill, 2010) and decreased (Goldstein et al., 2005; Dreher et al., 2007). Similar diverging patterns have also been observed in the insula and ACC (Shafir et al., 2012; Amin et al., 2006; Frank et al., 2010; Dreher et al., 2007).

Hence, the aim of this randomized, double-blinded, placebo-controlled trial was to investigate if COC use would induce more pronounced mood symptoms than placebo in women with previous history of COC-induced adverse mood. Secondly, we aimed to determine if COC use is associated with changes in brain reactivity in regions previously associated with emotion processing and responsivity to ovarian steroid hormones. In order to enhance the likelihood of detecting differences between placebo and COC users, we exposed the women to a levonorgestrel-containing COC.

We hypothesized that COC use in these susceptible women would be associated with increased reporting of mood symptoms, together with increased amygdala, insula and anterior cingulate cortex reactivity. In addition, we wanted to explore if COC use would alter brain activity in cortical areas, such as the middle and inferior frontal gyri, previously known to be related to emotion processing as well as ovarian hormones.

Materials and methods

Participants

The study was carried out at the Department of Obstetrics and Gynecology at Uppsala University Hospital between January 1, 2010 and June 30, 2011. Healthy women (18–45 years), with regular menstrual cycles (25–31 days) and subjective reports of mood deterioration during previous COC use were included if they did not meet any of the exclusion criteria and accepted to use back-up contraception during the study period. Presence of previous COC-induced negative mood was determined by a semi-structured interview.

Women who reported at least one of the following symptoms in relation to previous COC use were included: depressed mood, decreased interest in usual activities, anxiety, mood swings or irritability. Women were recruited by advertisement in local newspapers.

The exclusion criteria were family history of venous thromboembolism, neurological disorders, presence of any ongoing psychiatric disorder, and present use or use within two months prior to inclusion of the following treatments: hormonal contraceptives, cortisol, levothyroxine, and psychotropic drugs including serotonin reuptake inhibitors and benzodiazepines. The presence of psychiatric disorders was evaluated using a structured psychiatric interview, the Swedish version of Mini International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998). Furthermore, participants with pacemakers, cardiac defibrillators, aneurysm clips, cochlear implants or other implants that use magnets, batteries or wires were excluded. All participants had negative pregnancy tests.

The women were fully informed about the study aims and procedures and gave written informed consent prior to inclusion. The study procedures were in accordance with ethical standards for human experimentation, and the study was approved by the Independent Research Ethics Committee, Uppsala University and the Medical Products Agency in Sweden.

Study design

The study was an investigator-initiated, double-blinded, randomized, parallel-group clinical trial during which the participants were treated with either an oral COC (ethinyl estradiol (EE) 30 μg/0.15 mg levonorgestrel, provided by Bayer Pharma AB) or placebo (Bayer Pharma AB) during one treatment cycle. Following a pretreatment cycle (allowing for baseline assessments), women started taking the COC or placebo tablets once daily on the first day of menses and continued treatment for 21 days.

Apoteksbolaget Production and Laboratories (the National Corporation of Swedish Pharmacies) in Stockholm prepared identical capsules containing either COC or placebo. The packing and randomization was done by Apoteket Production and Laboratories, Stockholm, Sweden. The randomization was determined by a computerized random-number generator in blocks of four and allocation was implemented by use of numbered containers. During the study, the participants and study personnel were not informed about which treatment the patient received and randomization codes were kept secret at the Uppsala University Hospital Pharmacy until completion of the study. Compliance was assessed by counting the remaining capsules at the final visit. None of the women had remaining capsules at the end of the study and there were no reports of missed pill intake.

During the pre-treatment and treatment cycles, women filled out daily, prospective symptom ratings of mood and physical symptoms on the previously validated Cyclicity Diagnoser (CD) scale (Sundstrom et al., 1999). The CD scale consists of nine negative mood parameters (depression, interest in usual activities, fatigue, irritability, anxious/worried, mood swings, sense of being out of control, difficulties in concentrating and disordered sleep), two positive mood parameters (cheerfulness and energy), and four somatic symptoms (food cravings, bloating, breast tenderness, and menstrual bleeding). The CD scale is a Likert scale ranging from 0 to 8, with 0 representing a complete absence of a particular symptom, and 8 reflecting the maximal intensity of a particular symptom.

FMRI scans were performed during the follicular phase of the pre-treatment cycle (day 1–10 after onset of menses, mean cycle day of scanning day 4 ± 3) and during the last week of the treatment cycle (day 15–21 of the treatment cycle). The pretreatment time-point was chosen to correspond with a phase of low ovarian steroid levels in order to maximize the possibility to detect a change in brain activation from COC use. The time-point during the treatment cycle was chosen to represent COC use at steady state and to distinguish the COC effect from placebo. In order not to compromise blinding, no assessments of luteinizing hormone surge were performed during the study. Consequently, the menstrual cycle timing in placebo users could not be definitively ascertained.

At these time-points, women filled out the State-Trait Anxiety Inventory (STAI-S) (Hodgues and Spielberger, 1969) and the self-rated version of the Montgomery-Åsberg Depression Rating Scale (MADRS-S) (Montgomery and Asberg, 1979). The STAI-S measures state anxiety on a scale ranging from 20 to 80 and the MADRS-S scores reflect depressive symptoms during the past three days on a scale ranging from 0 to 54.

fMRI — scans and paradigm

MR imaging was performed using a 3T whole body scanner (Achieva 3T X Philips scanner Philips Medical Systems, Best, The Netherlands) equipped with an 8-channel head coil. An anatomical T_1-weighted reference data set to a voxel size of 0.8 mm × 1.0 mm × 2.0 mm and 60 slices was acquired at the beginning of each scanning session. During stimulus presentation blood oxygen level dependent (BOLD) imaging was performed using a single shot echo planar imaging sequence with a echo time/repetition time 35/3000 ms, flip angle 90°, acquisition matrix 76×77, acquired voxel size 3.0 mm × 3.0 mm × 3.0 mm and 30 slices.

The participants were lying on their back in the scanner with the head lightly fixated by Velcro strips. During scanning, visual stimuli were presented through goggles mounted on the head coil (Visual System, NordicNeuroLab, Bergen, Norway). The stimulus paradigm was implemented using the commercial software package E-prime (Psychology Software Tools, Sharpsburg, PA, USA). In order to synchronize the paradigm and the MR-scanner, trigger pulses from the scanner were fed to the paradigm-controlling PC through SyncBox (NordicNeuroLab, Bergen, Norway).

To activate the emotional areas of the brain, an emotion processing task based on Hariri et al. (2002) was used. This paradigm involves a contrast between a task that requires matching of emotional facial expressions and a simple sensory-motor control task. The emotion task consisted of three images of faces (angry and afraid Ekman-faces) and the sensory-motor control task of three geometrical shapes (circles or ellipses) (Fig. 1). The target face or shape was displayed at the top and the participants were instructed to compare the target with the two images below and decide which one displayed the same emotion or form as the target image. The participants responded by pressing a button with

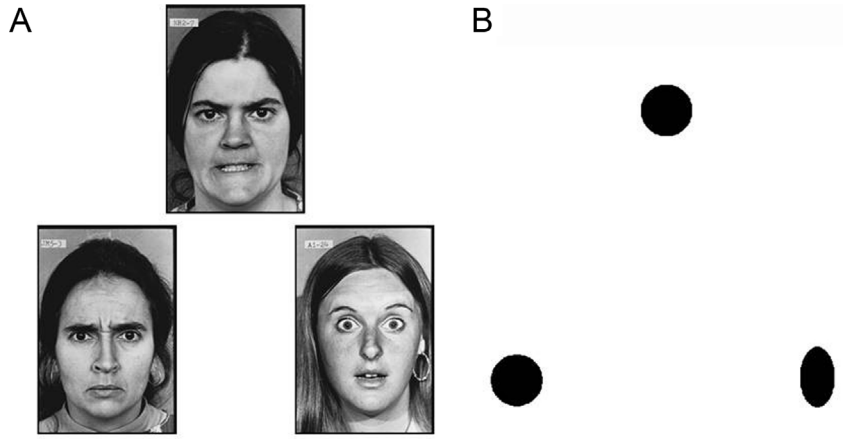

Figure 1 The emotion task (A) and the sensory-motor control task (B). Participants were requested to compare the top target slide with the two lower images and indicate which one expressed the same emotion or had the same form as the target.

the left or right index finger. Emotion and sensory-motor control task trials were presented in blocks of 6, in which images were presented for 4 s, interspaced with a fixation cross (for 2 s for the sensory-motor control task and a randomly selected duration of 2, 4 or 6 s for the emotion task). The expressed emotion, or spatial orientation, of the target varied from trial to trial, and each emotion block had an equal mix of emotions as well as sex of the actors. Accuracy and reaction times were registered for each trial.

The DICOM images from the scanner were converted to nifti-files using MRicron, a freeware package, available at http://neuro.debian.net/pkgs/mricron.html. The data was analyzed in MatLab (MathWorks, Natick, MA, USA) using SPM8, available at http://www.fil.ion.ucl.ac.uk/spm/software/spm8/. BOLD images were realigned to a mean image of each session, slice timed to the middle slice of each whole brain volume, co-registered with the individual anatomic scan and normalized into MNI-space using normalization parameters obtained from a segmentation of the individual anatomic scan. Finally, smoothing was performed using an 8 mm Gaussian kernel (full width, half maximum). For each participant BOLD signal was regressed on the stimulus function (boxcar, onsets and durations of facial stimuli and geometrical shapes) and six movement parameters obtained from the realignment step. The BOLD signal was convolved with the canonical hemodynamic response function provided by SPM. For each individual, contrast maps of the reactivity for facial stimuli contrasted against the geometrical shapes and fixation crosses were obtained. The contrast maps were then used for second level, random effect group comparisons. Differences between women receiving COC or placebo were estimated using independent *t*-tests during pretreatment and treatment cycles, respectively. Within group differences between pretreatment and active/placebo treatment were carried out in each group by paired *t*-tests. Regions of interest (ROI) included the bilateral amygdala, insula, ACC, inferior frontal gyri and middle frontal gyri and were created using the AAL-definitions (amygdala, insula and ACC) and TD-labels (inferior and middle frontal gyri) from the WFU Pickatlas (Lancaster et al., 2000; Maldjian et al., 2003). Spatial localizations are reported in Talairach coordinates. Analyses within SPM for interactions and *t*-tests in the a priori defined ROI's were performed with $p < 0.001$ and cluster size >5 corrected for volume (with the exception of the small volume of the amygdala where no cluster size threshold was applied).

1.1. Statistical analyses

Power calculations were based on Borgstrom et al. (2008), assuming a difference between COC and placebo users in mean summarized negative mood scores on the CD scale of 4.0, with a SD of 3.0. Given a sample size of 20 women in each group, and an expected dropout of 25%, the study had 94% power to detect a difference between treatments.

Demographic data were compared between groups by Student's *t*-tests or Chi-square tests. Based on the daily scores on the CD-scale, mean weekly scores for each symptom were calculated. For this study, only the negatively expressed mood symptoms were considered. During the pretreatment cycle, the mean symptom scores during the fourth week (i.e. the luteal phase) were compared between groups, as the late luteal phase is generally regarded as the most symptomatic period of the menstrual cycle. During treatment, the mean scores of the last treatment week (i.e. week three) were compared between groups. For assessment of change in mean symptom ratings between pretreatment and treatment cycles, the third week of the pre-treatment cycle was compared with the third (and final) week of treatment. The time-intervals for the third and fourth pretreatment cycle week were based on backward counting from the next onset of menses. As the mean CD scores were normally distributed, these analyses were carried out by use of independent *t*-tests and paired *t*-tests, respectively.

Besides the main fMRI analyses, subgroup analyses were conducted in COC users who deteriorated in mood and in placebo users who remained unaffected by treatment. We used a strict definition of COC-induced mood deterioration, as follows: (1) Summarized negative mood symptom scores (depressed mood, mood swings, anxiety/worried, and irritability) from 21 pretreatment days (cycle days 1–21) were compared with 21 treatment days (cycle days 1–21) by use of Wilcoxon Matched-Pair Signed-Rank Test and a *p*-value less than 0.05 was required for each individual subject. (2) Symptom scores exhibiting a statistically confirmed difference between the pretreatment and treatment cycles were

checked manually to ensure at least a 100% increase from baseline in summed negative mood symptoms during the last seven days of the treatment cycle. (3) The mean summed symptom scores had to exceed a score of 9.0 during the last seven days of the treatment cycle. Women who remained unaffected by placebo fulfilled none of these criteria.

All values in the text and tables are displayed as mean $\pm$ SD, unless otherwise stated. The SPSS statistical package was used for the analyses (IBM, Armonk, NY, US). *p*-values of less than 0.05 were considered to be statistically significant.

Results

Forty women were screened for the study. Of these, four did not fulfill inclusion and exclusion criteria and one subject dropped out prior to randomization. Hence 35 women were randomized to COC or placebo. One woman dropped out of the study immediately after randomization leaving 34 participants in the study. In addition, the scans of two women in the placebo group (pretreatment) and two women in the COC group (one at both sessions and one at pretreatment) were later excluded from the fMRI analyses due to excessive movement during the fMRI acquisition (peaks of more than three mm in the *x*/*y*/*z*-axis or more than two degrees of head rotation). The final sample for the pretreatment fMRI comparison thus consisted of 15 women randomized to placebo and 15 women randomized to the COC. During treatment 17 women randomized to placebo and 16 women randomized to the COC were available for analyses. Data from both scanning sessions were available for 15 placebo users and 15 COC users (Fig. 2).

Depressed mood (88.2%) was the most commonly reported side effect of previous COC use, followed by mood swings (82.4%), irritability (70.6%), decreased interest in usual activities (44.1%), anxiety (38.2%), disordered sleep (20.6%), feelings of guilt 8.8%, and difficulties concentrating (5.9%).

Women randomized to placebo or COC did not differ in terms of age, parity, educational level, previous history of COC use or previous experience of premenstrual syndrome (Table 1). With the exception of higher scores of disordered sleep in women randomized to COC ($T = -2.5$, $p < 0.05$), no differences in daily mood symptom scores, self-rated anxiety or self-rated depression were evident between the

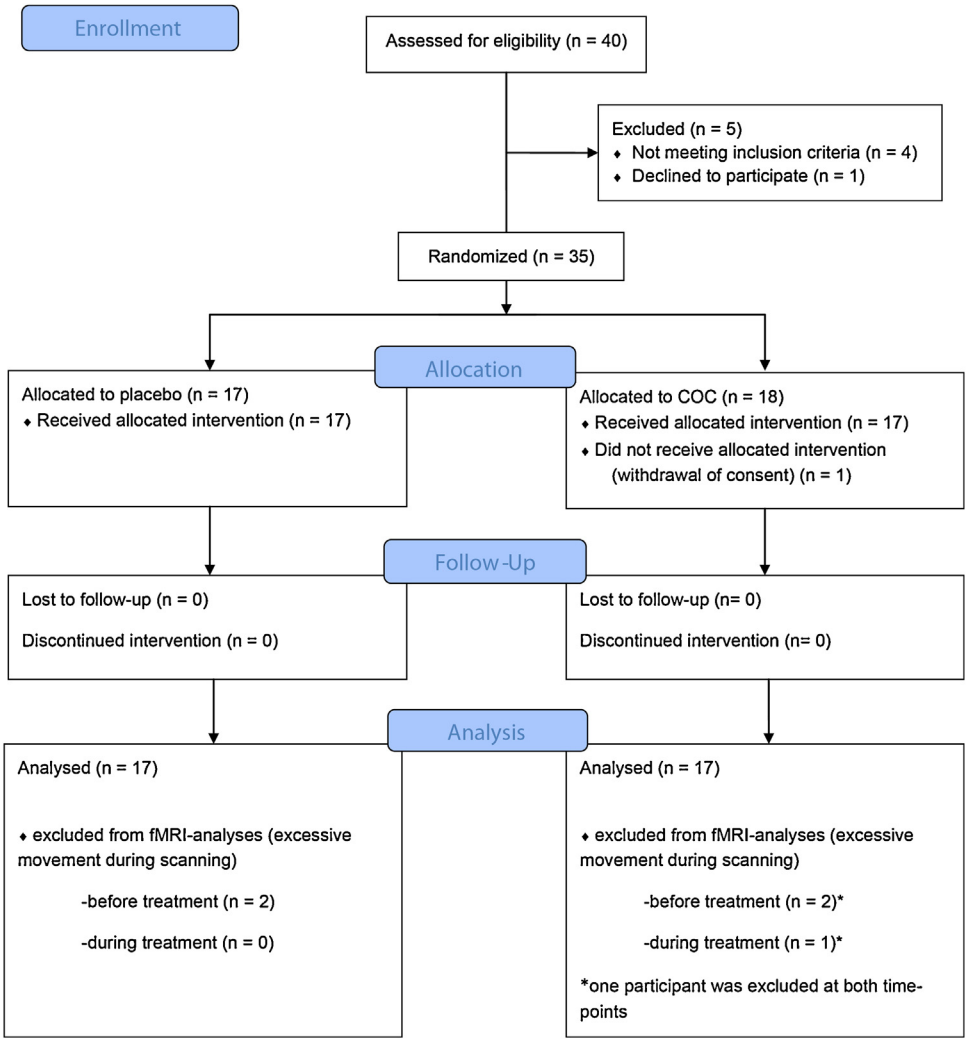

Figure 2 Subject flow and allocation to the intervention and control conditions.

Table 1 Demographic data and clinical variables in women randomized to a levonorgestrel-containing COC ($n = 17$) or placebo ($n = 17$). Data are presented as mean ± SD or as absolute number and frequency.

Demographic data and clinical variables	Placebo ($n = 17$)	COC ($n = 17$)
Age (years)	24.5 ± 3.3	25.5 ± 5.0
Education (years)	15.6 ± 1.6	15.0 ± 2.3
Smokers, *n* (%)	1 (5.9%)	3 (17.6%)
Steady relationship, *n* (%)	9 (52.9%)	10 (58.8%)
Parous subjects, *n* (%)	0 (0%)	0 (0%)
Previous induced abortion, *n* (%)	4 (23.5%)	2 (11.8%)
Self-reported premenstrual syndrome, *n* (%)	9 (52.9%)	5 (29.4%)
Menstrual cycle length (days)	28.4 ± 2.3	27.3 ± 2.7
Age at hormonal contraceptive start (year)	17.0 ± 1.7	16.3 ± 1.9
Total duration of previous COC use (years)	4.4 ± 2.8	4.3 ± 3.0
Number of previously tested COC brands, *n*	2.7 ± 1.7	2.4 ± 0.8
Time since last use of COC, months	17.4 ± 4.2	26.8 ± 6.6

No significant differences were found between groups.

COC and placebo group during the pretreatment cycle (Table 2).

Emotional symptoms

During the last week of the treatment cycle COC users had higher scores of depressed mood ($T = -2.3$, $p < 0.05$), mood swings ($T = -3.4$, $p < 0.01$), and fatigue ($T = -3.1$, $p < 0.01$) in comparison with placebo users (Table 2). Compared to the pretreatment cycle, COC users also increased their scores of depressed mood ($T = -2.4$, $p < 0.05$), mood swings ($T = -4.3$, $p < 0.001$) and fatigue ($T = -2.3$, $p < 0.05$), whereas placebo users had virtually unchanged mood scores (Table 2). As expected, COC users also had higher scores of physical symptoms such as breast tenderness ($T = -2.3$, $p < 0.05$) and bloating ($T = -3.7$, $p < 0.01$) in comparison with the pretreatment assessment (Table 2). In addition, women randomized to COC had significantly higher scores of self-rated depression ($T = -2.5$, $p < 0.05$), during the last week of the treatment cycle compared to their pretreatment ratings. Self-rated anxiety did not differ between groups or phases. According to the definition used for mood deterioration six (35.3%) COC users and one placebo user (5.8%) displayed clear-cut mood deterioration, whereas seven COC users (41.2%) and seven (41.2%) placebo users were completely unaffected by the trial. Remaining subjects fell in-between these criteria. Eight (47.1%) women randomized to placebo and nine (52.9%) women randomized to COC correctly guessed their treatment at the end of the study.

Table 2 Mean daily ratings on the CD-scale during the last week of the pretreatment cycle, during the last week of the treatment cycle and change from pretreatment cycle in women randomized to a levonorgestrel-containing COC ($n = 17$) or placebo ($n = 17$). Data are reported as mean ± SD.

Mood symptoms	Pretreatment cycle week four		Treatment cycle week three		Change from corresponding pretreatment week[d]	
	Placebo ($n = 17$)[c]	COC ($n = 17$)	Placebo ($n = 17$)[c]	COC ($n = 17$)	Placebo ($n = 17$)[c]	COC ($n = 17$)
Depressed mood	1.0 ± 0.7	1.4 ± 0.8	1.0 ± 1.0	2.0 ± 1.4[a]	0.4 ± 0.9	1.0 ± 1.7[b]
Mood swings	1.7 ± 1.5	2.1 ± 1.6	1.1 ± 1.0	2.6 ± 1.5[a]	0.1 ± 1.1	1.5 ± 1.3[b]
Irritability	1.4 ± 1.4	2.0 ± 1.4	1.2 ± 0.9	1.9 ± 1.3	0.2 ± 0.9	0.5 ± 1.8
Anxious, worried	1.4 ± 1.3	1.6 ± 1.0	1.0 ± 1.1	1.4 ± 1.0	0.03 ± 0.8	0.06 ± 1.1
Difficulties concentrating	1.5 ± 1.0	1.8 ± 1.2	1.2 ± 1.0	2.0 ± 1.6	0.05 ± 0.9	0.2 ± 1.1
Fatigue	1.6 ± 0.9	1.7 ± 1.2	1.0 ± 1.0	2.5 ± 1.5[a]	0.2 ± 1.2	0.7 ± 1.3[b]
Disordered sleep	0.8 ± 0.7	1.9 ± 1.6[b]	0.7 ± 0.5	1.8 ± 1.3[a]	−0.05 ± 0.8	0.6 ± 1.2
Out of control	0.6 ± 1.0	1.2 ± 1.3	0.5 ± 0.6	1.2 ± 1.3	0.2 ± 0.4	0.5 ± 1.2
Bloating	1.4 ± 1.5	1.3 ± 0.9	0.6 ± 1.2	1.5 ± 1.3	0.1 ± 1.0	0.7 ± 1.3[b]
Breast tenderness	1.4 ± 1.7	0.9 ± 1.5	1.0 ± 1.0	2.0 ± 1.4[a]	0.4 ± 0.9	1.0 ± 1.7[b]
STAI-S[e]	29.4 ± 5.4	28.9 ± 4.9	28.4 ± 5.2	31.4 ± 7.9	−0.3 ± 4.0	2.3 ± 7.0
MADRS-S[e]	4.3 ± 1.3	5.2 ± 4.8	5.4 ± 3.7	8.9 ± 6.5	1.1 ± 3.5	3.7 ± 6.0[b]

[a] Significantly greater than the placebo group, $p < 0.05$–0.01.
[b] Significantly greater than corresponding week during the pretreatment cycle, $p < 0.05$–0.01.
[c] Two women in the placebo group never returned their CD ratings, but STAI-S and MADRS-S scores are available for all participants.
[d] Mean difference in mood scores between the third week of treatment and the third week of the pretreatment cycle.
[e] STAI-S and MADRS-S were obtained at the time of the fMRI scanning, in the follicular phase of the pretreatment cycle.

Table 3 Reaction times and number of errors during the emotional and sensory-motor control tasks in women randomized to a levonorgestrel-containing COC ($n = 17$) or placebo ($n = 17$). Data are reported as mean ± SD.

Performance	Pretreatment cycle		Treatment cycle	
	Placebo ($n = 17$)	COC ($n = 17$)	Placebo ($n = 17$)	COC ($n = 17$)
Reaction time (ms)				
Faces	2182 ± 255	2115 ± 233	2135 ± 272	1951 ± 308
Shapes	941 ± 138	907 ± 100	902 ± 147	881 ± 123
Errors (*n*)				
Faces	1.9 ± 1.5	2.2 ± 1.6	2.1 ± 2.2	1.9 ± 2.0
Shapes	0.4 ± 0.6	0.6 ± 0.9	0.5 ± 1.0	0.5 ± 0.8

No significant differences were obtained between groups or phases of the menstrual cycle.

fMRI task and BOLD response

Both groups identified emotions and shapes with similar speed and accuracy (Table 3).

During the pretreatment cycle no emotion-induced differences in BOLD signaling were detected between women subsequently randomized to placebo or COC (Table 4). However, during the last week of the treatment cycle COC users had lower reactivity in the left insula, left middle frontal gyrus, and bilateral inferior frontal gyri than placebo users (Table 4 and Fig. 3). Compared to the pretreatment cycle, the COC users had decreased reactivity in the bilateral inferior frontal gyri during the last week of active treatment. Placebo users, on the other hand, had decreased reactivity in the right amygdala in comparison with their pretreatment cycle (Table 4 and Fig. 4). When these analyses were repeated in the sub-group of women who displayed COC-induced mood deterioration, as compared to placebo users with no mood change, lower reactivity was only seen in the left insula (Table 4).

No serious adverse events occurred during the study.

Discussion

The major findings of the present study were that women with subjective reports of previous COC-induced mood deterioration displayed depressive mood and mood swings when re-exposed to COC. COC users also had higher scores of depressed mood and mood swings in comparison with placebo users and these COC-induced mood symptom changes were

Table 4 Emotional BOLD-signal reactivity in regions of interest (amygdala, ACC, insula, middle frontal gyrus and inferior frontal gyrus) in women randomized to a levonorgestrel-containing COC or placebo during the pretreatment and treatment cycles.

	Hemisphere	*x*	*y*	*z*	*z* score	*p* value	Cluster size (voxels)
Between-group differences							
Pretreatment cycle	No significant differences between groups						
Treatment cycle							
COC >placebo	No significant differences between groups						
COC < placebo							
Middle frontal gyrus	L	−9	27	38	3.4	<0.001	6
Inferior frontal gyrus	R	45	31	−3	4.4	<0.001	20
	R	48	22	−10	3.6		
	L	−45	14	11	3.6	<0.001	8
Insula	L	−33	22	−3	4.0	<0.001	21
Within-group differences							
COC users							
pretreatment > treatment							
Inferior frontal gyrus	L	−45	20	5	3.8	<0.001	37
	R	48	19	−2	3.5	<0.001	5
Placebo users							
pretreatment > treatment							
Amygdala	R	27	1	−17	3.4	<0.001	4
Sub-group differences							
COC users with mood deterioration < unaffected placebo users							
Insula	L	−33	22	−3	4.0	<0.001	16

xyz coordinates are given in Talairach stereotactic space.
p values are corrected for multiple comparisons across search volume of ROI.
L, left hemisphere; R, right hemisphere.

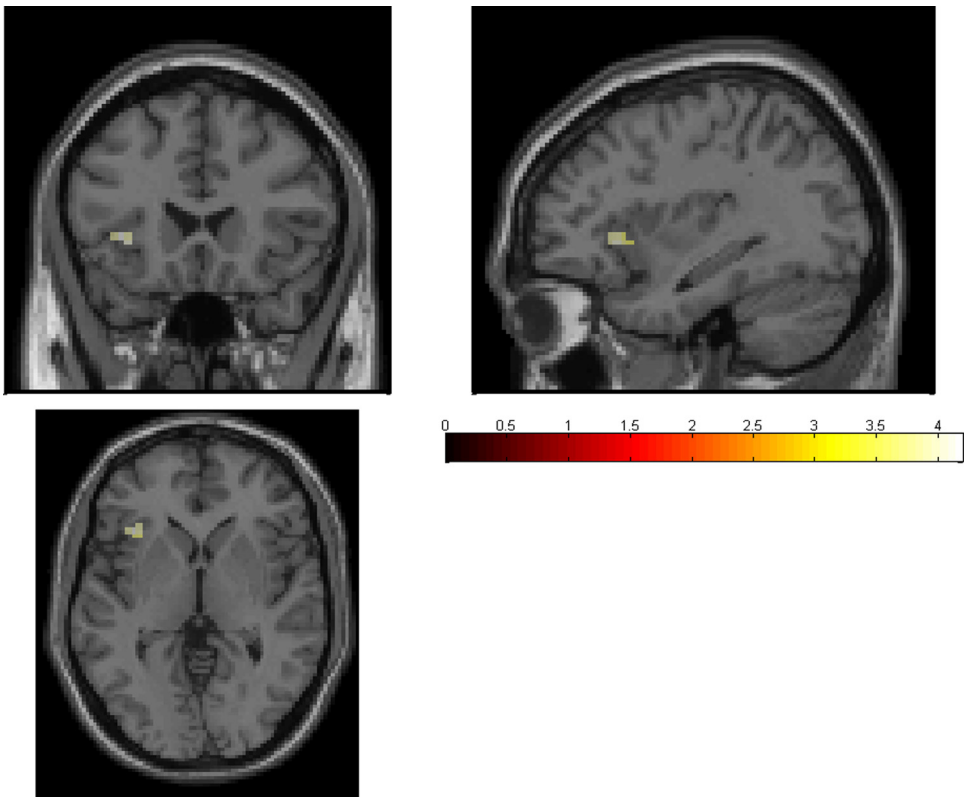

Figure 3 During the last week of the treatment cycle COC users had lower reactivity in the left insula than placebo users (Tailarach coordinates: −33, 22, −17, cluster size: 21 voxels). Brighter colors indicate higher T-scores. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

accompanied by altered reactivity in the emotion circuit of the brain especially in the right amygdala and left insula.

Even though 4–10% of COC users complain of adverse mood (Ernst et al., 2002; Kelly et al., 2010), drug-related causality has not been established. Previous placebo-controlled COC trials in healthy women have not been able to demonstrate any differences in depressed mood between COC and placebo, presumably because the majority of women remain unaffected (Leeton et al., 1978; Graham et al., 1995; O'Connell et al., 2007). This study is the first to establish that a levonorgestrel-containing COC, in fact, is associated with mood worsening. Even so, although the present study specifically included women with previous history of COC-induced mood deterioration, only one third of these susceptible women experienced a clear-cut mood worsening during COC use. Further large-scale placebo-controlled studies are needed to investigate the true estimates of drug-related mood worsening in healthy never-users.

No differences in amygdala reactivity were evident between groups during the pretreatment or treatment cycles. However, a decrease in right amygdala reactivity was observed in placebo users between the pretreatment and treatment cycles, whereas this decrease was absent in the COC treated women. This finding may suggest decreased habituation to emotional stimuli in COC users. Previous studies have suggested that the right amygdala rapidly habituates to emotional stimuli in general (Fischer et al., 2000) and to facial displays in particular (Breiter et al., 1996; Fischer et al., 2003; Milad et al., 2006). We have previously shown that amygdala habituation between scanning sessions is affected by menstrual cycle phase, and that the habituation effect is more pronounced if the first exposure is scheduled during the follicular phase, as was the case in the present study (Gingnell et al., 2012). Hypothetically, if COC use slows habituation in the amygdala, this could result in higher vigilance to emotional stimuli, which ultimately could lead to mood deterioration. An alternative explanation is that the decreased amygdala reactivity in placebo users was a result of normal hormonal fluctuations of the menstrual cycle, which in that case, would be disrupted in COC users. Unfortunately, in order not to compromise blinding, the present study design is unable to confirm in which cycle phase placebo users were at the time of their second scanning. For this reason, it is difficult to compare the results of placebo users with previous studies addressing amygdala reactivity across the menstrual cycle. Nevertheless, most longitudinal studies in healthy women suggest higher amygdala reactivity to emotional stimuli in the late luteal phase compared to the follicular phase (Andreano and Cahill, 2010; Ossewaarde et al., 2010; Gingnell et al., 2012). Further studies to elucidate the role of amygdala reactivity in COC users could benefit from more sophisticated designs, for instance by adding gonadotropin releasing agonist treatment to the placebo and COC regimens.

COC users also displayed reduced left insula reactivity in comparison with placebo users. It has been suggested that increased insula activation may underlie some depressive and anxious states (Mitterschiffthaler et al., 2003; Simmons et al., 2006; Stein et al., 2007; Strigo et al., 2008), and insula plays an important role in anticipation of aversive

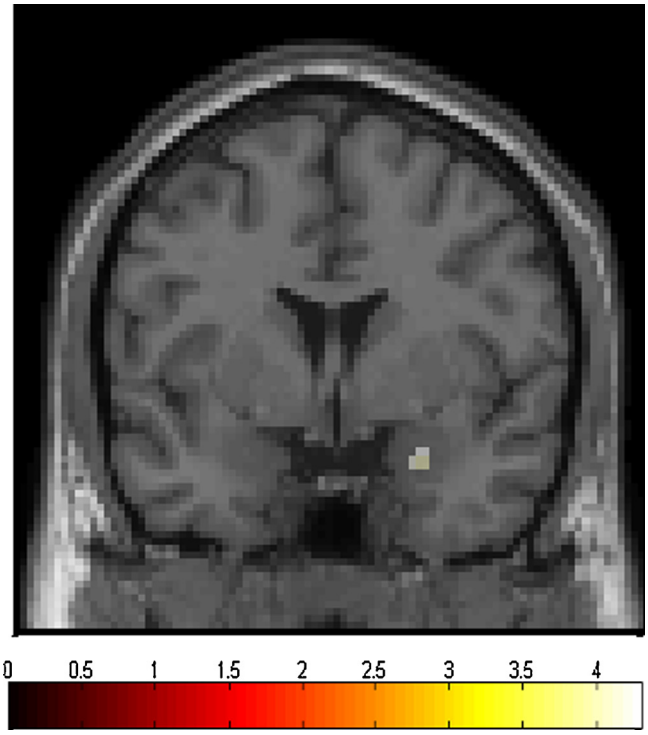

Figure 4 Compared to the pretreatment cycle, women randomized to placebo had lower right amygdala reactivity during last week of treatment (Tailarach coordinates: 27, 1, −17, cluster size: 4 voxels). Brighter colors indicate higher T-scores. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

stimuli across several modalities (Paulus and Stein, 2010). However, the left insula, specifically, may also be activated by positive emotional feelings (Bartels and Zeki, 2004; Leibenluft et al., 2004; Johnstone et al., 2006; Jabbi et al., 2007; Takahashi et al., 2008). Given the relatively subtle changes in mood in our non-depressed COC users, the decreased left insular cortex reactivity could hypothetically reflect lower reactivity in areas that otherwise are responsive to positive or salient emotional stimuli. The robustness of the decreased left insula reactivity in COC users is strengthened by the fact that this finding remained in the smaller fraction of women who actually displayed a clear-cut COC-induced mood worsening during the trial. The notion that COC might reduce positive affectivity is further strengthened by a cross-sectional study by Jarva and Oinonen (2007), where COC users had reduced positive affective reactivity compared to non-users. Alternative explanations include the possibility that the insular findings relate to the physical aspects of COC use, reflecting alterations in physiological homeostasis. The insula is involved in introception (including a range of sensations of relevance for COC use such as pain (Vincent et al., 2011), hunger, muscular and visceral sensations (Craig, 2002) and maintenance of physiological homeostasis (Sanfey et al., 2003)). COCs inhibit endogenous hormonal fluctuations and an array of physical symptoms related to the menstrual cycle, including mastalgia and dysmenorrhea. COC use could thus be expected to reduce the need for introceptive vigilance for physical symptoms in the insula and thereby perhaps also reducing insula reactivity to external stimuli. However, the first treatment cycle on COCs is in fact known to be associated with increased reporting of physical symptoms, which also turned out to be the case in this study. For this reason, it is more likely that the decreased left insula reactivity is associated with the reported increased mood symptoms and emotional processing rather than a reduction of introspective reactivity to physical symptoms.

Apart from the left insula, the ROI analyses also revealed a decreased reactivity in the left middle frontal gyrus, and bilateral inferior frontal gyri among COC users. The inferior frontal gyrus is involved in a number of functions important for social interaction, including speech processing, verbal language production, empathy, and emotional distraction (Wang et al., 2008; Liakakis et al., 2011). Although the relevance of decreased reactivity in the inferior frontal gyri during COC treatment remains to be clarified in terms of mood alterations, the decreased reactivity during hormonal exposure in the inferior frontal gyri is in accordance with previous studies, using cognitive (Craig et al., 2007, 2008) as well as emotional tasks (Andreano and Cahill, 2010; Shafir et al., 2012), across various hormonal states or treatments.

There are a number of limitations that should be considered for the interpretation of our findings. First, this study included women with a history of prior adverse mood symptoms from COC and may not be generalized to all women starting COC treatment. The women in our study were bound to have negative expectations of treatment, which may have influenced the results. However, this bias was balanced by the frequency of women who correctly guessed their treatment in the active treatment and placebo groups. It is thus plausible that COC given to never-users or users without previous negative experiences would result in no alterations in brain activation, although this remains to be proven. Another limitation of the study is that information of previous psychiatric disorders is lacking. Previous depression has been associated with mood worsening during COC use (Joffe et al., 2003), and the current study could have shed some light on the drug-related causality of this association. Preferably, also both fMRI scans should have been performed in the same menstrual cycle, and, scanning sessions in placebo users should have been scheduled according to menstrual cycle phase using LH-assays in order to fully determine the contribution of ovarian steroid fluctuations in this group. However, any measurement of mid-cycle luteinizing hormone-surge in participating women or continuation of the study into the next cycle would have compromised blinding of the study. It should also be noted that the sample size was limited, at least for comparison of emotional symptoms, and that clinical trials on oral contraceptives normally report increased frequency of side effects during the first cycles of treatment. Possibly, a longer study period would have resulted in an attenuation of side effects in the treatment group. Finally, as a number of studies have indicated that the most intense side effects are reported during the pill-free interval (Sulak et al., 2000; Kelly et al., 2010), supposedly due to hormone withdrawal, it is also possible that more distinct findings could have been obtained if women had been assessed during this time interval.

In conclusion, women with subjective reports of previous COC-induced mood deterioration may experience a worsening of depressive symptoms and mood swings when re-exposed to

COC. Furthermore, COC use may affect insula and inferior frontal gyri reactivity and retard amygdala habituation, at least in the sub group of women who previously have experienced mood related side effects. These findings are of relevance for the understanding of how COCs influence mood. Placebo-controlled fMRI studies in COC sensitive women could be of relevance for future testing of adverse mood effects of new oral contraceptives.

Contributions

M. Gingnell, J. Wikstrom, M. Fredrikson and I. Sundstrom-Poromaa designed the study. M. Gingnell, J. Engman and L. Moby performed data collection. M. Gingnell, J. Engman, A. Frick, M. Fredrikson and I. Sundstrom-Poromaa undertook the statistical analyses. All authors contributed to and have approved the final manuscript.

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Conflicts of interest

I. Sundstrom-Poromaa serve occasionally on advisory boards or act as invited speaker at scientific meetings for MSD, Bayer Health Care, and Lundbeck A/S. None of the other authors have conflicts of interest to report.

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