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No pills, more skills: The adverse effect of hormonal contraceptive use on exposure therapy benefit

Friederike Raeder[a], Franziska Heidemann[a], Manfred Schedlowski[b], Jürgen Margraf[a], Armin Zlomuzica[a,*]

[a] Ruhr University, Faculty of Psychology, Mental Health Research and Treatment Center, Bochum, Germany
[b] Institute of Medical Psychology and Behavioral Immunobiology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

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ABSTRACT

Hormonal contraceptive use can aggravate existing symptoms of anxiety and depression and influence the response to pharmacologic treatment. The impact of hormonal contraceptive use on non-pharmacological treatment efficacy in anxiety disorders is less well explored. Oral contraceptives, which suppress endogenous sex hormone secretion, can alter fear extinction learning. Fear extinction is considered the laboratory proxy of exposure therapy in anxiety disorders. This study set out to examine whether oral contraceptive use is related to exposure-based treatment response in specific phobia. We recruited spider-phobic women (n = 28) using oral contraceptives (OC) and free-cycling women (n = 26, No-OC). All participants were subjected to an identical in-vivo exposure. Exposure-based symptom improvement was assessed with several behavioral and subjective indices at pre-treatment, post-treatment and six-weeks follow-up. No–OC women showed higher pre-exposure fear levels on the FSQ and SPQ. OC women showed slightly less pronounced exposure benefit compared to their free-cycling counterparts (No-OC woman) as reflected by lower levels of fear reduction from pre-treatment to follow-up on the subjective level. After correction for multiple testing, OC and No-OC women showed differences in self-report measures (SPQ, FAS and SBQ) from pre- to follow-up treatment but not from pre-to post-treatment. These findings implicate that oral contraceptive use can account for differential exposure-based fear symptom improvement. Our study highlights the importance of monitoring and managing hormonal contraceptives use in the context of non-pharmacological exposure-based interventions.

1. Introduction

Anxiety disorders belong to the most frequent mental diseases (Kessler et al., 2005). There is a clear gender difference in the prevalence of anxiety disorders, with women being affected about twice as likely as men (Regier et al., 1990; Kessler et al., 2005; Bandelow and Domschke, 2015) and showing a greater illness burden (McLean et al., 2011). However, great fluctuations in the course of illness and symptom severity exist in women with anxiety disorders (Pigott, 2003; McLean et al., 2011), especially during critical phases which are associated with major hormonal changes such as puberty and menopause (Vesga-Lopez et al., 2008; Hickey et al., 2012; Hoyt and Falconi, 2015). In addition to physiological and neurological factors, which may account for developmental changes in anxiety and depression in women (Donner and Lowry, 2013), the rather unsystematic use of hormonal contraceptives can aggravate existing psychopathological symptoms in women (Hall et al., 2015). Ideally, psychopharmacological treatment options should therefore be tailored according to gender-specific changes in brain and behavior throughout the lifespan (Wise et al., 2008; Bolea-Alamanac et al., 2018). Likewise, hormonal contraceptive use can limit the effectiveness of psychotropic drugs in anxiety and depression (Jensvold et al., 1996; Hall et al., 2015; Berry-Bibee et al., 2016) which requires a systematic management of contraception in combination with pharmacological treatment (Hall et al., 2015).

The possible interaction of hormonal contraceptive use and psychological treatment response received much less attention. This is surprising given the great wealth of evidence for an association between circulating sex hormones, hormonal contraceptive use and cognitive and emotional behavior (Andreano and Cahill, 2009; Donner and Lowry, 2013; Pletzer and Kerschbaum, 2014). The modulating role of oral contraceptives and naturally occurring changes in estrogen on emotional learning in women is of special clinical relevance (Nielsen et al., 2011, 2013; Glover et al., 2015; Maeng and Milad, 2015; Merz et al., 2018). Considerable evidence from human and animal studies

* Corresponding author. Mental Health Research and Treatment Center, Ruhr University Bochum, Massenbergstr. 9-13, 44787, Bochum, Germany.
E-mail address: armin.zlomuzica@rub.de (A. Zlomuzica).

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suggests that estrogen mediates the amount and rate of fear extinction learning and its later recall (Milad et al., 2009; Glover et al., 2015; Maeng and Milad, 2015). Oral contraceptives may interfere with these processes due to suppressing endogenous estrogen secretion, thus leading to impaired fear extinction (Graham and Milad, 2013; Cover et al., 2014; Hwang et al., 2015; Maeng and Milad, 2015; Merz et al., 2018).

Since extinction is believed to be the underlying process for exposure therapy (Graham and Milad, 2011; Vervliet et al., 2013; Craske et al., 2018), considering the impact of sex-specific hormonal levels and hormonal contraceptive use in the context of exposure treatment efficacy seems highly relevant but is insufficiently studied (see also Glover et al., 2015). To our knowledge, only one recent study exists showing an association between hormonal status, OC use and exposure therapy outcome (Graham et al., 2018). Replication of findings and further investigation of possible associations between hormonal contraceptive use and differential therapy outcome measures would be valuable. In the present study, we analyzed the effect of hormonal contraceptive use on immediate and long-term effects of exposure treatment in medication free spider-phobic women. Free-cycling women and women using hormonal contraceptives were subjected to two sessions of exposure training. Therapy efficacy as a function of hormonal contraceptives usage was assessed by using an extended set of phobic-related questionnaires and a behavioral assessment.

2. Material and methods

2.1. Participants

Participants were recruited via bulletin board notices at the campus of the Ruhr-University Bochum as well as via announcements in social media networks. The exclusion criteria covered any neurological condition, the abuse of alcohol and drugs as well as the use of high-dose medication. Only participants who had no other current comorbid diagnoses that were considered more severe than spider phobia were included. The final sample encompassed 54 spider-phobic women with a mean age of 24.1 years. The assessment of spider phobia (according to DSM-IV-TR) was undertaken by a trained interviewer by means of the short diagnostic interview for mental disorders (Mini-DIPS; Margraf, 1994). Our sample was divided into two subgroups: Women who took oral contraceptive agents (OC-Group, $n = 28$) and women who took no oral contraceptive agents (No–OC–Group, $n = 26$). Women in the OC group were taking a combined monophasic pill, which included a range of varying types and doses of estradiol and progestin. All of these compounds included Ethinylestradiol in a varying range from 0.02 to 0.03 mg. Progestin encompassed either desogestrel (0.15 mg), levonogestrel (0.1–0.15 mg), dienogest (2 mg), drospirenon (3 mg), or chlormadinin acetat (2 mg). We excluded women who were taking a single-agent progestogen pill ($n = 3$) and one woman who used the arm implant implanon, since we wanted to assess the potential effect of one type of oral conceptive use (i.e., combined monophasic compounds) which could potentially be different to single-agent progestin and non-oral contraceptives, due to their differential mechanisms of action.

All experimental procedures were approved by the local ethics committee of the Ruhr-University and carried out in accordance with the Declaration of Helsinki. All participants provided written informed consent and could receive six course credits if applicable for their participation.

2.2. Exposure training

All participants received exposure training, which covered two sessions including 60 min of guided exposure. The procedure was based on a modified version of the protocol by Öst (1997), involving a hierarchy of 14 steps with increasing difficulty (for a detailed description, see Preusser et al., 2017). Each step was first demonstrated by the experimenter and then practiced by the participant. Fear levels (SUDs) were collected at the beginning of each step. Each of the steps lasted until the participants' SUDS had decreased to a fear level of 30 or below. When this point of fear reduction was reached, the next step was initiated by the experimenter. First, the steps of the hierarchy were accomplished with a vibrating spider (Pholcidae, 1 cm). Second, they were repeated with a house spider (*Tegenaria domestica*, 1 cm). Each exposure session was terminated when either 60 min had elapsed or all steps had been successfully completed with both spiders.

2.3. Assessments

Control variables and diagnostic interview. To control for differences in depression, anxiety and stress, the Depression Anxiety Stress Scales (DASS; cf. Zlomuzica et al., 2016) were applied. Each participant was also screened with the Mini-DIPS (Margraf, 1994), to ensure the presence of spider phobia.

Spider fear-related questionnaires. German versions of the Spider Phobia Questionnaire (SPQ; Hamm, 2006) the Fear of Spiders Questionnaire (FSQ; Rinck et al., 2002) and the Spider Phobia Beliefs Questionnaire (SBQ; Pössel and Hautzinger, 2003) were used to measure fear of spiders. On each questionnaire, higher scores indicate greater fear of spiders.

Behavioral Approach Test (BAT). The BAT was used to measure fear and avoidance of a house spider (i.e., the same spider that was used for the exposure session), which was placed in a plastic container at the far end of the room. Participants were instructed to approach the spider as fast and close as possible until their fear becomes intolerable. The BATs were scored on a scale from 0 (= refused to enter the room) to 10 (= touched the spider with the bare fingertip).

Subjective Units of Distress Scale (SUDS). During the exposure session, the Subjective Units of Distress Scale (SUDS; Wolpe, 1973) served as the primary fear measure. Scores on this scale range from 0 (= no fear) to 100 (= excessive fear).

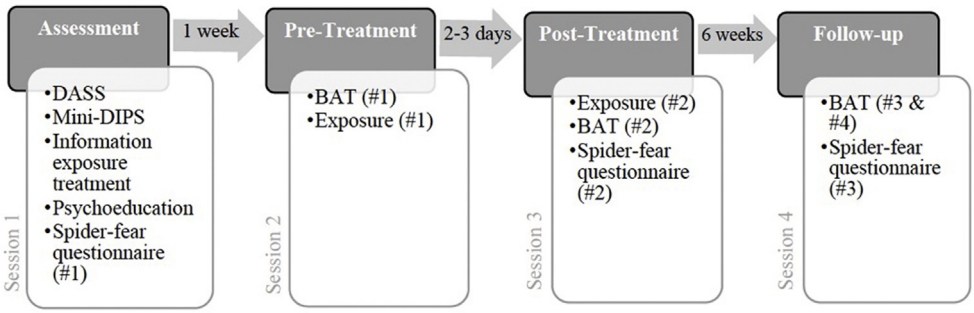

Fig. 1. Illustration of the experimental design across all sessions. DASS: Depression Anxiety Stress Scales. BAT: Behavioral Approach Test.

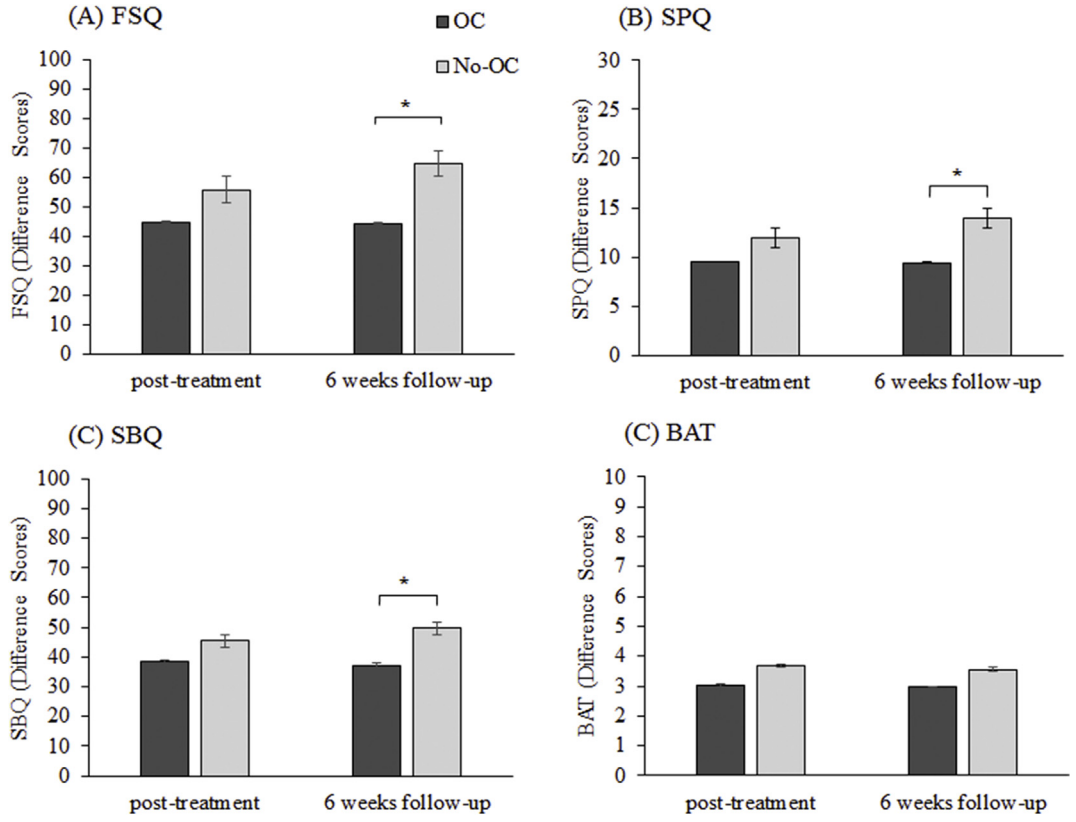

Fig. 2. Improvements across all outcome measures: a) FSQ Score, b) SPQ Score, c) SBQ Score, and d) the behavioral approach test (BAT) from pre-treatment to post-treatment, as well as from pre-treatment to the six weeks follow-up in both groups (OC women vs. No-OC women). Data is represented as mean difference scores. The error bars reflect one standard error of the mean. *p < .05.

2.4. Experimental design and procedure

The complete study involved four appointments (see Fig. 1). Session 1 involved the Mini-DIPS, completion of the DASS scales as well as the spider-fear related questionnaires (#1). They further received psychoeducation on spider phobia and information about the exposure-training. Session 2 was conducted approximately 1 week later. In this session, the BAT was explained and participants received information on the SUDs scale. Following these explanations, the first BAT (#1) was applied. The next step involved the completion of the first exposure session. Session 3, which involved the second exposure session, took place around 2–3 days later. After the exposure treatment and a short rehearsal of BAT instructions, participants engaged in the BAT (#2) and filled in the second round of spider-fear related questionnaires (#2). The last session, session 4, comprised the follow-up assessment was conducted 6 weeks later. In this follow-up, the last BAT (#3) was conducted. At the end of the final session, the spider-fear related questionnaires (#3) were completed again and participants received a full debriefing.

2.5. Statistical analyses

All data was analyzed in SPSS version 25 for Windows (Armonk, NY: IBM Corp.). We assessed whether exposure-induced improvement on outcome measures of therapeutic success (i.e., scores on the FSQ, SPQ, SBQ, as well as BAT outcome) differed in OC vs. No-OC women using a series of mixed ANOVAs. Due to drop-out, data at follow-up comprised only a total of 48 participants. Dropout rates were comparable in both subgroups (OC-Group, $n = 4$; No–OC–Group, $n = 5$). Changes from pre-treatment to post-treatment and pre-treatment to follow-up were analyzed separately by single 2 x 2 mixed ANOVAs. For these analyses, *time* (pretreatment vs. posttreatment; pretreatment vs. follow-up) was entered as within-subjects factor and *group* (OC vs. No-OC) as a between subjects factor. We further computed the same set of analyses with age as a covariate to assess for potential effects of age (i.e., 2x2 mixed ANCOVA). To control for potential pretreatment differences, we conducted additional univariate ANCOVAS with *group* (OC vs. No-OC), and *time* (posttreatment; follow-up) and *pretreatment score* as a covariate. We additionally applied Bonferroni correction to control for multiple testing on the questionnaires. Therefore, results regarding the questionnaires were considered significant at $p < .016$.

3. Results

3.1. Participant characteristics and control variables

Groups were comparable in terms of depression, anxiety and stress-tension levels (Depression: OC: $M = 3.54$, $SD = 4.33$; No-OC: $M = 2.48$, $SD = 4.19$; Anxiety: OC: $M = 3.21$, $SD = 3.32$; No-OC: $M = 3.33$, $SD = 3.62$, Stress: OC: $M = 5.70$, $SD = 4.09$, No-OC: $M = 7.81$, $SD = 5.46$; all $t(52) < 1.75$, $p > .09$). Furthermore, no significant group differences were evident on the level of self-reported fear on the SBQ ($t(52) = 1.85$, $p = .07$), or during the behavioral approach test (BAT score ($t(52) = -1.10$, $p = .28$) at pre-exposure. However, pre-exposure levels differed slightly on the FSQ ($t(52) = 2.12$, $p = .04$) and SPQ ($t(52) = 2.18$, $p = .03$), with higher fear levels in the No–OC–Group (No-OC: FSQ, $M = 81.23$, $SEM = 3.21$; SPQ, $M = 21,69$, $SEM = .74$; OC: FSQ, $M = 71.67$, $SEM = 3.14$; SPQ, $M = 19.5$, $SEM = .68$). Additionally, we observed a difference in age between OC using and No-OC using women ($t(52) = 3.671$; $p < .01$), with OC using women ($M = 21.8$, $SD = 2.53$) being younger than No-OC using women ($M = 26.6$, $SD = 6.5$).

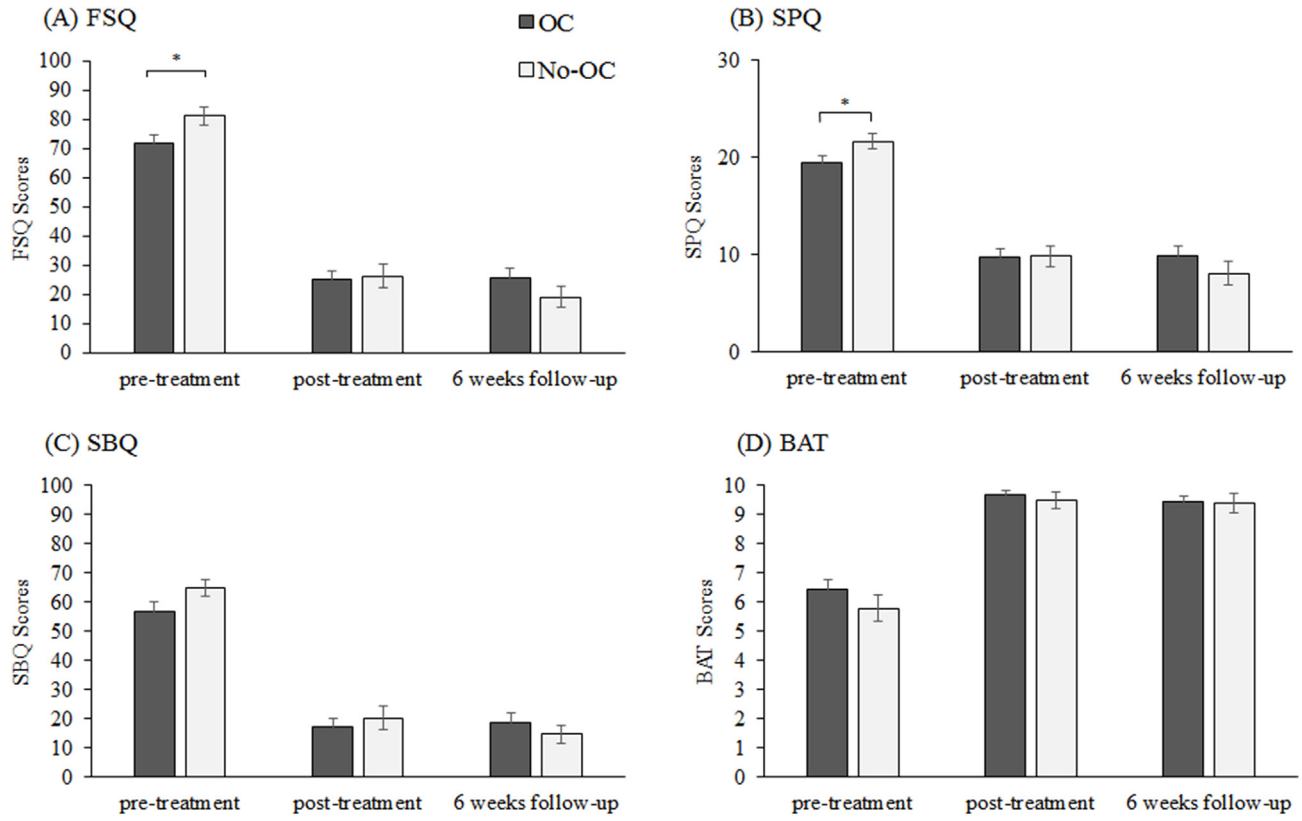

Fig. 3. Raw scores across all outcome measures a) FSQ Score, b) SPQ Score, c) SBQ Score, and d) the behavioral approach test (BAT) on all three assessment points for OC-women and No–OC–women. The error bars reflect one standard error of the mean. *p < .05.

3.2. Treatment outcome measures

With regard to exposure duration and the amount of exposure steps completed by the participants, we did not observe a difference between the OC and No-OC group (*exposure duration*: $t(52) = -0.860$, $p = .39$, *exposure steps*: $t(52) = .686$, $p = .49$). The mean exposure duration in the OC-Group was 106.36 min ($SD = 25.21$) and 100.32 min ($SD = 25.87$) in the No–OC–Group. In the OC-Group, the mean exposure steps reached were 11.18 steps ($SD = 4.07$) and 11.88 steps ($SD = 3.27$) in the No–OC–Group.

Exposure-induced changes from pre-treatment to post-treatment. The results are displayed in Figs. 2 and 3. As indicated by a significant main effect for time on each assessment outcome, exposure proved to be highly effective in reducing subjective fear scores and promoting approach behavior from pre- to posttreatment (FSQ: $F(1,52) = 365.22$, $p = .000$, $\eta_p2 = .877$; SPQ: $F(1,52) = 380.04$, $p = .000$, $\eta_p2 = .882$; SBQ: $F(1,52) = 337.57$, $p = .00$, $\eta_p2 = .869$; BAT: $F(1,52) = 175.15$, $p = .000$, $\eta_p2 = .774$). Additionally, no significant main effect for group was found on all outcome measures (FSQ: $F(1,52) = 2.15$, $p = .15$, $\eta_p2 = .040$; SPQ: $F(1,52) = 1.32$, $p = .26$, $\eta_p2 = .025$; SBQ: $F(1,52) = 2.30$, $p = .14$, $\eta_p2 = .043$; BAT: $F(1,52) = 1.17$, $p = .28$, $\eta_p2 = .022$). We did not observe an interaction effect for group and time on all measures, considering that the Bonferroni corrected significance level of $p < .016$ was applied on the questionnaires (FSQ: $F(1,52) = 3.05$, $p = .08$, $\eta_p2 = .056$; SPQ ($F(1,52) = 4.21$, $p = .04$, $\eta_p2 = .025$; SBQ: $F(1,52) = 1.58$, $p = .21$, $\eta_p2 = .043$; BAT: $F(1,52) = .67$, $p = .41$, $\eta_p2 = .022$). Using the factor age as a covariate did not alter the results. Across all measures (i.e., FAS, SPQ, SBQ and BAT) we found a significant effect of time ($Fs(1,52) > 7.72$, $ps < .008$, $\eta_p2 > .161$), but no effects for age ($Fs(1,52) > .60$, $ps > .37$, $\eta_p2 < .016$.), group ($Fs(1,52) > .32$, $ps > .09$, $\eta_p2 < .055$) or for the interaction terms ($Fs(1,52) > .28$, $ps > .09$, $\eta_p2 < .056$).

Results of our additional univariate ANCOVA, to assess for the effects without the potentially confounding influence of pretreatment differences, also indicated no difference in posttreatment scores between both groups on the FAS ($F(1,52) = .381$, $p = .540$, $\eta_p2 = .008$), the SPQ ($F(1,52) = 2.197$, $p = .145$, $\eta_p2 = .042$), the SBQ ($F(1,52) = .117$, $p = .734$, $\eta_p2 = .002$), and the BAT ($F(1,52) = .026$, $p = .872$, $\eta_p2 = .001$).

Exposure-induced changes from pre-treatment to six weeks follow-up. Six weeks follow-up data was only available for only $N = 45$ subjects (OC: $N = 24$; No-OC: $N = 21$). Results on the FSQ indicated a significant main effect for time ($F(1,43) = 368.14$, $p = .000$, $\eta_p2 = .895$) as well as an interaction effect for group ($F(1,43) = 11.64$, $p = .001$, $\eta_p2 = .213$). The same pattern of findings was found for changes in SPQ scores, with a significant main effect for time ($F(1,43) = 274.34$, $p = .000$, $\eta_p2 = .862$) and an interaction with group ($F(1,43) = 11.05$, $p = .002$, $\eta_p2 = .201$). Similarly, a significant main effect of time ($F(1,43) = 354.83$, $p = .000$, $\eta_p2 = .892$) and a significant group x time interaction ($F(1,43) = 7.64$, $p = .008$, $\eta_p2 = .151$) was found for the SBQ. Similar to the comparison between pre- and post-measures, we found a significant main effect for time on the BAT ($F(1,43) = 135.31$, $p = .000$, $\eta_p2 = .755$), but no interaction ($F(1,43) = 0.54$, $p = .47$, $\eta_p2 = .012$). Subsequent simple effect analyses for each interaction only indicated a difference between the OC-Group and the No–OC–Group on the pre-test for the FSQ $F(1,43) = 7.414$, $p = .009$, $\eta_p2 = .147$) and the SPQ ($F(1,43) = 7.34$, $p = .010$, $\eta_p2 = .143$), but not on the SBQ ($F(1,43) = 3.67$, $p = .062$, $\eta_p2 = .079$) and the BAT ($F(1,43) = .55$, $p = .464$, $\eta_p2 = .012$). We conducted additional gain score analyses which indicated a stronger reduction of fear on the FSQ in the No–OC–Group ($M = -64.52$, $SEM = 4.17$) than in the OC-Group ($M = -45.04$, $SEM = 3.90$; ($F(1,43) = 11.64$, $p = .001$, $\eta_p2 = .213$). The same results were evident for the SPQ (No-OC: $M = -14.0$, $SEM = 1.04$, OC: $M = -9.32$, $SEM = .95$, $F(1,43) = 11.05$, $p = .002$, $\eta_p2 = .201$) and the SBQ (No-OC: $M = -49.64$, $SEM = 3.36$, OC: $M = -36.94$, $SEM = 3.14$, F

(1,43) = 7.64, p = .008, $\eta_p 2$ = .151). On the BAT, we did not observe a difference in the gain scores between both groups (No-OC: M = 3.55, SEM = .41, OC: M = 3.13, SEM = .39, F(1,43) = .54, p = .467, $\eta_p 2$ = .012).

Moreover, no significant main effect for group was found on all outcome measures (FSQ: F(1,43) = .65, p = .42, $\eta_p 2$ = .015; SPQ: F(1,43) = .24, p = .63, $\eta_p 2$ = .005; SBQ: F(1,43) = .34, p = .56, $\eta_p 2$ = .008; BAT: F(1,43) = .54, p = .67, $\eta_p 2$ = .012). In sum, while the main effects for time display a significant long-term reduction in fear and approach distance after exposure, we were able to observe a stronger reduction of fear for the No-OC group in comparison to women who take OC. As for the previous analyses, we entered age as a covariate in our design and performed the same analyses as a mixed ANCOVA. These subsequent analyses demonstrated no influence of age (Fs (1,43) > .02, ps > .36, $\eta_p 2$ < .019). Across all questionnaires (i.e., FAS, SPQ, and SBQ) we found a significant time x group interaction effect (Fs(1,43) > 5.82, ps < .020, $\eta_p 2$ > .127). Across all measures (including the BAT), we did not find any other significant effects (Fs (1,54) > .04, ps > .39, $\eta_p 2$ < .028).

The outcomes of our additional univariate ANCOVA, were mainly supportive for our previous outcomes at a p = .05 significance level. We observed significant differences between OC and No-OC women on the FAS and the SPQ, only marginally nonsignificant differences on the SBQ and definitely insignificant differences on the BAT (FAS (F (1,43) = 4.504, p = .040, $\eta_p 2$ = .097); SPQ (F(1,43) = 7.613, p = .008, $\eta_p 2$ = .150); SBQ (F(1,43) = 3.831, p = .057, $\eta_p 2$ = .084); BAT (F(1,43) = .045, p = .833, $\eta_p 2$ = .001).

4. Discussion

The main finding of the present study was a slightly less pronounced reduction in subjective indices of fear after exposure in OC women relative to No-OC women, indicating that women taking oral contraceptives tend to profit less from exposure therapy relative to women who do not use oral contraceptives. While we observed a general reduction of fear from pre- to post-treatment, a significant difference between both groups was shown at 6 weeks follow-up. This pattern of findings was consistently shown across different subjective measures (displayed by stronger reductions in SPQ, FSQ and SBQ scores in the No-OC group from pre-treatment to 6-weeks-follow-up). However, the effect was not found on the behavioral level (evidenced by changes in BAT scores).

OC use can have profound effects on emotional functions such as fear and stress (Montoya and Bos, 2017). Much of these effects can be attributed to estrogen, the main gonadal hormone. The ovarian production of estrogens and progesterone is inhibited by oral contraceptives. Women using contraceptives thus exhibit reduced levels of circulating estrogens and progesterone. The administration of OC in rats impairs fear extinction recall, with this deficit being ameliorated by terminating OC treatment or by administering estrogen-receptor agonists before fear extinction (Graham and Milad, 2013). Corresponding deficits in fear extinction recall were demonstrated in women using OC when compared with naturally cycling women (Graham and Milad, 2013). Deficient fear extinction learning in women using OCs has been attributed to altered neuronal activations of brain regions underlying fear extinction (Merz et al., 2012; Hwang et al., 2015). Extinction is analogous to exposure therapy in anxiety disorders (Graham and Milad, 2011; Vervliet et al., 2013; Craske et al., 2018). Thus, although this has not been assessed in this study and the interpretation is purely speculative at this stage, OC women might exhibit deficient fear extinction (Graham and Milad, 2013) which in turn might account for the less pronounced symptom reduction after exposure relative to No-OC women. This hypothesis was discussed in a recent review (Merz et al., 2018). Future studies need to determine whether decreases in circulating levels of estradiol indeed contribute to differences in extinction and exposure therapy benefit between women with OC and No-OC women.

In a similar recent study Graham et al. (2018) demonstrated an association between endogenous estradiol, hormonal contraceptive use, and exposure therapy outcome in spider phobic women. Our findings are partially in line with these observations. Most importantly, both studies provide compelling evidence of altered fear extinction as a function of OC use in the therapy setting. In extension to the findings by Graham et al. (2018), we showed that the effects of hormonal contraceptive use on exposure induced symptom improvement can be consistently found across three self-report instruments for measuring spider fear. The latter is important because not all self-report instruments are equally sensitive to detect therapeutic changes as they further differ in certain aspects. For instance, we used both the SPQ and the FSQ (but see Graham et al., 2018), which provides a more detailed picture on possible therapy-induced changes in fear in the non-phobic range (Szymanski and O'Donohue, 1995; Muris and Merckelbach, 1996). The FSQ can be used to detect changes in different domains of subjective spider fear (i.e., fear of harm; Muris and Merckelbach, 1996). The additional use of the SBQ is valuable to assess the extent of possible therapy related changes in negative, irrational ideas about the spider (Arntz et al., 1993). Modification of threat beliefs regarding spiders is crucial in changing the response to phobic stimuli (Thorpe and Salkovskis, 1997). Interestingly, the consistent interaction effects with group on all three measures suggests that exposure was highly effective in reducing both, subjective fear and irrational misconceptions about spiders at follow-up, with more pronounced effects in free-cycling women.

It is noteworthy that the No–OC–Group showed higher pre-exposure fear levels on the FSQ and SPQ. To our knowledge, the effects of hormonal contraceptives on symptom severity in patients with anxiety disorders has not been examined systematically so far. Thus, at this moment, it can only be speculated how oral contraceptives and estrogen levels might affect anxiety levels in clinical populations and how this effect is further modulated during behavioral treatment. In this instance, accumulated evidence from basic research suggests that estrogens can excert both anxiogenic and anxiolytic effects in humans and rodents which might differ on the subtype of estrogen receptor utilized (Borrow and Handa, 2017).

Some differences between our and the Graham et al. study warrant further consideration. We did not observe group differences at the behavioral level, i.e., during the BAT which is in contrast to the findings by Graham et al. (2018). The latter might simply reflect a ceiling effect since we used two sessions of a highly effective exposure therapy protocol. In support of this conclusion, the majority of participants in this study succeeded to master the highest level of the BAT at post-treatment and follow-up (OC-Group: 82.1%, No–OC–Group: 80.8%). This was the case irrespective of whether they use hormonal contraceptives or not. Notably, scores on the FSQ and SPQ highly correlate with behavioral indices of spider fear during the BAT (Muris and Merckelbach, 1996). Thus, the interpretation that exposure efficacy in OC and No-OC women differs across different outcome measures seems rather unlikely. However, a desynchrony of therapy effects between OC and No-OC women cannot be fully excluded (see Raeder et al., 2019). Furthermore, the use of a six weeks follow-up (versus a 12 weeks follow-up in the Graham et al. study) might have been too short to detect differences on the behavioral level. However, it remains to be noted that a direct comparison to the study by Graham et al. is not possible since we used a slightly different sample (medication free participants without comorbid phobias), different treatment outcome measures (FSQ, SBQ and SPQ in addition to a modified BAT) and a different treatment protocol (two sessions of exposure with a six week follow-up).

Strengths of our study involve the inclusion of medication free, treatment-seeking individuals with marked and clinically significant fear of spiders. Other strengths are the use of a highly standardized therapy protocol without further cognitive interventions and the use of different therapy outcome measures providing a more detailed picture

on the effects of OC use on therapy benefit. A major limitation of our study is the absence of direct measures of serum estradiol and progesterone levels. Interestingly, Graham et al. (2018) did obtain single serum measurements of estradiol and progesterone, and related the impairments in exposure therapy to the reduction in estradiol in OC women. For example, participants using hormonal contraceptives who displayed the lowest estradiol in the sample also showed the least improvement. The implementation of such measures, i.e. ideally the assessment of relative hormonal levels via repeated assays in addition to a rigorous menstrual cycle assessment, would be valuable to derive a complete understanding on the role of estrogens in exposure therapy benefit. In addition, information on endogenous changes in estrogen levels over the course of the menstrual cycle in its interaction with OC use is lacking which should be considered in future studies.

Nevertheless, our study further extends and replicates emerging findings on the important role of OC in fear extinction to the exposure therapy setting. Exposure is the most effective treatment option for different anxiety disorders (Hofmann and Smits, 2008). While the underlying therapy mechanisms are assumed to be comparable for all anxiety disorders, it still remains to be explored whether our findings can be generalized to other kinds of anxiety disorders and different types of exposure therapy. Since the effects of OC on extinction might be temporary (Graham and Milad, 2013), clinical studies investigating the association between OC use and long term benefit of exposure therapy (Raeder et al., 2019) and/or generalization of exposure therapy benefit (Preusser et al., 2017; Raeder et al., 2019) would be valuable. Finally, there is a need for more mechanistic studies to further dissect the effects of hormonal status (as moderated by OC use) on fear conditioning processes in spider-phobic individuals (cf. Mosig et al., 2014).

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.09.016.

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