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The not-so-bitter pill: Effects of combined oral contraceptives on peripheral physiological indicators of emotional reactivity

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ABSTRACT

Combined oral contraceptives (COC) are used by millions of women worldwide. Although findings are not entirely consistent, COC have been found to impact on brain function and, thus, to modulate affective processes. Here, we investigated electro-physiological responses to emotional stimuli in free cycling women in both the early follicular and late luteal phase as well as in COC users. Skin conductance response (SCR), startle reflex, corrugator and zygomaticus activity were assessed. COC users showed reduced overall startle magnitude and SCR amplitude, but heightened overall zygomaticus activity, although effect sizes were small. Thus, COC users displayed reduced physiological reactions indicating negative affect and enhanced physiological responses signifying positive affect. In free cycling women, endogenous 17β-estradiol levels were associated with fear potentiated startle in both cycle phases as well as with SCR and zygomaticus activity during the follicular phase. Testosterone was associated with corrugator and zygomaticus activity during the luteal phase, while progesterone levels correlated with corrugator activity in the follicular phase. To the contrary, in COC users, endogenous hormones were not associated with electro-physiological measures. The results further underscore the importance of considering COC use in psychophysiological studies on emotional processing.

1. Introduction

Combined oral contraceptives (COC) constitute a safe and convenient contraceptive method for millions of women worldwide with generally very high user satisfaction (Skouby, 2010). COC contain synthetic progesterone and estrogen analogues and are the most frequently prescribed type of hormonal contraceptives (Burkman et al., 2011; Christin-Maitre, 2013). Diverse types of progestins are used in COC with varying pharmacological properties, including different (anti-)androgenic effects depending on their respective parent molecule (Sitruk-Ware, 2004). Most modern COC contain ethinyl estradiol (EE) as estrogen component. EE dosage has been substantially decreased compared to earlier formulations due to the development of new progestins (Christin-Maitre, 2013). Low dosage COC with ≤35 mcg EE are now standard (Bitzer and Simon, 2011). Reductions in dosage also resulted in calls for a redesign of the conventional 28-day regimen (21 days active/7 days placebo; Sulak, 2008). Shortening or eliminating the pill-free interval has been suggested to reduce hormone withdrawal symptoms and intermenstrual side effects (Burkman et al., 2011).

Aside from controlling reproduction, COC impact on additional physiological systems. Adverse health effects have been comprehensively researched and resulted in the development of new COC formulations (Burkman et al., 2011). With confirmation of estrogen receptor (ER; Osterlund et al., 2000a; Osterlund et al., 2000b) and progesterone receptor (PR; Kato et al., 1994) expression in several brain regions, there is also increasing interest in the potential impact of COC on cognitive and affective processes. Still, Warren et al. (2014) concluded in a recent review that with regard to cognition, evidence of COC's effect is still inconsistent and indecisive with studies involving widely varying methods.

Regarding emotion, negative affective symptoms like mood swings, depression, and irritability have been reported by a minority of COC users with varying frequencies (Joffe et al., 2003; Kelly et al., 2010; Oddens, 1999). Recently, findings on COC and adverse mood symptoms were summarized in a review (Sundström-Poromaa and Segebladh, 2012). The authors emphasized that due to the lack of placebo-controlled trials precise estimates are at this point not available. However, if present at all, adverse symptoms appear to manifest more often during the pill-free interval (see also Sulak, 2008). Furthermore, COC with an androgenic progestin component (e.g., levonorgestrel) produced more negative effects on mood and emotional well-being than COC containing anti-androgenic progestins (e.g., drospirenone or dienogest; Sundström-Poromaa and Segebladh, 2012). Nevertheless, recent

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findings also stress that the majority of COC users do not experience overall decreases in mood (Böttcher et al., 2012; Duke et al., 2007; Toffol et al., 2012) with some studies also reporting beneficial effects (Cheslack-Postava et al., 2015; Oinonen and Mazmanian, 2002; Svendal et al., 2012).

Although the majority of COC users do not report mood worsening, subtle effects of COC on affective processing have been found in a number of paradigms. COC use has been linked to worse performance in detecting negative emotional facial expressions (Hamstra et al., 2014), although others found no difference to free cycling women (Radke and Derntl, 2016). Further research indicated that the association between COC use and emotion recognition might be moderated by genetic variance in the mineralocorticoid receptor gene (Hamstra et al., 2015). Emotional memory has been suggested to be impacted by COC use in interaction with stress hormones (Nielsen et al., 2011; Nielsen et al., 2013). Research on fear conditioning revealed a more easily acquired conditioned eye-blink response (Beck et al., 2008) and poorer extinction recall in COC users (Graham and Milad, 2013).

Recently, effects of COC use have been investigated with structural and functional neuroimaging. Differences in gray (Pletzer et al., 2010) and white matter (De Bondt et al., 2013) between COC users and free cycling women were found. A longitudinal study reported decreased gray matter volume in the left amygdala and the anterior parahippocampal gyrus after three months of COC use (Lisofsky et al., 2016). In addition, differential effects depending on androgenic versus anti-androgenic COC progestin compounds have been reported (Pletzer et al., 2015). COC use has also been linked to changes in resting state functional connectivity in the default mode network and a network associated with execute control (Petersen et al., 2014). Furthermore, COC users presented with reduced cortical thickness in the lateral orbitofrontal cortex and the posterior cingulate cortex, i.e., in regions implicated in responses to rewards and the evaluation of internal as well as external stimuli (Petersen et al., 2015). The authors report that the effect was mainly driven by women in the follicular phase (Petersen et al., 2015). Women with a history of past COC-related mood problems showed depressive symptoms and mood swings upon re-exposure to COCs in a double-blind placebo-controlled study. Their affective symptoms were paralleled by distinct activation in several emotion processing brain regions, particularly the right amygdala and the left insula (Gingnell et al., 2013).

Results from neuroimaging studies employing emotional paradigms vary. COC users showed decreased bilateral amygdala responses to negative emotional stimuli compared to free cycling women (Petersen and Cahill, 2015). During fear extinction learning, activation patterns in amygdala, thalamus, anterior cingulate, and ventromedial prefrontal cortex revealed more marked CS+/CS− differentiations in COC users compared to free cycling women while there were no differences during fear acquisition (Merz et al., 2012). However, another study reported generally higher activation of insular and cingulate cortices, amygdala, hippocampus, and hypothalamus in free cycling women with high estradiol levels compared to COC users during fear conditioning, late extinction learning, and early extinction recall (Hwang et al., 2015). Available fMRI findings on estrogen and progesterone effects on emotional and cognitive processing in free cycling women and COC users have been recently reviewed. Differential effects on several brain regions, i.e., amygdala, insula, anterior cingulate gyrus, and the inferior frontal cortex were found, albeit no consistent pattern emerged (Toffoletto et al., 2014).

In sum, despite ongoing research confirming a role for gonadal steroids in cognition and emotion, open questions remain. Moreover, differences in the affective paradigms employed and the physiological measures used to index affective responses render conclusions on the impact of COC on affective processing difficult. In the present study, we used an acoustic startle paradigm and examined a number of physiological responses in parallel. Women using COC were compared to free cycling women regarding skin conductance response (SCR), acoustic startle responses as well as the activity of corrugator supercilii and zygomaticus major, all of which have long been implemented in research on affect and emotion and continue to be widely used. Alterations in eccrine sweat gland activity are the cause of changes in skin conductance (Boucsein, 2012; Figner and Murphy, 2011). SCR is sympathetically regulated with several central neural structures exerting influence: (a) the hypothalamus and limbic system, (b) cortical regions and basal ganglia, and (c) the reticular formation in the brainstem (Boucsein, 2012). The first of these pathways is the one mostly involved in generating SCR to affective stimuli (Boucsein, 2012). SCR characteristically shows a latency of 1–3 s, a comparatively steep rise resulting in a short peak which is followed by a slower return to baseline (Figner and Murphy, 2011). SCR magnitudes reflect arousal rather than valence values of affective stimuli (Bradley et al., 2001).

Processing of affective material usually results in differential activity of facial muscles depending on stimulus valence. Unpleasant stimuli enhances *corrugator supercilii* activity while pleasant stimuli induce more marked activity in the *zygomaticus major* (review: Bradley et al., 2001) which are usually assessed via electro-myographic (EMG) recordings. Facial expressions in response to affective stimuli are facilitated by an underlying neural circuit including projections from the amygdala to the facial motor nucleus (Davis, 2000).

Finally, the startle reflex comprises a set of very fast reactions in response to unexpected and intense stimuli. It includes muscle contractions, the eye-blink reflex, heart rate acceleration and a stop of current actions (Koch, 1999). In human studies, the startle reflex is commonly assessed via EMG over the *orbicularis oculi* and sudden high-intensity noise bursts are most frequently used as startling stimuli (Blumenthal et al., 2005). The presentation of the latter reliably produces the acoustic startle reflex (ASR) whose modulation has been used for decades in various research settings (Grillon and Baas, 2003). Generally, ASR increases in the presence of additional unpleasant stimuli (fear potentiated startle; FPS) and decreases when pleasant ones are presented (pleasure attenuated startle; PAS; Davis, 2006; Koch, 1999). ASR modulation in humans is often facilitated with emotional images (Blumenthal et al., 2005). The ASR depends on a neural circuit comprising sensory receptors, the auditory nerve, the cochlear nucleus, the ventrolateral lemniscus, the nucleus reticularis pontis caudalis (PnC), and spinal motoneurons, while ASR modulation further involves the amygdala (Davis, 2006; Koch, 1999).

As outlined above, experimental findings on the impact of COC use on emotional reactivity so far are somewhat mixed. However, based on the absence of general negative affective symptoms in most COC users (Böttcher et al., 2012; Duke et al., 2007; Toffol et al., 2012) and their less pronounced response to negative stimuli at least in some studies (Hamstra et al., 2014; Hwang et al., 2015; Petersen and Cahill, 2015) we predict less marked responses indicative of negative affect in COC users.

2. Methods

2.1. Participants

Participants originally consisted of 74 female students of the Technische Universität Dresden. They were recruited during classes, via flyers on campus or through online information. All participants underwent a telephone screening to assess physical and mental health before partaking in the study. To be included, participants had to have normal or corrected to normal vision. Also, they should not have been diagnosed with hearing disorders in the past, should not have current hearing problems of any kind and no past or recent exposure to extremely loud noises. Reported current psychological problems were another exclusion criterion as were past diagnoses of psychological disorders. No severe physical impairment or illness (e.g., cardio-vascular diseases, diseases of the respiratory tract, liver diseases, diseases of