Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Brain Research

Research Report

Hormonal contraceptives masculinize brain activation patterns in the absence of behavioral changes in two numerical tasks

Belinda Pletzer[a,b,c,*], Martin Kronbichler[b,c,d], Hans-Christoph Nuerk[e,f], Hubert Kerschbaum[a,c]

[a]Department of Cell Biology, University of Salzburg, Austria
[b]Department of Psychology, University of Salzburg, Austria
[c]Center for Neurocognitive Research, Salzburg, Austria
[d]Neuroscience Institute, Christian Doppler Clinic, Paracelsus Medical University, Salzburg, Austria
[e]Department of Psychology, University of Tuebingen, Germany
[f]IWM-KMRC, Knowledge Media Research Center, Tuebingen, Germany

ARTICLE INFO

Article history:
Accepted 5 November 2013
Available online 11 November 2013

Keywords:
Number processing
Hormonal contraceptives
Synthetic steroids
Sex hormones
fMRI

ABSTRACT

The aim of the present study was to identify, whether and how oral hormonal contraceptives (OCs) alter women's number processing. Behavioral performance and brain activation patterns (BOLD-response) of 14 OC-users were evaluated during two distinct numerical tasks (number comparison, number bisection) and compared to 16 men (high testosterone), and 16 naturally cycling women, once during their follicular (low hormone levels) and once during their luteal cycle phase (high progesterone). For both tasks, reliable sex differences and menstrual cycle dependent modulation have previously been described. If progestogenic effects of the synthetic progestins contained in OC play a predominant role, OC-users should be comparable to luteal women. If androgenic effects of the synthetic steroids exert the progestogenic actions, OC-users should be comparable to men. Likewise, if neither of the above are the case, the reduction of endogenous steroids by OCs should make OC-users comparable to follicular women. Our findings suggest that OC-users resemble follicular women in their behavioral performance, but show male-like brain activation patterns during both tasks. Analysis of brain–behavior relationships suggests that OC-users differ from naturally cycling women in the way they recruit their neural resources to deal with challenges of the tasks. We conclude that OCs, which are used by 100 million women worldwide, may have profound effects on cognition that have not been recognized so far.

*Corresponding author at: Department of Psychology, Paris-Lodron University Salzburg, Hellbrunnerstrasse 34, A-5020 Salzburg, Austria. Fax: +43 662 8044 5126.
E-mail address: Belinda.Pletzer@sbg.ac.at (B. Pletzer).

0006-8993/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.brainres.2013.11.007

1. Introduction

Accumulating evidence shows that endogenous hormonal fluctuations, as observed during the menstrual cycle, affect a variety of behaviors and cognitive abilities in women. For example, women score lower on spatial tasks, but higher on verbal tasks, when estrogen plasma levels are high, like in the late follicular (2–3 days pre-ovulation) and subsequent luteal phase compared to the menstrual and early follicular phase, when estrogen and progesterone plasma levels are low (Hampson, 1990; Hausmann et al., 2000; McCormick and Teillon, 2001; Rosenberg and Park, 2002; Mordecai et al., 2008; Otero Dadín et al., 2009). These behavioral variations have been linked to cyclic changes in brain structure (Protopopescu et al., 2008; Pletzer et al., 2010) and function (Dietrich et al., 2001; Fernandez et al., 2003; Schoning et al., 2007; Craig et al., 2008; Konrad et al., 2008; Weis et al., 2008, 2010).

However, although the hormonal contraceptive pill – a means to controlling endogenous hormone fluctuations – is on the market for over 50 years now and used by 100 million women worldwide, little attention has been paid to how the contained synthetic steroids affect cognitive abilities and even less to their modulation of the related brain activation patterns.

The most commonly used hormonal contraceptive is the combined oral contraceptive pill (OC), which typically contains 0.02–0.04 mg ethinylestradiol and varying levels of heterogenous synthetic progestins. *Levonorgestrel*, derived from 19-nortestosterone, belongs to the so called second generation progestins and is still widely used, not only in combined OCs, but also in subdermal implants, intra-uterine devices and hormone replacement therapy. *Desogestrel, gestoden, dienogest* and *norgestimat* are so called third generation progestins, also derived from 19-nortestosterone. *Drospirenone* is a so called "new" progestin (fourth generation progestin), derived from spirolactone. These progestins and their metabolites differ in their binding affinity to steroid receptors, their transactivational activity on these receptors, their binding affinity to the sex hormone binding globuline, their effect on the enzymes relevant to the synthesis of endogenous steroids and their impact on blood glucose levels and the lipid profile (e.g. Sitruk-Ware, 2006).

It seems plausible that these synthetic progestins feminize the brain due to their actions on progesterone receptors. Also the reduction of endogenous testosterone levels in OC-users (e.g. Jung-Hoffman and Kuhl, 1987; Graham et al., 2007; Hietala et al., 2007) may contribute to feminizing effects of OC. On the contrary, synthetic progestins may via a 2-fold mechanism also exert androgenic effects, thereby masculinizing the brain. First, many synthetic progestins are derived from testosterone and able to activate androgen receptors (Sitruk-Ware, 2006; Wiegratz and Kuhl, 2006). Binding affinity to the androgen receptor and transactivational activity are the lower, the higher the generation of progestin. Nevertheless, some metabolites of 19-nortestosterone derived progestins are able to activate androgen receptors (Perez-Palacios et al., 1992). Importantly however, OC lead to a reduction of endogenous estradiol and progesterone levels (e.g. Sahlberg et al., 1987), thereby facilitating the conversion of testosterone into the physiologically more active dihydrotestosterone (Wright et al., 1983). Additionally, a variety of masculinizing effects in the brain are thought to be promoted by estrogen receptors following the local conversion of testosterone to estrogen via the enzyme aromatase (Roselli, 2007). Consequently, estrogenic actions of the ethinylestradiol compound may contribute to possible masculinizing effects of OC on the brain.

Evidence for behavioral differences between oral contraceptive (OC) users and non-users comes from a small number of solitary studies scattered over several decades and different countries (Sheldrake and Cormack, 1976; Garrett and Elder, 1984; Wright and Badia,1999; Kuhlmann and Wolf, 2005; Mordecai et al., 2008; Wharton et al., 2008; Nielsen et al., 2011).

Although sparse, these studies provide support for both feminizing and masculinizing effects of OC on behavioral performance. On the one hand OC users show increased verbal memory (Mordecai et al., 2008), increased recognition working memory during sleep deprivation (Wright and Badia,1999), a lack of memory impairment due to cortisol (Kuhlmann and Wolf, 2005) and better dream recall (Sheldrake and Cormack, 1976) compared to non-users. On the other hand, verbal reaction times are slower (Garrett and Elder, 1984) and mental rotation performance is enhanced in OC users compared to non-users (Wright and Badia,1999; Wharton et al., 2008). Wharton et al. (2008) nicely demonstrated that mental rotation performance does not only correlate with hormonal contraceptive use, but also with the androgenicity of the progestin component . Users of drospirenone-containing contraceptives performed worse on the mental rotation task than non-users. Furthermore, OC users perform like men in an emotional memory paradigm (Nielsen et al., 2011).

Even less is known about how OC affect the neural correlates of behavior, i.e. brain activation, and brain–behavior relationships. We recently demonstrated for the first time a profound difference in brain structure between hormonal contraceptive users and non-users (Pletzer et al., 2010) and to our knowledge, there are only two functional imaging studies, directly comparing brain activation patterns between oral contraceptive users and naturally cycling women during cognitive tasks (Rumberg et al., 2010; Marecková et al., 2012). During verb generation, oral contraceptive users do not differ from men in their brain activation patterns, but from naturally cycling women during both cycle phases (Rumberg et al., 2010). During face processing, oral contraceptive users show increased activation of the fusiform face area, compared to naturally cycling women (Marecková et al., 2012).

In the present study we seek to differentiate androgenic, progestogenic and endogenous hormone reduction effects of OCs on behavior and brain activation during number processing, by comparing OC-users separately to men (high testosterone), women during their follicular phase (low hormones) and women during their luteal phase (high progesterone). We aim to demonstrate the universality of these effects across two numerical tasks and several task modulations, for which we have recently demonstrated reliable sex differences and menstrual cycle dependent modulation in behavioral performance and brain activation patterns (Pletzer et al., 2011, 2013). In a number comparison task participants had to