NeuroImage 134 (2016) 597–606

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Hormonal contraceptive use is associated with neural and affective changes in healthy young women☆

Nina Lisofsky [a,b,*], Michaela Riediger [a], Jürgen Gallinat [b], Ulman Lindenberger [a,c], Simone Kühn [a,b]

[a] Center for Lifespan Psychology, Max Planck Institute for Human Development, Berlin, Germany
[b] Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Germany
[c] European University Institute, San Domenico di Fiesole, Italy

ARTICLE INFO

Article history:
Received 16 December 2015
Revised 13 April 2016
Accepted 18 April 2016
Available online 19 April 2016

Keywords:
Hormonal contraceptives
Amygdala
Affect
sMRI
Emotion regulation
Functional connectivity

ABSTRACT

Previous neuroimaging research has demonstrated that female gonadal hormones can alter the structure and function of adult women's brains. So far, we do not know how hormonal contraceptives affect female brain structure, in part because within-person longitudinal observations are lacking. Here, we compared 28 young women before and after three months of regular contraceptive intake with 28 naturally cycling women of comparable age. The goal was to explore within-person neural change in women using contraceptives. Neuroimaging, hormonal, cognitive, and affect data were collected at two time points for each participant. A voxel-wise whole-brain comparison of both groups revealed decreased gray matter volume in the left amygdala/anterior parahippocampal gyrus in women using contraceptives as compared to the control group. Resting-state functional connectivity of this region with the dorsolateral prefrontal cortex changed from positive to negative connectivity following contraceptive intake whereas the opposite held for the control group. An exploratory analysis revealed that gray matter volume in the left amygdala/anterior parahippocampal gyrus was associated with positive affect at the second time point. There were no systematic differences in cognitive performance change between the groups. These findings provide initial insights into effects of hormonal contraceptives on the human brain and expand previous findings on hormone-related amygdala/hippocampal complex plasticity. The affected brain regions may be related to psychological wellbeing, underlining the importance of future studies on contraceptive-induced brain changes.

1. Introduction

Hormonal contraceptives are the most common contraceptive method in the Western world (Johnson et al., 2013; United Nations, 2015). To give one example, about one third of adult women in Germany use hormonal contraceptive pills (hereafter also “the pill”), with higher proportions found at younger ages (Federal Centre for Health Education (BZgA), 2011; in a sample in the US, 17% of women aged 15–44 years used the pill, with higher proportions at younger ages: Jones et al., 2012). During the natural menstrual cycle, female gonadal hormones (estrogen and progesterone) change in a regular temporal pattern enabling fertility. Hormonal contraceptives suppress ovulation by modifying the natural fluctuation of gonadal hormones. Given that a growing body of literature indicates that female gonadal hormones have the potential to alter the human adult brain (Comasco et al., 2014; De Bondt et al., 2013; Lisofsky et al., 2015a; Toffoletto et al., 2014), the question arises whether hormonal contraceptives might also change the brain.

Despite a growing literature on effects of hormones on brain plasticity, we know surprisingly little about the ways in which hormonal contraceptives affect their users' brain structure. To our knowledge, there are no longitudinal studies investigating structural brain changes in women following intake of the pill. Some cross-sectional studies compared gray matter volume of women using hormonal contraceptives with that of non-users, yielding inconsistent results (De Bondt et al., 2013; Petersen et al., 2015; Pletzer et al., 2010; Pletzer et al., 2015). In light of potential pre-existing differences between contraceptive-users and non-users, it is not known whether findings obtained in studies with a between-person design will parallel observations based on within-person changes following use of hormonal contraceptives (Oinonen et al., 2008; Raz et al., 2005). Moreover, the studies that have been conducted so far reported effects of contraceptives after relatively long and habitual exposure to contraceptives (mostly over years). Data on more immediate within-person neural changes are lacking.

To the best of our knowledge, only two neuroimaging studies have assessed women before and after exposure to hormonal contraceptives,

☆ Nina Lisofsky was a pre-doctoral fellow of the International Max Planck Research School on the Life Course (LIFE, www.imprs-life.mpg.de; participating institutions: Max Planck Insitute for Human Development, Freie Universität Berlin, Humboldt-Universität zu Berlin, University of Michigan, University of Virginia, University of Zurich).

* Corresponding author at: MPI for Human Development, Lentzeallee 94, 14195 Berlin, Germany.
E-mail address: Lisofsky@mpib-berlin.mpg.de (N. Lisofsky).

http://dx.doi.org/10.1016/j.neuroimage.2016.04.042
1053-8119/

albeit with a focus on functional rather than on structural brain alterations. Both studies used a randomized placebo-controlled design to test differences in brain activity before and after 21 days of hormonal contraceptive intake (Gingnell et al., 2013, 2015). One of the studies applied a cognitive control paradigm and revealed that contraceptive intake had only little effect on brain reactivity during response inhibition (Gingnell et al., 2015). The other study used an emotional face matching task and observed reduced activity in insular and frontal regions in the contraceptive group and reduced activity in the amygdala in the placebo group following treatment (Gingnell et al., 2013). The latter study only included women who had reported previous negative mood effects following hormonal contraceptive use, which limits the generalizability of the results. Nevertheless, the findings add to research showing altered amygdala responses in naturally cycling women after a single progesterone dose (Van Wingen et al., 2008). Altered amygdala reactivity potentially underlies mood changes that have been discussed as relatively common side-effects of hormonal contraception leading to its discontinuation (Rosenberg and Waugh, 1998).

Longitudinal and cross-sectional studies assessing contraception-related mood changes have yielded inconsistent results. The use of hormonal contraceptives was found to be associated with increases, decreases or no overall change in negative affect (Gingnell et al., 2013; Jarva and Oinonen, 2007; O'Connell et al., 2007; Oinonen and Mazmanian, 2002; Ott et al., 2008; Rosenberg and Waugh, 1998; Shahnazi et al., 2014; Svendal et al., 2012). It is unclear whether the inconsistency of findings reflects actual differences between women in their mood-related responses to hormonal contraceptives, or whether they are due to differences in study design or pill types (Pletzer and Kerschbaum, 2014). Potential associations of mood changes and brain structural changes induced by hormonal contraceptives have not yet been investigated.

We conducted a longitudinal magnetic resonance imaging (MRI) study including an age-matched control group with the aim to investigate (1) structural brain alterations following three months of hormonal contraceptive intake in healthy young women, (2) brain function (i.e., resting-state functional connectivity) of regions showing structural alterations in women using hormonal contraceptives, (3) affective changes in women starting to use contraceptives and potential associations with structural brain changes, and (4) the impact of hormonal contraception on cognitive performance. This study part followed up on previous inconsistent findings regarding cognitive functioning in relation to hormonal contraception (Gogos et al., 2014; Warren et al., 2014).

This study focused on the group-by-time interaction in gray matter volume in a whole brain analysis. In previous work, amygdala function was found to be especially sensitive to endogenous as well as exogenous hormonal variation in women (Lisofsky et al., 2015b; Petersen and Cahill, 2015; Van Wingen et al., 2008). Also, altered amygdala activity and amygdala volume were found to correlate in clinical populations (e.g., Kalmar et al., 2009; Siegle et al., 2003). Hence, we hypothesized that amygdala volume and potentially functional connectivity would perhaps also be altered in women using hormonal contraceptives. Based on previous indications of affective changes in women taking contraceptives (e.g., Gingnell et al., 2013), we speculated that three months of contraceptive use might also have an impact on positive and/or negative affect.

2. Materials and methods

2.1. Participants

Women planning to start hormonal contraceptive (the pill) use were recruited via flyers in local gynecologists' practices. Healthy women aged 16 to 35 were included in the study. Exclusion criteria were: The use of hormonal contraceptives within a period of six months prior to the study phase, previous pregnancy beyond 8 weeks of gestation, hormonal disorders, MR incompatibility, or a history of psychiatric or neurological illness (based on self-report). For participants under the age of 18, written informed consent was obtained from their parents. The study was conducted according to the Declaration of Helsinki, with approval from the Ethics Committee of the German Society for Psychology. Thirty-one women were included in the "pill group." Three participants dropped out before the second measurement time point (one women could not be recontacted and two women did not have time to take part again). Therefore, the final sample consisted of 28 participants in the pill group (mean age 21.25 years, range 16–33 years. Twenty-eight young women of similar age who were not taking hormonal contraceptives were enrolled as a control group (mean age 21.5 years, range 16–28 years). The same exclusion criteria applied to the participants in the control group. Sample characteristics for both groups are shown in Table 1.

2.2. Overview of design and procedure

The study design is depicted in Fig. 1. All women participated in two measurement occasions: time point 1 (T1) and time point 2 (T2). The timing of test sessions in relation to the participants' menstrual cycle is described in detail below. For participants in the pill group, T1 took place before they started use of hormonal contraceptives. T2 was scheduled in the pill-free week of the third pill cycle (each pill cycle consisted of three weeks continuous daily pill use and one pill-free week, lasting about one month). The rationale for scheduling the second measurement occasion in the pill-free week was to ensure that potential differences in brain structure are not solely driven by acute effects of the last pill intake. For participants in the control group, T2 was scheduled approximately three months after T1. At each time point, cognitive, psychological, and neuroimaging data were acquired in two test sessions. In the cognitive test session, participants carried out a number of computer-based cognitive tasks (see below) and completed the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988). Throughout the cognitive test session, three saliva samples were provided by the participants. Measurement sessions took place in the morning (starting before noon between 8:00 and 12:00 am), unless this was impossible to schedule for the participants. In the MRI session, participants were measured in the scanner and completed the PANAS again. For most participants (38 of 56 participants), the cognitive and MRI sessions were scheduled on two separate days (median number of days between the two measurement sessions: 1, interquartile range: 2, in four occasions the two sessions had to take place in different cycles, keeping cycle phase constant). If two separate measurement sessions were not possible due to a participant's time constraints, the cognitive and MRI sessions were scheduled one after another on the same day, keeping their order constant across participants.

2.3. Sample description and timing of measurement waves

For all naturally cycling women (participants in the pill group at T1 as well as participants in the control group at T1 and T2), measurements were scheduled in the early follicular phase (day 1–10 after begin of menses, mean cycle day: 5.6 (±3.3)). For women in the pill group

Table 1
Sample characteristics.

Variable	Pill group	Control group
Age (in years)	21.25 (±4.02)	21.5 (±2.82)
Years of education	14.31 (±3.2)	14.68 (±2.46)
Participants who ever used HC	15	20
Previous HC use (in months)	43.79 (±55.8, median = 29)	43.95 (±32.9, median = 39)

HC = hormonal contraceptives; "Previous HC use" for women who had ever used hormonal contraceptives.