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Highlights

- We measured cognition and PPI in men and in women during different hormonal stages
- Women using the contraceptive pill or women during the high hormone stage outperformed men on cognition
- Different hormonal states in women had little effect on baseline PPI

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**Natural and synthetic sex hormones: effects on
higher-order cognitive function and prepulse inhibition**

Running title: Contraceptive pill effects on cognition and prepulse inhibition

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ABSTRACT

Little is known about the effects of the commonly-used oral contraceptive pill (OC) on cognition. This study compared matched healthy women across the menstrual cycle (early-follicular ‘Low E/P’, mid-luteal ‘High E/P’), women using the combined OC, and men. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was used to assess immediate and delayed memory, visuospatial ability, language and attention. Assessment of prepulse inhibition (PPI) included 21 pulse-alone trials (115 dB) and 42 prepulse-pulse trials (74, 78, 86 dB). The OC and High E/P groups outperformed men on the total RBANS score, an overall measure of cognition. For the immediate memory/learning and attention domains, the OC group outperformed men; for the delayed memory domain, the OC and High E/P groups outperformed men. In conclusion, high levels of natural or synthetic sex hormones had a positive effect on higher-order cognition but had little effect on baseline PPI.

KEYWORDS: oral contraceptive pill (OC); PPI; RBANS; menstrual cycle; gender differences; female; male; estrogen; progesterone; cognition

INTRODUCTION

Estrogens and progestins are groups of sex steroid hormones predominantly found in women, but are also found in smaller concentrations in men. During the menstrual cycle, there are two peaks of estrogen secretion, one just before ovulation and a smaller peak during the mid-luteal phase. Progesterone levels remain low during the follicular phase and there is one peak in its secretion during the mid-luteal phase (Ganong, 1979; Ross and Vande Wiele, 1974). Synthetic estrogens and progestins are used in preparations such as the commonly-used combined oral contraceptive pill (OC). Among young Australian women the OC is the most popular contraceptive method, with 76% of women having ever used it and 45% of 20-24 year olds currently using it (Yusuf and Siedlecky, 2007).

Sex hormones have a number of non-reproductive effects; of interest here are their effects on cognitive function. Women have been found to perform better on verbal and memory tests and poorer on spatial ability tests during the high estrogen/progesterone phase of the menstrual cycle (Hampson, 1990; Maki et al., 2002; Rosenberg and Park, 2002; Sherwin, 2012). A number of studies have examined the effects of hormone replacement therapy on cognition in post-menopausal women (LeBlanc et al., 2001; Maki and Sundermann, 2009; Zec and Trivedi, 2002). Overall, it is suggested that estrogen has a small positive effect on cognition, particularly verbal memory (Joffe et al., 2006; Sherwin, 2012; Zec and Trivedi, 2002), however the positive effect may depend on the cognitive domain (Bayer and Hausmann, 2009), type of estrogen (Maki and Sundermann, 2009) and the time period when the estrogen was administered (Craig and Murphy, 2010; Maki, 2006; Sherwin, 2012). Less is known about the effect of estrogen administration in healthy, pre-menopausal women or of the effect of the OC on cognition. OC users showed enhanced verbal memory during the

active pill phase compared to the inactive pill phase, while naturally cycling women showed no change across the menstrual cycle (Mordecai et al., 2008). Other studies showed that OC use improved spatial attention (Cicinelli et al., 2011) but had no effect on recognition memory (Wharton et al., 2008). On the other hand, mental rotation task performance is dependent on the type of progestin used in the OC (Griksiene and Ruksenas, 2011), whereby highly androgenic OCs improved performance (Wharton et al., 2008). The present study measured various domains of cognitive function, including memory, attention, language and visuospatial ability, in OC users and non-users.

Prepulse inhibition (PPI) is a measure of sensorimotor gating or information processing. It is proposed to reflect a normal protective mechanism in the brain that filters irrelevant sensory, motor or cognitive information, thus allowing for coherent thought (Braff and Geyer, 1990). Deficits in gating incoming information may result in information overload and misinterpretation of stimuli (Braff et al., 2001). There is an extensive literature describing how PPI is disrupted in schizophrenia (Braff et al., 2001), and other illnesses including bipolar disorder (Gogos et al., 2009), suggesting that PPI deficits are the result of abnormalities within a specific brain circuit rather than a specific psychopathology (Swerdlow et al., 2001).

A limited number of studies have recently examined PPI in sex hormone affected states, such as during the menstrual cycle, pregnancy and premenstrual dysphoric disorder (Kask et al., 2008a; Kask et al., 2008b; Kumari et al., 2010). For example, women have the greatest PPI during the early follicular (low estrogen/progesterone) phase of the menstrual cycle (Jovanovic et al., 2004; Kumari et al., 2010; Swerdlow et al., 1997). Kask and colleagues (2008a) found that women had lower PPI during late pregnancy, a time of high circulating

1 levels of estrogen and progesterone, compared to the postpartum period when these hormone
2 levels decline (Kask et al., 2008a). Further, lower levels of PPI were found in cycling women
3 compared with post-menopausal women (Bannbers et al., 2010), where menopause is a time
4 of dramatic decline of sex hormone levels. These studies suggest that sex steroid hormones,
5 such as estrogen, play a role in modulating PPI, whereby high levels of estrogen may reduce
6 PPI. We previously showed that estrogen treatment reversed drug-induced disruptions of PPI
7 in healthy women and in female rats (Gogos et al., 2010b; Gogos et al., 2006; Gogos and Van
8 den Buuse, 2004), and suggested that the dopaminergic system is involved in mediating the
9 effects of estrogen on PPI (Chavez et al., 2010; Gogos et al., 2010b). Little is known about
10 the effects of the OC on PPI. One study found that women with adverse mood-related side-
11 effects from the OC had lower levels of PPI, compared to women with no adverse effects of
12 the OC (Borgstrom et al., 2008). This study did not, however, statistically compare PPI in
13 OC users with naturally cycling women or with men; this will be examined in the present
14 study.

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36 Although millions of women worldwide either currently or have previously used OCs
37 (Burkman et al., 2011), surprisingly little is known about their effects on the brain. This
38 study aimed to examine the effects of natural and synthetic sex hormones on cognitive
39 function, particularly higher-order cognition and PPI. Healthy, pre-menopausal women who
40 were either currently using the OC or were naturally cycling (follicular or mid-luteal phase),
41 and healthy men, were tested.

METHODS

Participants

The present study tested 60 healthy participants (45F:15M) aged between 20-43 years (see Table 1 for demographic information). All participants were recruited from the local community via advertisements and word-of-mouth. The procedures described in this study were approved by the Mental Health Research and Ethics Committee (Melbourne Health, VIC, Australia) and participants gave their written, informed consent prior to testing.

Participants were excluded if they reported a history of brain trauma, neurological illness, concurrent substance abuse, irregular menstrual cycles, were pregnant or breastfeeding, or had an estimated full-scale verbal IQ<80 as indicated by the National Adult Reading Test (Nelson, 1982). Participants were free from psychiatric illness (self-reported and screened for current symptoms using the Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 1993)) and excluded if they had a first degree relative with schizophrenia or bipolar disorder. Handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971).

Study Design

The study used a cross-sectional design with four groups: (1) the 'OC' group (n=16) included women currently taking the combined oral contraceptive pill for at least 2 months, and were on $\geq$ day 9 of active pills before being tested (Table 1); (2) the 'Low E/P' group (n=15) included women with a natural menstrual cycle who were tested during the early follicular phase of the menstrual cycle (days 2-8), at a time of low circulating estradiol and progesterone; (3) the 'High E/P' group (n=14) included women with a natural menstrual cycle who were tested during the mid-luteal phase of the menstrual cycle (days 19-25), at a time of high circulating estradiol and progesterone; and (4) healthy men (n=15). The stage of

the menstrual cycle was determined by asking the participant for the previous two menstruation dates and confirming the next menstruation date after testing. Of the 16 participants in the OC group, all were taking an oral contraceptive where the active constituent was ethinylestradiol (20 µg n=2, 30 µg n=12, 35 µg n=2) combined with either levonorgestrel (100 µg n=2, 125 µg n=4, 150 µg n=6), cyproterone acetate (2 mg n=1), dienogest (2 mg n=1), drospirenone (3 mg n=1) or norethisterone (500 µg n=1).

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The RBANS is a brief, standardized tool, which provides a general, overall evaluation of several cognitive domains (Randolph, 1998). The RBANS was measured as previously described (Gogos et al., 2010a); each participant was individually tested using Form A and it took 30 min to complete. Briefly, the RBANS comprised 12 subtests that were used to calculate 5 index scores. These were combined to form the total score, a summary score of global cognitive performance. Index scores were age-adjusted and standardized such that the normal mean was equal to 100 with a standard deviation (SD) of 15, based on a normative sample (Randolph, 1998). The 5 cognitive domains were: (1) immediate memory/learning (subtests: list learning, story memory), (2) visuospatial/constructional ability (figure copy, line orientation), (3) language (picture naming, semantic fluency), (4) attention (digit span, coding), (5) delayed memory (list recall, list recognition, story recall, figure recall). Three participants (1 male, 1 High E/P, 1 Low E/P) were excluded from the cognitive data analysis only as they were not fluent in English.

Prepulse inhibition

PPI was measured as previously described (Gogos et al., 2009) using the EMG Startle System (San Diego Instruments, CA, USA). Briefly, electromyogram (EMG) activity of the right

orbicularis oculi was recorded using two silver/silver chloride electrodes; a reference electrode was attached to the right mastoid (average impedance <15 kOhms). The EMG system delivered acoustic stimuli binaurally to the participant via headphones (Maico, San Diego Instruments). Before being tested for PPI, all participants refrained from smoking for >20 min and underwent a hearing test indicating that they could hear ≥ 30 dB. EMG activity was amplified (full scale 0.25), band-pass filtered (10-1000 Hz) and recorded for 250 msec following stimulus onset (sample interval=1 msec). The startle amplitude output was in mV, where 1 mV=0.1 μ V at the electrode.

The PPI task took 20 min to complete, during which participants were instructed to minimize movement, ignore the sounds and keep their eyes open during the task. The task began with 3 min of 70 dB white noise, which continued throughout the session. This was followed by 67 trials presented in a pseudorandom order at variable intervals (12-24 sec). There were 21 pulse-alone trials (115 dB, 40 msec), which were grouped in 3 blocks: (1) the first 7 trials of the session, (2) 7 trials interspersed with the prepulse-pulse trials, (3) the last 7 trials. There were 42 prepulse-pulse trials consisting of a 20 msec prepulse of 74, 78 and 86 dB (4, 8 and 16 dB above background; 7 of each) followed 60 msec (21 trials in total) or 120 msec (21 trials in total) later by the startling pulse of 115 dB. There were also 4 control trials where no sound was presented. The startling pulse and the prepulse-pulse trials involved bursts of white noise with near instantaneous rise-fall times.

All EMG recordings were screened for spontaneous eye-blink activity and trials were excluded (9% excluded) if excessive EMG activity occurred during 20 ms post-startle stimulus onset (baseline shifted >90 mV). Raw EMG data were smoothed: rolling average 3, filter order 4, pass frequency 350, response criterion 2. The amplitude of the startle response

was defined as the peak EMG response within 20-100 msec post-stimulus. The following measurements of the startle response were conducted: PPI (where %PPI is: [(amplitude of block 2 pulse-alone trials – amplitude of prepulse-pulse trials)/amplitude of block 2 pulse-alone trials] x 100), startle reactivity (amplitude of block 1 pulse-alone trials), startle amplitude relevant for PPI (amplitude of pulse-alone trials in block 2), habituation (decrement in the pulse-alone amplitudes across blocks 1 and 3). Two participants (1 male, 1 Low E/P) were deemed significant PPI outliers by the statistical software package SPSS (v.17, 2008, Chicago, IL, USA) and were excluded from the PPI analysis only.

Data analysis

Group differences in terms of demographic factors were examined using one-way analysis of variance (ANOVA) or Pearson's chi-square using SPSS. Normality was checked using the Kolmogorov-Smirnov statistic. A p -value of $p < 0.05$ was considered significant. Significant main effects of group were followed up with Bonferroni corrected post-hoc tests. Partial eta-squared (η^2) was used to determine effect sizes (small=0.01, medium=0.06, large=0.14).

One-way ANOVAs were conducted to compare groups on the RBANS total score, the five index scores (immediate memory/learning, visuospatial/constructional ability, language, attention, delayed memory) and twelve subtests.

PPI and startle data were normally distributed and therefore analyzed with repeated-measures ANOVA. For PPI data, the main effects and interactions were analyzed for group (4 levels), stimulus onset asynchrony (SOA; 60 or 120 ms) and prepulse intensity (PP4, PP8, PP16). In order to simplify data presentation, average % PPI is graphed (i.e. the average of PP4, PP8,

PP16). For startle reactivity, amplitude and habituation, the main effects and interactions were analyzed for group (4 levels) and block (1 or 2 levels, depending on the analysis).

RESULTS

Demographic variables

One-way ANOVA showed that the four groups were not significantly different in terms of age, predicted full-scale IQ, education and BPRS (Table 1). Pearson's chi-square analysis showed that the four groups were not significantly different in terms of the number of smokers or handedness. In female participants with a natural cycle, there was no significant difference in average cycle length between the Low E/P and High E/P groups (Table 1).

Repeatable Battery for the Assessment of Neuropsychological Status

The RBANS total score differed significantly among the four groups ($F_{(3,53)}=6.0$, $p=0.001$, $\eta^2=0.25$): the OC group had the highest score, followed by the High E/P group, then Low E/P group, and Male participants had the lowest score (Table 2). Bonferroni post-hoc tests showed that the OC group performed similar to the High E/P group, slightly better than the Low E/P group (trend, $p=0.1$), and significantly better than the Male group ($p=0.003$). The High E/P group also performed better than the Male group ($p=0.01$). Although the groups were matched for age, IQ and education, an ANCOVA including these variables as covariates was also performed to ensure that these variables were not responsible for the observed group differences; the RBANS total score was still significantly different among groups ($F_{(3,50)}=4.0$, $p=0.01$, $\eta^2=0.19$).

Three of the five index scores showed a significant main effect of group (Table 2) and within each of these three domains, the following subtests were also different among groups: immediate memory/learning index ($F_{(3,53)}=3.3$, $p=0.03$, $\eta^2=0.16$), list learning subtest ($F_{(3,53)}=3.8$, $p=0.01$, $\eta^2=0.18$); delayed memory index ($F_{(3,53)}=6.1$, $p=0.001$, $\eta^2=0.26$), list

recall subtest ($F_{(3,53)}=7.5$, $p<0.001$, $\eta^2=0.30$), list recognition subtest ($F_{(3,53)}=3.4$, $p=0.02$, $\eta^2=0.16$), story recall subtest ($F_{(3,53)}=3.3$, $p=0.03$, $\eta^2=0.16$), figure recall subtest ($F_{(3,53)}=3.5$, $p=0.02$, $\eta^2=0.16$); attention index ($F_{(3,53)}=3.0$, $p=0.04$, $\eta^2=0.15$), coding subtest ($F_{(3,53)}=3.6$, $p=0.02$, $\eta^2=0.17$). Bonferroni post-hoc comparisons for the index scores showed that for immediate memory/learning and attention, the OC group scored higher than the Male group ($p=0.02$ and $p=0.08$, respectively). For delayed memory, the OC group performed similar to the High E/P group, but better than the Low E/P ($p=0.05$) and Male groups ($p=0.006$). Further, the High E/P group performed better than the Male group ($p=0.02$). Bonferroni comparisons of the subtests showed a similar pattern of group differences as the index scores.

Prepulse inhibition

The 4 group x 2 SOA x 3 prepulse intensity ANOVA revealed no main effect of group. There was a significant main effect of SOA ($F_{(1,54)}=32.5$, $p<0.001$, $\eta^2=0.38$; Fig 1A) and prepulse intensity ($F_{(2,108)}=142.3$, $p<0.001$, $\eta^2=0.73$), reflecting the expected increase in PPI (i.e. greater reduction in startle) with increasing SOA and increasing prepulse intensity, respectively. There was an SOA x prepulse intensity interaction ($F_{(2,108)}=20.9$, $p<0.001$, $\eta^2=0.28$), reflecting that the increase in PPI with increasing prepulse intensity was particularly clear at the 60 ms SOA (data not shown). There were no significant interactions with group, suggesting that all the groups exhibited similar PPI (Fig 1A).

Based on previous literature suggesting that PPI varies across the menstrual cycle (Jovanovic et al., 2004; Kumari et al., 2010; Swerdlow et al., 1997), an ANOVA comparing the High E/P and Low E/P groups only was also performed. There was a significant main effect of SOA ($F_{(1,26)}=25.9$, $p<0.001$, $\eta^2=0.50$) and prepulse intensity ($F_{(2,52)}=51.2$, $p<0.001$, $\eta^2=0.66$), and an SOA x prepulse intensity interaction ($F_{(2,52)}=14.6$, $p<0.001$, $\eta^2=0.36$). There was no main

effect of group, however there was a significant SOA x prepulse intensity x group interaction ($F_{(2,52)}=3.9$, $p=0.03$, $\eta^2=0.13$), suggesting that the High E/P and Low E/P groups exhibited different PPI depending on the SOA and prepulse intensity (Fig 2). Indeed, the High E/P group showed reduced PPI compared with the Low E/P group, particularly at the 60 ms SOA (average PPI at 60 ms SOA: 18% vs. 31%, 120 ms SOA: 36% vs. 43% respectively). However, when analyzing the 60 ms and 120 ms SOA separately, there was no significant group difference or a prepulse intensity x group interaction. When analyzing each prepulse intensity level, there was a significant SOA x group interaction at PP4 ($F_{(1,26)}=5.6$, $p=0.03$, $\eta^2=0.18$), but not at PP8 or PP16. This suggests that at PP4, the Low E/P group has significantly greater PPI than the High E/P group at the 60 ms SOA only (Fig 2).

Based on the literature suggesting that smoking can influence PPI (Della Casa et al., 1998; Postma et al., 2006), the effect of smoking on PPI was examined by using smoking status as a covariate. There were no significant main effects or interactions with smoking, nor did it change the PPI findings. The analyses were repeated comparing groups for non-smokers only and the findings were similar to the whole-group results (data not shown).

Startle amplitude

Startle reactivity (Fig 3A), as measured by the amplitude of block 1 pulse-alone trials, was not different across the four groups.

Given that blocks 1 and 3 differ from block 2 in the variety of trial types included, data analysis was conducted for these blocks separately. When analyzing blocks 1 and 3 of startle amplitude data, there was a significant main effect of block ($F_{(1,54)}=79.2$, $p<0.001$, $\eta^2=0.59$), reflecting the reduction in startle amplitude after repeated administration of the startling pulse

(i.e. habituation; Fig 3B). There was no main effect of group, or a block x group interaction, reflecting similar habituation across groups.

When analyzing block 2 data alone, which is the block relevant for PPI, there was no significant effect of group ($p=0.3$), reflecting similar startle amplitudes across groups (Fig 1B).

DISCUSSION

This study examined higher cognitive function and PPI in healthy, pre-menopausal women who were either currently using the OC or were naturally cycling. Further, gender differences were examined by comparing these groups to healthy age-, IQ- and education-matched men. There were marked gender differences in cognition, where women in the OC or High E/P groups performed better than men. There was a tendency for women using the OC to perform better on cognitive tasks than women in the Low E/P group. Overall, there were no differences across the groups in terms of PPI and startle amplitude.

It is believed that one of the primary methods by which OCs act as birth control, is by preventing ovulation. Specifically, they inhibit the mid-cycle surge of follicle stimulating hormone and luteinizing hormone from the pituitary, consequently, endogenous estradiol secretion is reduced and progesterone production is stopped (Fitzgerald et al., 1999; Rivera et al., 1999). However, while natural endogenous hormone levels may be reduced dramatically in women using the OC (Mordecai et al., 2008; Rapkin et al., 2006), the levels of the synthetic sex hormones used in the OC are high. In fact, within two hours of administration of a contraceptive pill containing ethinylestradiol and the progestin levonorgestrel (similar to the OC used by 12 of the 16 women in the present study), plasma concentrations of these synthetic steroids reach their peak (100 pg/ml and 6 ng/ml, respectively) (DiLiberti et al., 2011). These peak levels are similar to those of 17β -estradiol and progesterone in women during the mid-luteal (High E/P) phase of the menstrual cycle (DiLiberti et al., 2011; Mordecai et al., 2008). In the OC group, all women were using combined OCs containing ethinylestradiol and a progestin, though there were various doses of ethinylestradiol and various types of progestins. The sample size of the current study was however too small to separate participants accordingly. Further, while the androgenicity associated with the

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progesterin type has been shown to have effects on cognitive performance, this has been shown with spatial tasks, and not memory tasks where the present study has shown the most marked effects (Wharton et al., 2008). Effectively, all participants in the OC group can be considered to be in a high estrogen state and even with some variability within this group, significant effects on cognitive function were observed.

The RBANS total score, giving an overall indicator of cognitive performance, was highest in the OC group followed closely by the High E/P group, which were both higher than the Low E/P group and significantly higher than the Male group. The specific cognitive domains responsible for these group differences were immediate learning/memory, delayed memory, and attention; group differences were further reflected on most of the subtests for these domains. The RBANS total and index scores are standardized such that the average level of performance is 100 ± 15 (Randolph, 1998). The current results indicate that performance of all groups was well within one standard deviation of the normal mean. In line with previous literature, the current findings showed marked gender differences on the memory and attention domains (Beatty et al., 2003; Maylor et al., 2007). However, the present results showed no gender differences with the language or visuospatial/constructional domains, two traditionally gender-selective domains (Beatty et al., 2003; Maylor et al., 2007). We previously reported no gender differences in any of the RBANS domains in healthy controls (Gogos et al., 2010a), where the majority of female participants were in a low estrogen state. In the current study, the gender differences were that women with high levels of sex hormones (either natural or synthetic) outperformed men, whereas the Low E/P and Male groups performed similarly. This suggests that sex hormone status of female participants may be the determining factor on whether or not a gender difference in cognition is observed in studies.

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2 The effects of sex hormones, particularly estrogen, on cognition have been previously
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4 examined. The cognitive domain that is generally the most affected by estrogen is verbal
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6 memory (Maki and Sundermann, 2009; Rosenberg and Park, 2002; Zec and Trivedi, 2002).
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9 In the current study, the greatest group differences were observed for the RBANS memory
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11 domains, which are measures of short-term verbal learning and memory (immediate
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13 learning/memory domain) and long-term verbal and visual memory (delayed memory
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15 domain). The present study found that the OC group and High E/P groups had similar overall
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17 cognitive function, including the memory domains, suggesting that high levels of either
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19 synthetic or natural sex hormones has similar effects on cognitive performance. Further,
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21 there was a tendency for the OC group to outperform the Low E/P group on cognitive
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23 performance, which was most marked for the delayed memory domain. The previous limited
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25 literature on OC use and memory has been inconsistent, whereby OC use enhanced verbal
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27 memory (Mordecai et al., 2008), or had no effect on verbal memory (Rosenberg and Park,
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29 2002) or recognition memory (Wharton et al., 2008). These studies, including the present
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31 study, employ different designs, have limited sample sizes and compare OCs with various
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33 progestins. This highlights the need for large, double-blind, placebo-controlled studies to
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35 determine the extent to which cognition, such as memory, is affected by OC use (i.e.
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37 synthetic sex hormone administration).
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49 It was expected that PPI levels would differ across the groups, based on previous literature
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51 suggesting gender differences in PPI (Kumari et al., 2008; Swerdlow et al., 1993) and a
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53 modulating effect of sex hormones on PPI (Gogos et al., 2006; Swerdlow et al., 1997). The
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55 present study found that women had greater PPI, under certain stimulus conditions, during
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57 the early follicular phase of the menstrual cycle (Low E/P group), compared to the luteal
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phase (High E/P group), which is in agreement with others (Jovanovic et al., 2004; Kumari et al., 2010; Swerdlow et al., 1997). The present results did not show a significant gender difference in PPI, where others report that men have greater PPI than women (Kumari et al., 2008; Kumari et al., 2004; Swerdlow et al., 1993). However in the present study, the male group did show a slight tendency, albeit not significant, towards higher PPI compared to the High E/P women (27% vs. 18% at the 60 ms SOA, Fig 1). There were no group differences in startle amplitude or habituation, suggesting that the PPI results were not influenced by changes in startle. Interestingly, OC users had PPI that was not significantly different from any of the other groups, whereby we would now expect this group to be similar to the High E/P group, based on the cognition findings. A previous study also found no difference in PPI among post-menopausal women who were either users or non-users of hormone replacement therapy (Bannbers et al., 2010), however, when they separated women according to estradiol serum concentration, they found that women with moderate estradiol concentrations had lower PPI than women with low estradiol. In contrast, Kumari et al. (2010) showed that progesterone levels (obtained by saliva sampling), but not estradiol, were associated with PPI. We previously found that estradiol administration in healthy pre-menopausal women had no effect on baseline PPI, although estradiol treatment was able to reverse a drug-induced disruption of PPI (Gogos et al., 2006). Thus, it appears that sex steroid hormones play a role in modulating drug-induced disruptions of PPI, but have less of an effect on baseline PPI. The present findings of an effect of OC use and High E/P states on higher-order cognitive function but not on PPI, suggests that different neural pathways are mediating each of these processes. Some studies (Csomor et al., 2008; Holstein et al., 2011; Roussos et al., 2009), but not all (Kishi et al., 2012), have found a relationship between the level of PPI and working memory. This was not found in the present study; however, the memory tasks used were different in each of these studies.

The present study may be limited by the cross-sectional design, thus OC users were self-selected rather than randomly allocated and likely to be women who respond well to the OC (Bannbers et al., 2010), or women who are more sexually active. While the present study did not ask participants about their sexual orientation, Rahman and colleagues found sexual orientation-related differences in PPI, verbal fluency and spatial memory (Rahman et al., 2003a; Rahman et al., 2003b; Rahman et al., 2003c). Further, our sample was highly educated, possibly applying a selection bias in our sample. Plasma hormone measurements were not collected; these levels could have further verified the menstrual cycle phase. However, plasma measurements are also limited in that they provide a peripheral rather than a central measure of sex hormone levels. Finally, the RBANS was used to give an overall indicator of cognitive performance; it is a brief cognitive test but not a comprehensive neuropsychological test battery. Nevertheless, in the present study, the RBANS was sensitive enough to differentiate performance across the groups.

Relatively little is known about the effects of OC use on cognition and PPI. In summary, this study showed that exogenous oral administration or high levels of natural circulating estrogen and progesterone (as occurs with the pill or during the mid-luteal phase of the menstrual cycle, respectively) had a positive effect on overall higher-order cognition. This effect was mostly due to changes in the cognitive domains of immediate and delayed memory, and attention. In contrast, different hormonal states in women had little effect on baseline PPI and startle amplitude. Importantly, in the present study, the groups were carefully matched for age, IQ and education. These results highlight the important role of sex steroid hormones in cognitive function in pre-menopausal women, and in particular that OC use had beneficial effects on cognition.

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FIGURE LEGEND

Figure 1: Male (n=14) and female participants tested for prepulse inhibition (PPI) of the acoustic startle response. Female participants were tested either while taking the combined oral contraceptive pill (OC, n=16), during the early follicular phase of the menstrual cycle (Low E/P, n=14), or the mid-luteal phase of the menstrual cycle (High E/P, n=14). (a) Mean + SEM average % PPI, where average % PPI is the average of the 3 levels of prepulse intensity and is shown at two stimulus onset asynchrony levels (60 and 120 ms). (b) Mean + SEM startle amplitude (mV) for the second block of seven 115 dB pulse-alone trials; trials that were interspersed with the prepulse trials.

Figure 2: Female participants tested for prepulse inhibition (PPI) of the acoustic startle response during the early follicular phase of the menstrual cycle (Low E/P, n=14) or the mid-luteal phase of the menstrual cycle (High E/P, n=14). Data is mean + SEM % PPI across three prepulse intensities (PP4, PP8, PP16) for the 60 ms (a) and 120 ms (b) stimulus onset asynchrony levels.

Figure 3: Male (n=14) and female participants tested for the acoustic startle response. Female participants were tested either while taking the combined oral contraceptive pill (OC, n=16), during the early follicular phase of the menstrual cycle (Low E/P, n=14), or the mid-luteal phase of the menstrual cycle (High E/P, n=14). (a) Mean + SEM startle amplitude (mV) for startle reactivity, which refers to the startle responses to the first block of seven 115 dB pulse-alone trials. (b) Mean + SEM startle amplitude (mV) for the first and last seven pulse-alone trials (blocks 1 and 3, i.e. habituation).

TABLES

	Female			Male
			High E/P	
	OC (n=16)	Low E/P (n=15)	(n=14)	(n=15)
Age (years)	25 (2.6)	28 (5.2)	26 (5.8)	29 (6.2)
Predicted IQ	111 (6.9)	108 (5.5)	110 (6.7)	109 (6.8)
Education (years)	19 (2.1)	18 (2.6)	17 (2.5)	17 (2.4)
# Regular smokers	3	5	2	2
BPRS	26 (1.7)	28 (2.9)	26 (2.0)	27 (3.4)
Handedness (L/R)	3/13	0/15	0/14	3/12
Cycle length (days)	-	30 (5.8)	28 (1.8)	-
Cycle day when tested	14 (4.9)	4 (1.8)	21 (1.9)	-

Table 1 - Demographic information: Data represent mean (SD) unless otherwise stated.

OC: women tested while taking the combined oral contraceptive pill; Low E/P: women tested during the early follicular phase of the menstrual cycle; High E/P: women tested during the mid-luteal phase of the menstrual cycle. Predicted IQ was determined using the National Adult Reading Test; # Regular smokers represents the number of participants who smoke everyday; BPRS is the Brief Psychiatric Rating Scales.

	Female			Male
		Low E/P	High E/P	(n=14)
	OC (n=16)	(n=14)	(n=13)	
RBANS:				
Total Score*	107 (9.6)	98 (13.1)	106 (11.8)	93 (8.1)
Immediate memory*	111 (15.8)	104 (16.1)	107 (14.5)	95 (11.1)
Delayed memory*	104 (6.8)	94 (7.5)	103 (8.0)	92 (13.5)
Visuospatial ability	96 (11.5)	93 (15.7)	97 (15.6)	92 (16.3)
Language	110 (9.2)	105 (10.4)	109 (11.6)	103 (9.3)
Attention*	108 (11.3)	97 (17.9)	105 (12.7)	94 (15.3)

Table 2 – Cognitive function: Data represent mean (SD). OC: women tested while taking the combined oral contraceptive pill; Low E/P: women tested during the early follicular phase of the menstrual cycle; High E/P: women tested during the mid-luteal phase of the menstrual cycle; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status.

* $p < 0.05$ using one-way ANOVA comparing the four groups.

(b) **Startle amplitude: Block 2**

(a) 60 ms stimulus onset asynchrony

(b) 120 ms stimulus onset asynchrony

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