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Cognitive function in association with high estradiol levels resulting from fertility treatment

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ABSTRACT

The putative association between hormones and cognitive performance is controversial. While there is evidence that estradiol plays a neuroprotective role, hormone treatment has not been shown to improve cognitive performance. Current research is flawed by the evaluation of combined hormonal effects throughout the menstrual cycle or in the menopausal transition. The stimulation phase of a fertility treatment offers a unique model to study the effect of estradiol on cognitive function.

This quasi-experimental observational study is based on data from 44 women receiving IVF in Zurich, Switzerland. We assessed visuospatial working memory, attention, cognitive bias, and hormone levels at the beginning and at the end of the stimulation phase of ovarian superstimulation as part of a fertility treatment. In addition to inter-individual differences, we examined intra-individual change over time (within-subject effects).

The substantial increases in estradiol levels resulting from fertility treatment did not relate to any considerable change in cognitive functioning.

As the tests applied represent a broad variety of cognitive functions on different levels of complexity and with various brain regions involved, we can conclude that estradiol does not show a significant short-term effect on cognitive function.

1. Introduction

Cognition is a core feature of human brain function, associated at any age with functional performance (Ford et al., 2010). There is an ongoing debate on if and how estradiol (E2) influences cognition. It has been shown to affect actual cognitive performance as well as to influence reparatory mechanisms involved in long-term mental health (Craig & Murphy 2007; Brotfain et al., 2016; Rapp et al., 2003), but study results are controversial.

E2 levels vary during the menstrual cycle and decrease after menopause. Therefore, associations between E2 and cognitive performance are relevant for women's cognitive function during and beyond their reproductive years. Estrogens are one of the most frequently utilized medical drugs. About 151 million women worldwide use contraception containing estrogen, and 12 million women undergo postmenopausal estrogen therapies, most of them over many years (Collaborative Group

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on Hormonal Factors in Breast Cancer, 2019). At the same time, many women decide against postmenopausal hormone therapy and live 30 or more years with E2 levels that are naturally very low.

It is crucial to improve our understanding of regulatory mechanisms and strategies for adequate cognitive function. Understanding of the impact of E2 on cognitive performance will help health professionals to improve counselling on hormonal treatment and to target appropriate E2 levels.

Several epidemiologic and physiologic studies support an association between high E2 levels and better cognitive performance. For example, cognitive control and verbal and spatial memory are reported to improve, and the number of working memory errors produced on the spacial working memory has been found to be reduced during high E2 phases of the menstrual cycle (Hampson and Morley, 2013; Sundström Poromaa and Gingnell, 2014). Pregnant women, who have E2 levels above the maximum level of a menstrual cycle, show working memory performance that equals or even significantly exceeds the performance of non-pregnant controls matched for age and educational level (Hampson et al., 2015).

Cognitive changes related to attention, memory, and processing speed after menopause, i.e. when E2 levels drop, are greater than would be expected from the effects of age alone (Halbreich et al., 1995). The menopausal transition is accompanied by mild deficits in concentration and processing speed (Kok et al., 2006), but various factors other than hormonal changes are presumably involved (e.g., impaired sleep quality). In a 14-year longitudinal study of 403 women during menopausal transition, verbal recall declined independently from normal aging (Epperson et al., 2013). Other studies indicating a supporting role of estrogen for cognitive performance in postmenopausal women corroborate such findings (Albert & Newhouse, 2019; Henderson, 2008; Rettberg et al., 2014; Russell et al., 2019). Cognitive impairment in women who experience a longer period with low ovarian hormone levels because of early menopause without hormone therapy or higher parity further reinforces the negative impact of estrogen decline (Georgakis et al., 2016; Rocca et al., 2007; Sherwin, 1988; Song et al., 2020).

However, other results indicate only a small or neglible effect of E2 on cognitive function. When compared to non-pregnant women, pregnant women show estrogen-related differences only in working memory but no significant differences in other cognitive functions, i.e. memory, attention and object recognition processes (Hampson et al., 2015). Menopausal status (early and late menopausal transition and early and late postmenopause) was not related to significant differences in episodic verbal memory measured by a supraspan word list recall task (Henderson et al., 2003). In the Study of Women's Health Across the Nation (SWAN), 2362 women aged 42–52 years observed longitudinally for 4 years showed improvement in verbal memory in pre- and postmenopause, but not in early or late perimenopause, i.e., the ability to learn may be compromised only temporarily (Greendale et al., 2009). In our own prospective longitudinal study, incorporating data from 2 consecutive menstrual cycles, we did not find a consistent and robust association between repeated measurements of estrogen and cognitive function, including working memory, attention, and cognitive bias (Leeners et al., 2017).

In line with these findings, attempts to reduce the prevalence of postmenopausal cognitive impairment by hormone therapy have not shown the desired outcome (Shumaker et al., 2003). Although there is evidence of a neuroprotective effect of E2 (Brotfain et al., 2016; Rapp et al., 2003), and estrogen deprivation is associated with the risk for Alzheimer's disease (Russell et al., 2019), several large studies failed to show a beneficial effect, or even found an unfavorable effect, of estrogen therapy on cognitive performance (Henderson et al., 2016; Rapp et al., 2003; Shumaker et al., 2003, 2004; Kantarci et al., 2018). Late initiation of estrogen therapy relative to age at menopause is one of the factors discussed that explain this finding (Espeland et al., 2004; Resnick et al., 2006; Shumaker et al., 2003).

Many studies investigating cognitive performance in relation to the menstrual cycle have flaws, which can lead to false-positive results (Leeners et al., 2017). Critical methodological issues include the lack of standardization of cycle phases, a lack of confirmation of the cycle phase through hormonal measurements, the timing of assessments within the menstrual cycle, the choice of tests to evaluate cognition, and many more. Available studies are very heterogeneous with regard to selected tests, and many studies have explored only one or a few aspects of cognitive function. Another major flaw is the investigation of the combined effects of E2 and progesterone, as findings may be biased by an interactional effect of both hormones (Toffoletto et al., 2014).

In women, the highest proportion of systemically available E2 is produced by growing follicles, which contain the human oocyte. During the follicular phase of the menstrual cycle, E2 levels rise from less than 200 pmol/l to about 800-900 pmol/l, secreted by a preovulatory follicle (Taylor et al., 2019). In the context of fertility treatment, E2 reaches levels significantly above those in a natural menstrual cycle, as the aim is to achieve not only 1 but rather between 5 and 15 mature oocytes, each of which contributes to the E2 level. While E2 values rise steadily to their maximum, where they persist for several days, other ovarian hormones remain stable. Therefore, in addition to studies in the menstrual cycle, the significant rise of E2 during the 9–13 day stimulation period in the context of fertility treatment represents a good quasi-experimental model to evaluate the isolated role of natural, but supraphysiological E2 levels in cognitive function.

We therefore benefited from this model to investigate the association between the two significantly different E2 levels and women's cognitive performance. Based on the literature, we expected that supraphysiological estrogen levels would influence cognitive function. Specifically, our hypothesis was that cognitive performance would be better at the end of the stimulation phase, when E2 levels are high. We expected attention, visual memory, and executive functions to be improved when maximum E2 levels were present at the end of a stimulation phase of fertility treatment.

Associations between E2 and cognitive function were evaluated (i) as scores per time period and (ii) as score changes over time. We also assessed (iii) whether associations between E2 and cognitive function were similar when different prefrontal and reticular regulatory systems were involved.

2. Materials and methods

2.1. Participants and design

We conducted a prospective quasi-experimental observational study investigating serial measurements of hormonal and neurocognitive parameters in 44 women receiving in vitro fertilization at the Department of Reproductive Endocrinology in Zurich, Switzerland. The study is part of a project designed to model hormonal changes in women and their association with neuropsychological function and emotion regulation (Hengartner et al., 2017; Leeners et al., 2017, 2019).

This study followed the guidelines of the World Medical Association Declaration of Helsinki 1964, updated in October 2013 and was conducted after approval by the Cantonal Committee (KEK_ZH-Nr 2013-0136). All participants provided written informed consent for study participation. Women were compensated for their expenditures associated with study participation. The study has been registered in clin.trial.gov (NCT02098668).

The study was conducted at the Department of Reproductive Endocrinology, University Hospital Zurich, Switzerland. All women included in the study sought medical support because of failure to conceive spontaneously; they underwent the standard procedure for diagnosis of fertility disorders, including a gynecological examination with transvaginal ultrasound to determine antral follicle count and uterine or adnexal abnormalities. Endocrinological disorders were evaluated by individual hormones (luteinizing hormone (LH), follicle stimulating

hormone (FSH), E2, anti-Millerian hormone, testosterone, 17 hydroxy progesterone, prolactin, thyroid stimulating hormone on specific indication) in serum samples collected in the early follicular phase (day 2–5). Semen analyses were conducted for the male partners. We investigated hepatitis B, hepatitis C, HIV, and chlamydia infection in both partners. Depending on the result of semen analysis, either a hydrosonography of the uterine cavity or a hydro-contrast-sonography/ hysterosalpingography was performed to control for uterine and/or tubal pathology. An interview served to verify inclusion and exclusion criteria, especially medical conditions related to cognitive performance, such as psychiatric diseases.

Sample size was determined on the basis of a power analysis with G*Power 3 (Faul et al., 2007). The calculation was based on a repeated measures within-factor MANOVA, expecting a medium effect size ($f = 0.25$), alpha error probability of 0.05, power (1-beta error probability) of 0.90, 2 measurements and a correlation among the repeated outcome measures of $r = 0.5$. According to these model specifications, a sample size of $n = 44$ participants was required.

A total of 44 women with a mean age of 36.7 ± 3.5 years (range 29–45) were evaluated, 26 of which received their first and 18 of which received a second treatment. In 13 women, fertility treatment was performed because of a mechanical problem, in 14 because of endometriosis, in 10 because of polycystic ovary syndrome (PCOS), in 6 because of idiopathic sterility, and in 34 women either because of a male factor only or because of a reduced sperm quality in addition to the female indications. Some of the couples had several causes of infertility. None of the women had received any hormonal treatment in the three months prior to the fertility treatment. Women with different indications for fertility treatment showed no differences in baseline E2 levels. Also, E2 levels did not vary from a group of naturally cycling women investigated previously (Leeners et al., 2017).

2.2. Hormone measurements and assays

For each woman, hormonal parameters were measured during fertility treatment, at the beginning and at the end of the follicle stimulation phase. At each visit, blood samples were collected between 7:00 am and 10:00 am and transferred immediately to the laboratory. A stimulation phase takes between 9 and 13 days, i.e. measurements were at least 9 and at maximum 13 days apart.

E2 was measured using electrochemiluminescence immunoassays ECLIA (Elecsys® Estradiol II) based on polyclonal antibody (Roche Diagnostics GmbH, Penzberg, Germany) with a functional assay sensitivity of 44 pmol/l and a coefficient of variation (CV) of less than 7.7%. As of 15 January 2015, the ECLIA (Elecsys® Estradiol III) based on monoclonal antibody (Roche Diagnostics GmbH, Penzberg, Germany), with a functional assay sensitivity to 91.8 pmol/l (25 pg/ml) and CV of less than 3.36%, was applied. Analyses were performed at the Institute of Clinical Chemistry, University Hospital Zurich. External quality controls were carried out at regular intervals by the society for promoting quality assurance in medical laboratories (INSTAND, Duesseldorf, Germany) and the Reference Institute for Bioanalytics (RfB, Bone, Germany).

2.3. Neuropsychological tests

The cognitive tests were performed at the same time as morning blood samples were taken. The neuropsychological tests were performed on a touch screen computer. Participants were placed in a quiet room to complete all the tests, with a trained study staff member present to explain the tests and answer any questions that might arise during the test. The overall test time for the 5 tests evaluating cognition was approximately 25 min.

To evaluate cognitive function, a validated, standardized computer-assisted test system (CANDIT: Computer Assisted Neuropsychological Diagnostics and Therapy, Candit.com) was used. Tests were selected to evaluate cognitive function in normal intelligent women, assuming absence of any brain injury. The test categories included attention (including Cancellation Screen Short, CPT Visual Short, and Divided Attention Bimodal Task), visual memory (Blockspan forwards and backwards), and executive functions (Cognitive Bias Test) and to measure brain structures involved in most complex information processing requirements (e.g., regulatory, stabilizing, planning, anticipating, mental shifting, coordinating, problem analysis, problem solving). These tests (and their adaptations) were applied in previous research on associations between cognitive functioning and hormones and cycle phases (e.g. Hampson and Morley, 2013; Mordecai et al., 2008; Solís-Ortiz and Corsi-Cabrera, 2008).

The **Blockspan** test (Corsi blocks task) is a well-established tool to investigate visuospatial working memory and executive resources (Doucet et al., 2013; Vandierendonck et al., 2004) by requiring forward and backward recall of path presentations. For the block task, a set of 9 identical blocks is shown on a monitor. Upon presentation of a series of blocks, which change their color in a consecutive order, a representation of the path has to be constructed and maintained in visual-spatial working memory. The sequence then has to be reproduced in the same order (phase 1) or in reverse order (phase 2). To reproduce the reverse order, executive control is required (Alvarez-Moya et al., 2011; Vandierendonck et al., 2004). The test makes it possible to measure figural/visual shorttime memory and memory span and evaluates cognitive performance related to the right hemisphere and the frontal lobe (Doucet et al., 2013; Vandierendonck et al., 2004). The Blockspan test showed a Cronbach's alpha of 0.993, a Spearman-Brown coefficient of 0.993, and a Guttman split-half coefficient of 0.993.

The Cognitive Bias Test (CBT) is a multiple choice procedure designed by Goldberg et al. (1994) as a bias (preference) task to evaluate complex cognitive functions. The CBT consists of designs characterized along five binary dimensions: shape (circle/square), color (red/blue), number (one/two identical components), size (large/small), and contour (outline/filled with a homogeneous color). Study participants have to rate similarity between two items. The designs, which are on different levels of difficulty, are presented twice to the study participant, in different vertical positions. Thus, 32 stimuli are generated, and a "similarity index" is computed between any two stimuli, ranging from 5 (identical) to 0 (differing along all five dimensions). The "similarity indices" between targets and subject's choices are summed across trials (Goldberg et al., 1994). In this study, we used correct responses as the outcome, i.e., higher scores on the CBT indicate better cognitive control. The CBT captures decision making, stress resistance, and impulse inhibition, whose regulation is predominately located in the frontal lobe (Goldberg et al., 1994). The CBT has a Cronbach's alpha of 0.983, a Spearman-Brown coefficient of 0.983, and a Guttman split-half coefficient of 0.983.

The Divided Attention Bimodal Task investigates the ability to control visual and auditory stimuli simultaneously, hence divided attention, which is located in the frontal lobe. The study participant has to react to predefined visual as well as auditory cues as quickly as possible. For each fitting visual cue, a specific tab has to be pressed with the left hand, and for each fitting auditory cue a specific tab has to be pressed with the right hand. The test includes 3 test phases, each including a series of 35 items and taking about 5.15 min to be perform (Parasuraman, 1998). The Divided Attention Bimodal Task also makes it possible to measure capacity for multitasking. The divided attention test has a Cronbach's alpha of 0.823, a Spearman-Brown coefficient of 0.815, and a Guttman Split-half coefficient of 0.804.

The Cancellation Screen Test is designed to assess concentration performance and focused attention at a self-directed work pace over a longer period of time (Brucki and Nitrini, 2008; Deng et al., 2019; Hatta et al., 2012). The test requires visual selectivity at fast speed on a repetitive motor response task. We used a computer-adapted version of a pen-and-paper version widely used in clinical and research settings (Deng et al., 2019). During the 7-minute administration, respondents are required to mark as quickly and as precisely as possible all apricots and

pears from left to right in 8 rows of 11 random fruits. Study participants are not allowed to go back. The target fruits remain visible on the top of the screen throughout the whole task. To perform the Cancellation Screen Test, the cerebellum, superior temporal lobe, precentral gyrus, frontal gyrus, and occipital and parietal areas are activated (Deng et al., 2019). In addition to attention, i.e., the ability to focus on a particular stimulus and to ignore extraneous stimulus, impulsivity and reduced control of behavior can be evaluated. The test also allows the investigation of fatigue during the task (De Jager et al., 2003; Pascualvaca et al., 1998). For the Cancellation Screen, Cronbach's alpha was 0.985, Spearman-Brown coefficient was 0.945, and Guttman split-half coefficient was 0.945.

In contrast to the Cancellation Screen Test, the Continuous Performance Test (CPT) Visual covers continuous attention and performance in a monotonous task under external impetus. It measures performance in areas of inattentiveness, impulsivity, sustained attention, and vigilance (Riccio et al., 2002; Riccio et al., 2001; Tana et al., 2010). During the task, a series of icons appears continuously on the screen; participants have to touch the screen whenever the icon "letter" is shown after the icon "bridge." The short version of the test lasts 5 min. In each task, the number of correct responses (hits), omission errors (misses), commission errors (false alarms), reaction time for hits, and reaction time variability were recorded and evaluated (Pascualvaca et al., 1998). The CBT makes it possible to evaluate the frontal lobe and the reticular system and has been used successfully in the evaluation of attention abilities in the context of autism, attention deficit hyperactive disease (ADHD), psychiatric disorders, stroke, as well as in the context of healthy individuals (Advokat et al., 2007; Barker-Collo et al., 2010). For the CPT Visual, Cronbach's alpha was 0.870, Spearman-Brown coefficient was 0.797, and Guttmans split-half coefficient was 0.769.

2.4. Confounders

2.4.1. Perceived stress questionnaire

The Perceived Stress Questionnaire (PSQ) (Fliege et al., 2005), developed by Levenstein et al. (1993), was used to evaluate subjectively perceived stress. The German version of the PSQ has been validated in a German sample ($N = 650$) (Fliege et al., 2001). Scales are composed of 5 items, each resulting in a total of 20 items that show good internal consistency, with Cronbach's α between 0.80 and 0.86. For each item, the study participants had to choose the most appropriate answer that applied to the past 24 h between the options "rarely," "sometimes," "often," and "mostly," i.e., a numerical scale ranging from 1 to 4, where 1 is the lowest value and 4 is the highest.

2.4.2. Positive and Negative Affect Schedule (PANAS).

Negative affect was measured with the respective subscale of the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988). This scale measures negative affect based on 5 items rated on a 5-point Likert scale ranging from 1 ("not at all") to 5 ("very severe"). Both the original scale (Watson et al., 1988) and the German adaptation used in the present study (Krohne et al., 1996) demonstrated good validity and reliability. In the present study, the internal consistency of the negative affect subscale was good (Cronbach's $\alpha = 0.84$).

As in the case of the PSQ, the PANAS was applied at the beginning (t1) and the end of the stimulation phase (t2).

2.5. Statistical analysis

The associations between repeated measures of cognitive functioning and estrogen levels were estimated using generalized estimating equations (GEE). These statistical models were introduced to fit regression analyses that account for within-subject correlation, which is an inherent part of longitudinal studies that rely on repeated outcome measures (Zeger et al., 1988). GEE are considered state of the art for longitudinal data analysis and superior to repeated measures ANOVA due to their psychometric properties (Ballinger, 2004; Gibbons et al., 2010). GEE use all available data and impute missing values under the assumption of missing completely at random (MCAR). Repeated measurements of cognitive test scores were successively entered as the outcome variables and the estrogen assays were entered as the predictor variable. Because cognitive test scores were approximately normally distributed, we fitted all models with normal distribution and identity link function. The within-subject covariance was specified with the "unstructured" correlation type to avoid having any constraints on the covariance structure, and a robust sandwich estimator was used to reduce the effects of outliers and influential observations. We additionally focused on within-subject effects by including absolute change values between the consecutive measurements of both cognitive functions and estrogen levels. Associations between intra-individual changes in cognitive functions and estrogen levels were tested with a series of linear regressions, where change in cognitive functions was modelled as the outcome and change in estrogen levels as the predictor variable. Results were reported with standardized regression coefficients (β) and their standard errors (SE). In bivariate analyses, these correspond to an effect size r. We used two-tailed significance testing and an α-level of 0.05. All analyses were performed with SPSS 24 for Windows.

3. Results

3.1. Cognitive functions in relation to estrogen levels per measurement occasion

Mean scores in cognitive functions and estrogen levels at both measurement occasions are shown in Table 1. Cognitive test scores did not vary during fertility treatment except for cancellation screen, which improved over time ($p < .001$). As expected, estrogen scores increased dramatically from the first to the second assessment ($p < .001$).

Next we tested overall associations between cognitive functions and estrogen levels using two different GEE models (see Table 2). In Model 1, we computed only the main effect of estrogen levels on cognitive test scores. In Model 2, we added the interaction effect between estrogen levels and time slope (measurement occasion) while controlling for the main effect of estrogen levels and time slope. No effect was statistically significant, and all effect sizes were negligibly small and therefore of no practical significance. Controlling for perceived stress (PSQ total score) and both positive and negative affect (PANAS positive and negative affect scales) did not alter the results for estrogen levels. Likewise, controlling for age and BMI did not influence the effect estimates for estrogen levels.

3.2. Cognitive functions in relation to intra-individual change in estrogen levels over time

Finally, intra-individual change in estrogen levels ranged from 122.0 to 11,746.0 pmol/l with a mean (SD) of 3553.9 (2472.4) pmol/l. This indicates that estrogen levels increased substantially in all women over the course of fertility treatment, although there was a lot of variation in the amount of this increase. However, with respect to intra-individual

Table 1
Cognitive test scores and estrogen during fertilization treatment.

Measures		Measurement occasion		Model effect P
		T1	T2	
	n	Mean (SE)	Mean (SE)	
Blockspan forwards	42	6.09 (0.12)	6.23 (0.14)	0.337
Blockspan backwards	42	5.75 (0.12)	5.91 (0.11)	0.180
Cognitive bias	44	32.71 (0.79)	33.66 (0.83)	0.068
Divided attention	44	95.63 (1.08)	93.91 (1.54)	0.174
Cancellation screen	42	379.55 (12.38)	423.71 (13.25)	<0.001
CPT visual	42	58.43 (0.37)	58.62 (0.36)	0.497
Estrogen (pmol/l)	44	54.54 (8.61)	3624.45 (374.97)	<0.001

Table 2
Associations between cognitive test scores and estrogen levels during fertility treatment.

Cognitive test	Model 1	Model 2
	β (SE)	β (SE)
Blockspan forwards	Main effect: −0.04 (0.07); p = .563	Interaction: 0.08 (0.15); p = .618
Blockspan backwards	Main effect: 0.03 (0.09); p = .753	Interaction: −0.01 (0.18); p = .950
Cognitive bias	Main effect: −0.08 (0.06); p = .177	Interaction: −0.03 (0.09); p = .720
Divided attention	Main effect: 0.08 (0.12); p = .500	Interaction: −0.08 (0.14); p = .564
Cancellation screen	Main effect: −0.08 (0.06); p = .169	Interaction: −0.04 (0.09); p = .683
CPT visual	Main effect: 0.06 (0.05); p = .194	Interaction: −0.22 (0.13); p = .095

Model 1: Main effect of estrogen only.
Model 2: Interaction between estrogen and time slope (reference is T1), controlling for main effects of both time slope and estrogen.

change in cognitive test scores, there were increases as well as decreases over time, while the mean change over time was close to zero in all tests except for cancellation screen, where most participants achieved higher scores at the second assessment. Table 3 shows the relationship between change in cognitive functions and change in estrogen levels according to linear regression analysis. Again, associations between cognitive functions and estrogen levels were statistically and practically non-significant. Controlling for perceived stress and both positive and negative affect did not alter the results for estrogen levels. Controlling for age and BMI had no effect either.

4. Discussion

Fertility treatments provide the possibility of using a unique quasi-experimental model to evaluate substantial changes in E2 levels and their impact on cognitive functions. Contrary to our hypothesis, this study showed no association between low and high E2 phases of an in vitro fertilization treatment and cognitive performance as measured by tests on attention, visual memory, and executive functions. Results covering cognitive function regulated in the frontal lobe and the reticular formation did not differ between measurements, nor did scores change over time.

Although E2 levels at the end of a stimulation phase are much higher than in a natural cycle, we saw no associations with cognitive function, a finding which confirms our previous results on the association between cognitive tests and natural hormonal changes related to the menstrual cycles (Leeners et al., 2017). As a practice effect would be expected to improve performance in cognitive tasks, such effect should add to a potential effect of E2. However, no differences between cognitive performance at both investigations could be demonstrated, which supports that E2 has no acute effect on cognitive performance. Since all t2 measurements were performed within a five-day interval about eleven days after the initiation of the stimulation phase, we do not expect individual differences in the timing between both measurements to explain our findings. Our previous results showed that neither small E2 values at the beginning of the menstrual cycle, nor medium E2 values resulting from the growth of one single follicle indicate any association with cognitive performance. The present findings extend our knowledge by confirming that also far higher E2 values stemming from simultaneous growth of the whole cohort of follicles, are not related to cognitive function.

Table 3
Associations between intra-individual change in prefrontal cognitive test scores and estrogen levels during fertility treatment.

Cognitive test	β (SE)	R^2	P
Blockspan forwards	0.07 (0.17)	0.005	0.682
Blockspan backwards	0.09 (0.16)	0.010	0.576
Cognitive bias	−0.11 (0.16)	0.013	0.492
Divided attention	0.02 (0.16)	0.001	0.888
Cancellation screen	−0.22 (0.16)	0.056	0.159
CPT visual	−0.07 (0.17)	0.005	0.674

While the neuroprotective role of estrogen in the case of brain injury is supported by biochemical studies (Brotfain et al., 2016), the present results do not support any neuroprotective role in acute cognitive performance in women without brain damage. In line with these results, several large clinical studies in perimenopausal women failed to show any association between E2 and cognitive function: the Study of Women's Health Across the Nation (SWAN), which found no relation between E2 levels in different phases of the menopausal transition, as well as several tests of cognitive performance (Greendale et al., 2009). In the Melbourne Women's Midlife Health Project, memory was similar regardless of menopausal status, number of years post menopause, current or prior use of estrogen, or duration of hormone treatment and was also unrelated to blood E2 levels (Henderson et al., 2003). In addition, 727 recently postmenopausal women showed no significant effects on cognition of either oral conjugated equine estrogen or transdermal E2 after an observation time of 4 years (Miller et al., 2019).

4.1. Specific cognitive functions and related brain regions

Effects of E2 in the brain may vary in relation to the different brain regions, and different effects might compensate each other. To adjust for the complexity of cognition, we selected a combination of cognitive tests that made it possible to investigate different cognitive functions of varying degrees of difficulty, i.e., figural/visual short-term memory, memory span (Blockspan), decision making, impulse inhibition, stress resistance (CBT), ability to control visual and auditory stimuli simultaneously (Divided Attention Bimodal Task), concentration performance under self-controlled work pace over a longer period of time, focused attention (Cancellation Screen Test), and continuous attention/performance under external impetus (CPT Visual). Neither tests related to attention, nor tests on visual memory, nor tests on executive function showed any statistically significant difference between the first measurements at the initiation of the stimulation phase, where E2 levels were low, and the second measurement at the end of stimulation phase, where E2 levels were high.

Altogether, the tests selected activate predominately frontal and deeper cortical structures. These structures are those that handle the most complex information processing requirements (e.g., regulatory, stabilizing, planning, anticipating, mental shifting, coordinating, problem analysis, problem solving, etc.). Therefore, the lack of a correlation between E2 and cognitive function in any of the tests applied makes an acute effect of E2 on actual cognitive accomplishments in women without cognitive impairments very unlikely.

4.2. Potential explanation for differences in results

Although a variety of studies report associations between E2 and cognitive performance, most published studies do not support such an association (Sundström Poromaa and Gingnell, 2014). Differences among results may be explained by physiological as well as methodological differences among studies, for example, the cross-sectional nature of many studies (e.g., (Halari et al., 2005; Hampson and Morley, 2013), which does not allow for the evaluation of causal relationships; differences may also be attributed to limitations in methodological approaches, data acquisition and statistical analysis, selective reporting, and publication bias (Bakker et al., 2012; Chan et al., 2004; Kvarven et al., 2020; McGauran et al., 2010). These systematic biases are also well documented, specifically in the field of neurosciences and psychoneuroendocrinology (Button et al., 2013; Hengartner, 2017; Ioannidis et al., 2014; Szucs and Ioannidis, 2017).

Another methodological issue is underpowered small sample sizes,

which may result in severely inflated effect sizes and both false-positive and false-negative results (Button et al., 2013). Many studies included fewer than 30 women (e.g., (Jacobs and D'Esposito, 2011; Schöning et al., 2007), and, in some often-cited studies, even fewer than 10 study participants (e.g., (Hausmann et al., 2000; Solís-Ortiz and Corsi-Cabrera, 2008; Solís-Ortiz et al., 2004).

Also, the use of different tests and outcome measures to evaluate cognitive function as well as their level of standardization hampers comparison of findings. Several authors have reported an improvement of test performance throughout the session, with some of the results confirming an effect of E2 (Beck et al., 2008; Bianchini et al., 2018; Holloway et al., 2011). Therefore, tests where the measured capacities can be acquired under hormonal influences will show different results than test where hormones have no impact on learning effects. As an E2-related improvement of skills throughout the testing session would also become visible in the total test result our data do not support such effect.

Several studies using the menstrual cycle to evaluate associations between cognitive performance and hormones made speculative inferences from cycle phase on hormone levels without actually evaluating the correlation between hormones and cognition (e.g., Rosenberg & Park, 2002; Solís-Ortiz et al., 2004; Solís-Ortiz and Corsi-Cabrera, 2008). However, strong inter-individual differences in estrogen levels throughout the menstrual cycle may result in false assumptions with regard to associations that were detected.

In addition, the design of many studies does not make it possible to determine the effects of individual hormones. For example, mid-luteal measurements cover combined effects of E2 and progesterone, and progesterone has been reported to influence cognition also (Pletzer et al., 2019). While E2 enhances glutamatergic and reduces GABA-ergic neurotransmission (excitatory effects), progesterone has an opposite, ultimately inhibitory, effect and can consequently counteract the effect of estrogen (Pletzer et al., 2019). Probably both hormones also exert opposite effects on dopaminergic neurotransmission (Barth et al., 2015). Furthermore, adrenal steroids can activate estrogen receptors (Conley et al., 2013), and dopamine may modify estrogen-related cognitive function (Colzato and Hommel, 2014). Part of the progesterone effects may be a result of a metabolization to E2. Animal studies using medroxyprogesterone, which is not readily metabolized to E2, did not find any beneficial effect of medroxyprogesterone on learning (Braden et al., 2010; Beck et al., 2012).

In order to disentangle the effects of E2 and progesterone, androgens, dopamine etc., it is necessary to understand the effects of E2 alone, about which this study contributes valuable information. Evaluation of the association between E2 and cognitive function during the stimulation phase of a fertility treatment provides an excellent model to evaluate the role of E2 without the confounding effect of other hormones. LH and FSH are not known to have any significant neuropsychological effect (Lee et al., 2010), and during a normal stimulation phase progesterone levels rise only minimally (Polyzos et al., 2020).

Comparison of study results is further hampered by the evaluation of natural hormones and of hormonal medication with modified molecules; the latter vary in the nature and intensity of their effect as well as in their metabolization (Cavalieri and Rogan, 2011). In addition to these direct E2 effects, further significant effects may be influenced by E2 metabolites (Samartzis et al., 2016). The type and quantity of estrogen metabolites formed varies among individuals (Crooke et al., 2011), and research on inter-individual differences in estrogen receptor expression, receptor dynamics, and synaptic regulation, which may also influence study results, is only at the beginning (Bojar et al., 2016; Fehsel et al., 2016; Hara et al., 2015; Ma et al., 2014). In fertility treatment, E2 is naturally secreted by growing follicles, i.e., a stimulation phase makes it possible to study effects of natural E2.

While many of the studies, for example on the risk of dementia in the context of E2, focus on long-term effects with the involvement of synaptic structures, mitochondria, the cholinergic system, etc. our investigation focuses on short-term effects, where other factors such as vascularization are involved. In addition, estrogen effects may depend on the duration of the estrogen effect. For example, in a study from Resnick et al. (2006), effects of estrogen treatment on memory were evident only after long-term therapy.

Last but not least, reporting and publication bias limits the dissemination of negative findings and consequently results in an overestimation of associations in the literature (Ioannidis et al., 2014; Szucs and Ioannidis, 2017).

4.3. Strengths and limitations

To the best of our knowledge, no study has ever tested associations between estrogen concentration and cognitive functioning in women undergoing fertility treatment. This quasi-experimental design allows to exclusively evaluate E2 while any other steroid hormone remains constant. As we evaluated serum E2 levels, we can provide information only on associations at a systemic level but not on local neurotransmitter effects of E2. All measurements were taken between 7:30 am and 10:00 am, so variations in either hormone values or cognitive performance throughout the day cannot have influenced our results. E2 values at the initiation of the stimulation phase compared well to those of a group of normally cycling women using a similar E2 measurement protocol (Leeners et al., 2017). As we can only compare two very different E2 levels, one of them being supraphysiological, we cannot provide any information on effects at other E2 levels. Although there might be an inverted U relationship between E2 and cognitive function, i.e. associations not becoming visible in this study, our previous research failed to show any associations between E2 and cognitive function in two consecutive menstrual cycles (Hengartner et al., 2017).

Our sample was considerably larger than those commonly assessed in this field; nevertheless, an even bigger sample would have been preferable.

Although we assessed a broad spectrum of cognitive functions and brain regions involved in the regulation of cognition, we do not cover the complete range of cognitive functioning. Additional tests would increase coverage but could also increase the probability of chance false-positive findings due to multiple testing.

While infertility per se is related to psycho-social burden (Cousineau and Domar, 2007; Gameiro et al., 2013; Pasch et al., 2016; Rockliff et al., 2014), the time period of a fertility treatment is experienced as less stressful than the period leading up to the treatment and is comparable to stress experienced outside fertility treatment (Hammarberg et al., 2001; Leeners et al., 2019; van Balen et al., 1996). Therefore, the circumstances of fertility treatment are unlikely to have biased our results. This was further supported by our analysis controlling for stress as measured by the PSQ and for affectivity (PANAS), which did not alter our unadjusted results. However, we did not use any laboratory parameter, such as cortisol to evaluate stress. As part of the study participants had received a previous treatment, they were more familiar with the treatment situation, however this did not translate into differences in stress related to the current treatment. Eventually this is due to the time interval between treatments, which was at least one year. Furthermore, all study participants met the criteria to undergo oocyte retrieval, i.e., experienced a successful stimulation phase; both E2 measurements were conducted in the same stimulation phase, so that conditions for t1 and t2 were comparable.

5. Conclusions

Although within our study design we could compare cognitive performance at two notably different levels of E2 without modification of any other parameter, neither the total group, nor the individual women, nor the direct investigation of associations with hormone values has shown any variation in cognitive performance. As evaluation of cognitive performance was evaluated using a series of established tests, which cover a broad spectrum of cognitive functions and associated brain

regions, our results show that an important effect of E2 levels on cognitive performance unlikely.

CRediT authorship contribution statement

BL, MH, TK: Conceptualization; KG, DW, MH: Data curation; MH Formal analysis. BL, MH, TK, ET, TM, FI, ME, SR: Funding acquisition. BL, TK, KG, DW, CS, LS: Investigation. BL, MH, TK: Methodology. BL, ET, FI, ME: Project administration. BL, TK, ET, TM, FI, ME, SR: Resources. MH, FI: Software. BL, TK: Supervision. MH, KG: Validation. BL, MH: Visualization. BL, MH, TK: Roles/Writing - original draft. BL, MH, TK, KG, ET, TM, FI, ME, SR, DW, LS, CS: Writing - review & editing.

Declaration of competing interest

None.

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