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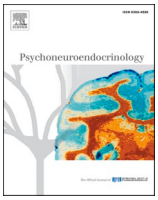

Estradiol driven change in hallucination proneness across the menstrual cycle as studied with a white noise paradigm

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ABSTRACT

The estrogen hypothesis for schizophrenia suggests neuroprotective effects of estrogen for the development of the disorder and for symptom severity, including auditory hallucinations. Furthermore, estrogen has shown enhancing effects on cognitive control, a function that is also implicated in auditory hallucinations. Whether estrogen affects the tendency to hallucinate in healthy participants, and the potential mediating role of cognitive control, has not yet been studied. Therefore, the current study aimed to test these relationships by using a white noise paradigm in combination with a N-back working memory task in which cognitive load could be manipulated. The paradigm used simulates a hallucinatory state by induction of negative emotions and drainage of cognitive resources. The simultaneous exposure to white noise elicit experiences of hearing voices (false alarms). In a between-subject design, forty-two participants were tested during the menstrual cycle in either the early follicular phase (low estradiol) or late follicular phase (high estradiol). A 2(Cycle Phase) x2(N-back task) ANOVA showed a main-effect of cycle phase on number of experienced hallucinations in the white noise task, with a significantly higher number of reported hallucinations in the early follicular phase. Furthermore, estradiol was found to predict number of hallucinations. No interaction effect of cycle phase and available cognitive resources was found. The results suggest an estradiol-related change in hallucination proneness across the menstrual cycle, but the idea that cognitive functioning mediates this relationship was not supported. Overall, the study supports protective effects of estradiol on hallucination proneness in line with the estrogen-hypothesis of schizophrenia, and that such effects are not specific to the disease.

1. Introduction

Auditory hallucinations(AHs) can be defined as the experience of hearing sounds, including voices, in the absence of an external auditory source (e.g. Larøi and Aleman, 2010). AHs is a core symptom in schizophrenia and psychosis in general, but is also experienced by 5–7% of the general population (Kusztrits et al., 2021; Linscott and van Os, 2013). AHs fluctuate over time (Bless et al., 2020), and internal physiological states such as hormonal oscillations may play a role (e.g. Bergemann et al., 2007), but have rarely been investigated in an experimental setting.

AHs are broadly assumed to arise from aberrant bottom-up signals in the (hyperactive) auditory cortex (Hjelmervik et al., 2020; Kompus et al., 2011) and a failure of down-regulating these signals due to limited cognitive resources (Hugdahl, 2009; Waters et al., 2012). Negative emotions can increase the rate of aberrant signals in the auditory cortex and increase AHs (Waters et al. (2012). The chances of perceiving bottom-up signals as real is called signal-detection rate. The signal detection theory states that all information recognition takes place in the presence of some uncertainty and that individuals constantly need to distinguish between noise (e.g., the noise in a crowd) and signals (e.g., someone calling your name in a crowd) (Bentall and Slade, 1985). Such

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distinctions become more challenging in noisy environments, hence, the chance of perceiving a noise that is not there (false alarms) increases. This has led to the use of white noise paradigms in hallucination research, which is usually composed from a heterogeneous mixture of sound waves at a wide range of frequencies. Laloyaux et al. (2019) recently introduced a white-noise paradigm (based on the model of Waters et al., 2012), showing that the number of false alarms/hallucinations heard in the white noise can be increased in healthy participants by combining two factors: 1) inducing negative emotions in the participants, and 2) draining the participant's cognitive resources (visual working memory task). Taken together, the emotional state and cognitive control resources seem critical for hallucinatory experiences.

The estrogen hypothesis for schizophrenia suggests protective- and antipsychotic effects of estrogen (da Silva and Ravindran, 2015). Supporting evidence comes from observations of sex differences in prevalence, symptom course, and onset (Seeman, 2002), as well as alternating symptomology across the menstrual cycle. For example, several studies find hallucinatory experiences (e.g. Sharma et al., 1999; Thorup et al., 2007), and AHs specifically, to be more common in female patients as compared to males (Rector and Seeman, 1992). A related syndrome – late onset psychosis chronic delusional syndrome – is characterised by positive symptoms with prominent and frequent hallucinations, and is believed to be related to a (peri)menopausal drop in sex hormone levels (Dubertret and Gorwood, 2001). Furthermore, psychotic symptoms have been found to change across the course of the menstrual cycle. One of the first studies in this respect observed a higher rate of admissions to psychiatric hospital during menstruation in participants with schizophrenia (Dalton, 1959). Similarly, high estrogen cycle phase or circulating estradiol has been associated with decreased global symptom score (Hallonquist et al., 1993), and reduction in positive symptoms (Bergemann et al., 2007; Goldstein and Link, 1988; Riecher-Rössler et al., 1994). These observational findings have been supported by clinical trials in which estrogen as adjunct treatment showed improvement in positive and general symptom-scores (Akhondzadeh et al., 2003; Kulkarni et al., 2001, 2008, but see Louzã et al., 2004). Selective estrogen receptor modulators – developed to avoid the adverse effects of estrogen – have also shown promising effects, but with more variation in type of symptoms affected (see Owens et al., 2017, for a review). According to Richer-Rössler et al. (1994), it is unclear whether estrogen-related changes in psychopathology across the menstrual cycle is specific to people with schizophrenia, or if similar effects can be observed in healthy participants. Hence, whether estradiol affects hallucination proneness in healthy participants has not previously been investigated.

Furthermore, cognition might be affected by estrogen. Ko et al. (2006) found circulating estradiol to be positively related to verbal cognition and executive functions in people with schizophrenia. A previous study on false memory rate – a common cognitive deficit in schizophrenia – found higher false memory rate in high-schizotypy individuals, but only when estradiol levels were low (Hodgetts, Hausmann et al., 2015). In addition, several studies of healthy individuals have found executive functions to improve during the high estrogenic late follicular phase in tasks, such as working memory (Jacobs and D'Esposito, 2011) and cognitive control (Hatta and Nagaya, 2009), including in the auditory domain (Hjelmervik et al., 2012; Morris et al., 2019, but see Hodgetts et al., 2015). The influence of estrogen on working memory seem to be especially strong when high level of cognitive control is required (Jacobs and D'Esposito, 2011; Keenan et al., 2001). Given the importance of cognitive resources in downregulation of spontaneous auditory signals, it is not unlikely that positive effects of estradiol on cognition could play a role in hallucination proneness.

In a 2(cycle phase) x2(cognitive resources) factorial design, the current study aimed to investigate the effect of estradiol on hallucination proneness in healthy participants, and possible mediating effects of cognitive control. This was done using an adapted version of Laloyaux et al.'s (2019) white noise paradigm. By inducing negative emotions in the participants and draining the cognitive resources, we induced a 'hallucinatory mind state' and increased the chances of experiencing AHs in the white noise. Participants were tested in a low (early follicular phase) or high (late follicular phase) estrogen cycle phase, and it was hypothesized (H1) that participants tested in the late follicular phase would experience fewer hallucinations as compared to participants tested in the early follicular phase (e.g. Owens et al., 2017). Due to the positive effects of estradiol on cognitive control (e.g. Jacobs and D'Esposito, 2011; Keenan et al., 2001) it was expected (H2) that differences between cycle phases would be especially prominent when cognitive resources are drained. To test this, two conditions were implemented: visual 1-back (leaving a high level of available cognitive resources) and 2-back task (leaving a low level of available cognitive resources; Laloyaux et al., 2019). In addition, we hypothesized (H3) that hallucination proneness would be higher in participants scoring high on schizotypy when tested in the low estradiol early follicular phase (Hodgetts et al., 2015) Lastly, we hypothesized (H4) that estradiol would negatively predict false alarm rate.

2. Methods

2.1. Participants

Forty-two right-handed healthy participants (out of fifty-nine originally tested: see section on hormone assays for exclusion criteria) with mean age of 22.1 (± 4.41, range 18–34) were tested once during one cycle phase of the menstrual cycle – in either early follicular phase (menstruation) or late follicular phase - on a white-noise task. Specifically, the testing occurred on days 2–4 and days 9–12 after the onset of menses. Both cycle phases are characterized by low progesterone levels, but differ in estradiol levels, which are typically higher in the late than early follicular phase (e.g. Schmalenberger et al., 2021). The number of participants collected was based on a power-analysis conducted prior to the data collection. Due to lack of any previous studies on hormone cycle and hallucination proneness, we based the analysis on the effect size (η^2 =0.12) from a previous study on cycle related attention modulation in the auditory domain. A power analysis in G-power (Faul et al., 2007) with a power of.95, alpha 0.05, repeated measures ANOVA with interaction effects (default settings) suggested a total number of participants of 36. Due to strict exclusion criteria for both cycle phase hormone levels (expected exclusion of 24%; Hjelmervik et al., 2018) and performance on the n-back task (expected exclusion of 13.6%; Laloyaux et al., 2019), we estimated a sample of n ≈ 60 (30 in each group) after adding 23 subjects (37.6% out of 60 =23).

A hearing test administered at the frequencies 500, 1000, 2000, 4000 and 8000 Hz found all participants to have sufficient hearing abilities. All participants had a regular menstrual cycle with a mean cycle length of 26–32 days and were tested in either the early follicular phase (day 2–4) or the late follicular phase (day 9–12). Cycle length was tracked for 2–3 months (depending on the information available. Some participants tracked their cycle routinely) prior to testing, which allowed for individual mean cycle length to be calculated. When planning participant's testing date, the starting point was the last self-reported onset of menses. From this date individual cycle length was used to estimate the occurrence of the next menstruation onset. Applying the back-counting procedure (commonly used in menstrual cycle studies, e.g. Schmalenberger et al., 2021) the predicted menstruation-onset was used to estimate the occurrence of the late follicular cycle phase (e.g. for a 28-days cycle, we counted back 17–20 days). To be included in the project, the participants had to self-certify that they had not been pregnant for the last six months, not used hormonal contraceptives or other hormone regulating medication during the last six months; Not having any psychiatric or neurological disorder. Data were collected at the University of Bergen (Norway) and Durham University (UK). The study was approved by the Regional Committee for Medical Research Ethics in Norway, and the local ethics committee at the University of Durham. Participants gave

their informed consent according to the Declaration of Helsinki.

2.2. Hormone assays

Three saliva samples were collected for each participant, before and after the white noise task, and the third sample was taken in the end of the session. SaliCap (IBL International) was used for collection of the saliva samples, and the analyses were conducted at the biolab at the Institute for biological and medical psychology, at Bergen university. The samples were analyzed for estradiol and progesterone levels using luminescence ELISA assays on an average amount of the three samples. For one participant, analysis was based on two saliva samples only as the first was removed due to miscoloring/contamination. Sensitivities for these steroids/assays are: Progesterone: Limit of Detection (LoD): 8,9 pg/ml,. 17-beta-Estradiol: LoD: 0,3 pg/ml (IBL International). Inter-assay coefficient of variation for progesterone was 18.4–23.4 (two levels), and for Estradiol 11.7–20.8 (two levels). The participants were instructed to refrain from food and drinks the last hour prior to the experiment. Further they were asked to rinse their mouth with water before the session. In order to maximize the chance of testing the participants in the cycle phases of interest, the backward counting method was used. Still, a certain error rate is expected, but to verify the cycle phase of a given participant based on estradiol and progesterone measurement from a single timepoint is problematic due to individual variations in hormone levels. Therefore, exclusion threshold was based on a previous sample, with the aim to exclude participants tested outside the intended cycle phase and thereby to obtain a difference in estradiol between the early and late follicular phase. This reference sample (Hjelmervik et al., 2018) had repeated measures of hormone levels on three different timepoints: Early follicular phase, late follicular phase, and luteal phase, which were estimated by backward counting procedure. Luteal progesterone indicated ovulation (Hjelmervik et al., 2018). Hence, the sample includes individuals in which luteal ovulation was confirmed by the following principle: Individual progesterone level measured in the luteal cycle phase was higher than for the early and late follicular phase tested in the same individual. All hormone levels were within expected ranges as reported by the manufacturer (IBL international). The following general principles were applied and exclusion thresholds were used based on hormone ranges reported in Hjelmervik et al. (2018): Estradiol and progesterone (pg/ml) were expected to be low in the early follicular cycle phase ($E \leq 5.3$, $P \leq 91.5$; within upper bounds of menstrual/early follicular estradiol and progesterone), while in the late follicular phase estradiol was expected to be high ($E \geq 1.6$; within lower bound of estradiol in the late follicular phase) and progesterone low ($P \leq 136.0$; within upper bound of late follicular progesterone). Participants having estradiol and progesterone levels outside these thresholds (Hjelmervik et al., 2018) were assumed tested outside of the intended cycle phase and therefore excluded. This resulted in the exclusion of fourteen out of fifty-nine participants. In addition, one participant was excluded due to missing data, and two were excluded due to performance scores below chance level (< 20%) on the n-back task. After exclusion, estradiol levels were shown to be significantly higher in the late follicular phase (M=4,32, SD=2.49) as compared to the early follicular phase (M=2.74, SD=1.31) as tested with a two-sided independent samples t-test ($t(40) = 2.65$, $p = 0.01$, $d = 0.77$). For progesterone, no difference between the late follicular (M=47.37, SD=28.57) and early follicular (M=41.14, SD=19.26) phase was found ($t(40) = 0.81$, $p = 0.42$, $d = 0.25$).

2.3. Materials

2.3.1. Emotion induction before the experiment

Before the experimental task, emotion induction was conducted in line with the study by Laloyaux et al. (2019). This was done by presenting pictures from the International Affective Picture System (IAPS; (Lang et al., 2008) together with anxiety inducing-questions that were adapted from Laloyaux et al. (2019); Lincoln et al. (2010). A total of 16 pictures and 16 corresponding anxiety-inducing multiple-choice questions (e.g. how many people are murdered in Norway each year?) was presented to the participants. The Positive and Negative Affect Schedule (PANAS; (Watson et al., 1988) was used to measure the participants' emotional state (negative and positive emotions) after the emotion induction and after the white-noise task. Restoration of positive emotions was done after the white-noise task by having the participants watch a funny video.

2.3.2. White-noise task

The paradigm used in the current study was adapted from Laloyaux et al. (2019). Participants completed a computerized N-back task containing emotional pictures, while simultaneously listening to white noise, and, by the end of each block, reporting whether they heard any words/sounds/voices in the noise. The experiment was conducted in a dark room. The stimuli (pictures and noise) were presented using the E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). Two different conditions were used: one leaving a high level of available cognitive resources and one leaving a low level, corresponding to the one- and two-back tasks, respectively. More specifically, participants were presented with a series of polygons (Vanderplas and Garvin, 1959). The polygons are used because they are not easily verbalized, and hence, prevent the participants from relying on their phonological loop to perform the task. In the one-back task the participants should press the key when the polygon on the screen was the same as the previous one, and in the two-back task press the key when the polygon was the same as the second to last one. Both conditions contained 20% of targets. Pictures from the IAPS (Lang et al., 2008) were presented between each polygon. This was done to maintain the negative emotional state of the participants. Pictures included were for example threatening people, robbery, riots, dead bodies, sad people, threatening animals, insects, wounds, dirty toilets, explosions, and plane or car crashes. A single trial comprised the following sequence (Fig. 1): A fixation cross; a picture from the IAPS; a fixation cross; a polygon. In total the task involved 2 training and 14 experimental blocks (7 for each of the N-back conditions) each consisting of 18 pictures and 18 polygons lasting for 500 and 1500 ms, respectively. The order of the block were 4 blocks of 2-back task, 4 blocks of 1-back task, 3 blocks of two-back and lastly 3 blocks of 1-back task. Simultaneously, participants were required to listen to recordings of white noise through headphones for each of the blocks. Participants were told that the white noise may contain hidden words, voices, or other sounds, and that they should pay attention to the noise while performing the N-back task. Prior to the experiment the participant went through at least two training blocks where real words – common Norwegian or English words – were imbedded in the white noise. In the experimental blocks no words or sounds were embedded in the noise. After each block, participants were asked to fill a paper questionnaire to assess whether or not they heard anything in the noise. The first question was as following: "During the task, did you hear anything such as a word, a meaningful noise/sound (for example, music, animals) or a voice? Yes/No". If they did, the next question allowed/required them to describe what they heard ("what was that word, noise/sound or voice that you heard?"). Lastly, participants indicated on a 7-point Likert scale: how certain they were ("To what extent are you sure you have heard something", ranging from "Absolutely uncertain" to "Absolutely certain"), the clarity of the sound ("To what extent was the word, noise/sound, voice clear", ranging from "Absolutely clear" to "Absolutely unclear"), and the emotional valence of the sound ("To what extent was the word, noise/sound, voice positive or negative", ranging from "Very negative" to "Very positive"). In the cases where participants heard multiple sounds in one block, they filled out one questionnaire for each.

The number of meaningful words or sounds (false alarms) was calculated and implemented in statistical analysis. Only words or sounds that were clearly identified and different from the white noise were

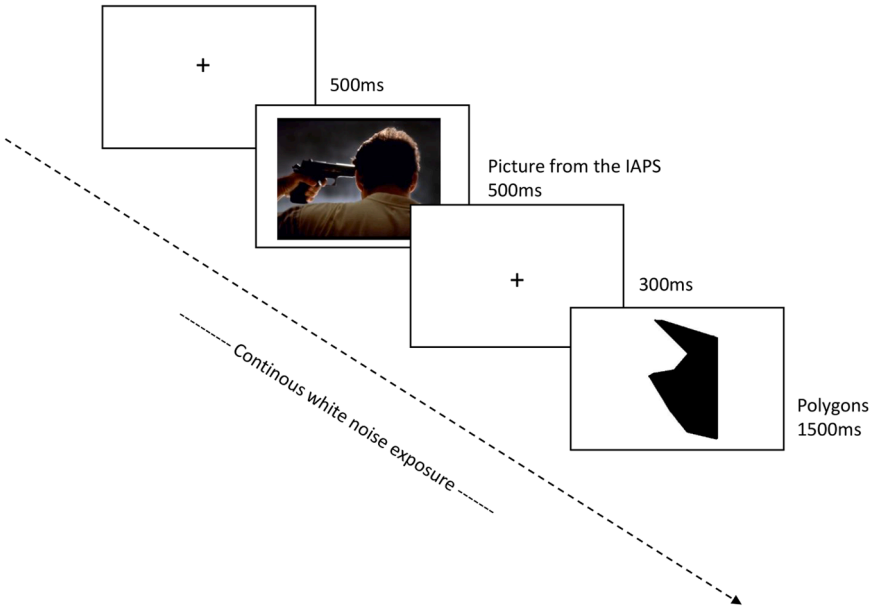

Fig. 1. Schematic representation of a single trial in the N-back task.

included. This could be a specific word (e.g. hearing a voice saying the word "Satan"), human sounds such as singing, crying or screaming, music (e.g. "I heard classical music"), or animal noises (e.g. meowing). Undefined sounds similar to white noise that were not taken into account was for example the sound of an engine, or the wind.

2.3.3. *Schizotypal personality questionnaire (SPQ)*

The schizotypal personality questionnaire - brief revised (SPQ-BR; Cohen et al., 2010) which is developed from the previous versions of SPQ (Raine, 1991) and SPQ-B (Raine and Benishay, 1995) was used to assess schizotypy. SPQ-BR is a 32-item questionnaire that are rated on a five-point scale ranging from 'strongly disagree' to 'strongly agree', in which higher scores indicate stronger schizotypy. The questionnaire consists of several factors: Cognitive/Perceptual (ideas of reference, suspiciousness, magical thinking and unusual perceptions), Interpersonal (no close friends; constricted affect, and social anxiety), and Disorganized (eccentric behaviour and odd speech). The Cognitive/-Perceptual factor score was used for analysis (hereafter referred to schizotypy) by summarizing the items.

2.4. *Statistical analysis*

In order to test the hypotheses that more false alarms would be reported during the menstrual cycle phase (H1) and especially during the high cognitive load (2-back) task (H2), a 2(Cycle Phase) x2(N-back) repeated measures ANOVA was conducted using SPSS (IBM SPSS version 28). Number of false alarms was entered as dependent variable. The ANOVA was then repeated with Schizotypy (Cognitive-perceptual dimension) as a continuous independent variable, in order to test for a potential interaction, i.e. whether the effect of cycle phase on hallucinations increases with higher schizotypy scores (H3). In addition, in order to verify that it was indeed estradiol that related to the menstrual cycle effect (H4), a multivariate regression analysis was conducted using estradiol, progesterone and the interaction of the two as predictors against the dependent variables, which were number of false alarms during 1-back and 2-back tasks. FDR correction (Benjamini and Hochberg, 1995) was implemented in order to control for multiple comparisons (Pike, 2011: Two-stage sharpened method), and adjusted *p*-values are reported in addition to the uncorrected *p*-values. Effect sizes are reported as percentage explained variance (partial η^2).

2.4.1. *Control analyses*

Analyses were conducted to assure that performances (accuracy and reaction time) on the n-back tasks were similar between the early and late follicular phase, and that both groups were equally affected by the emotion induction task (negative emotions PANAS). Two-way ANOVAs were used for this purpose. Cycle Phase served as independent variable in the analyses. Task served as a second variable for the n-back performance measures. Time served as the second independent variable in the emotion induction analysis, reflecting negative emotions measured before and after the n-back task.

2.4.2. *Exploratory analyses*

Individual mean scores of the variables Certainty, Clarity and Emotional valence of the false alarms/hallucinations heard in the noise were used as dependent variables in three different ANOVAs, with Cycle Phase (between-subject factor) and N-back task (within-subject factor) as independent variables. Mean scores were calculated as sum score divided by the number of blocks in which the participants reported false alarms.

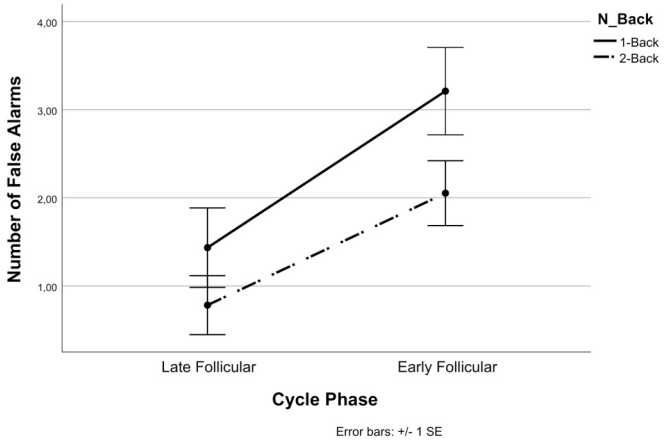

Fig. 2. Number of false alarms reported during the white noise task in the late and early follicular cycle phase during 1-Back and 2-Back tasks.

3. Results

The results from the 2(Cycle phase) x2(N-back task) ANOVA (H1; see Fig. 2) showed a main effect of Cycle phase ($F(1,40)= 8.19$, $p = 0.007$, FDRcorr= 0.01, $\eta^2 = 0.17$), with participants tested in the early follicular phase (M=2.63, SD=2.11) reporting more false alarms as compared to participants in the late follicular phase (M=.97, SD=1.14). In addition, a main effect of task was found ($F(1,40)= 12.66$), $p < 0.001$, FDRcorr= 0003, $\eta^2 = 0.24$), in which more false alarms were reported during the 1-back task (M=2.24, SD=2.31) than during the 2-back task (M=1.36, SD=1.71). No interaction effect of Cycle phase and N-back Task (H2) was found ($F(1,40)= 0.99$, $p = 0.33$, FDRcorr= 0.26, $\eta^2 = 0.02$).

The 2(Cycle Phase) x 2(Task) ANOVA was then repeated, now including Schizotypy as an additional independent variable,. The analysis was conducted with reduced n (=41) due to missing values on the schizotypy score. No significant interaction between Cycle Phase and Schizotypy (H3) was found ($F(1,38)= 0.95$, $p = 0.49$, FDRcorr= 0.31, $\eta^2 = 0.29$). Schizotypy was also not found to predict AH regardless of cycle phase ($F(1,38)= 0.60$, $p = 0.85$, $\eta^2 = 0.45$). The main effect of N-back task ($F(1,38)= 6.5$, $p = 0.02$, $\eta^2 = 0.32$) and Cycle Phase ($F(1,38)= 6.93$, $p = 0.02$, $\eta^2 = 0.33$) remained significant.

The multivariate regression analysis with estradiol and progesterone as regressors against false alarm scores during One- and Two-back tasks, showed an effect of estradiol across task ($F(1,38)= 4.99$, $p = 0.03$, FDRcorr= 0.03, $\eta^2 = 0.12$), reflecting a negative association between estradiol and number of false alarms across task (H4, see Fig. 3). In addition, and similar to previous analyses, a main effect of N-back task was found ($F(1,38)= 6.43$, $p = 0.02$, $\eta^2 = 0.15$), driven by a higher number of false alarms during 1-back vs. 2-back task. No other significant main or interaction effects were found (All $F(1,38)< 3.93$, $p > 0.06$, $\eta^2 < 0.09$).

3.1. Control analyses

Analyses were conducted to assure that performances on the n-back tasks were similar between the early and late follicular phase, and that both groups were equally affected by the emotion induction task. Repeated measures ANOVA on one-back performance showed main effects of task in the analysis of accuracy ($F(1.40)= 129.38$,$p < 0.001$, $\eta^2 = 0.76$) and reaction time ($F(1.40)= 83.21$, $p < 0.001$, $\eta^2 = 0.67$), reflecting generally higher accuracy in the 1-back condition (M=90.48, SD=10.49) as compared to 2-back condition (M=59.52, SD=17.18) and shorter reaction time in the 1-back (M=577.66, SD=89.95) as compared

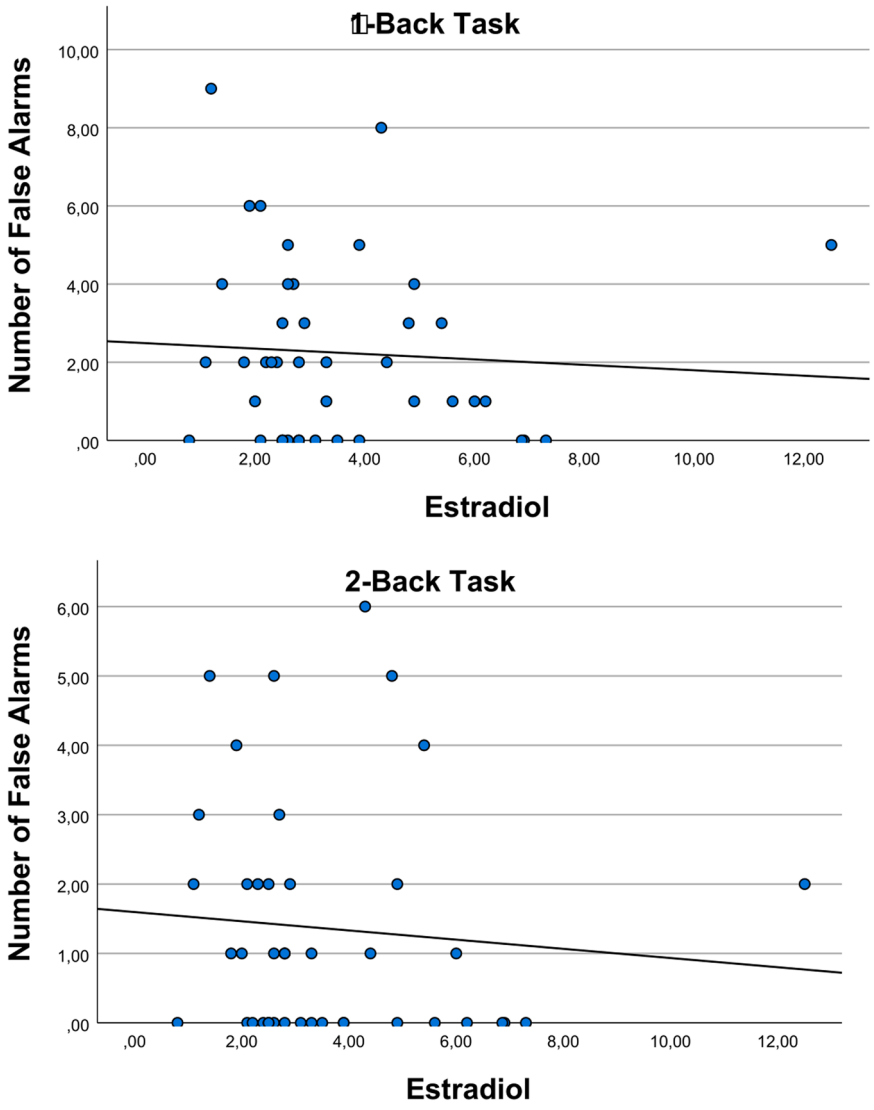

Fig. 3. Illustration of the relationships between estradiol (pg/ml) and number of false alarms reported during 1-Back and 2-Back tasks that came out significant in the multiple regression analysis. For details, please refer to text.

to the 2-back task (M=755.92, SD=155.19). Accuracy scores did not differ between the early and late follicular phase, and no interaction effect of Cycle phase and Task condition on accuracy was found (All $F(1,40) < 0.61$, $p > 0.61$, $\eta^2 < 0.02$). There was also no Cycle phase times Task interaction for reaction time ($F(1,40) = 1.39$, $p = 0.25$, $\eta^2 = 0.03$), but a main effect of cycle phase appeared ($F(1,40) = 4.47$, $p = 0.04$, $\eta^2 < 0.1$. To check whether cycle phase differences in reaction time could explain the difference in number of false alarms reported, the main analysis (H1) was re-run with reaction time scores as covariates. The cycle phase effect observed for number of false alarms remained significant ($F(38) = 6.8$, $p = 0.01$, $\eta^2 = 0.15$), suggesting that reaction time differences could not explain the effect.

The ANOVA addressing emotion induction showed no main effect of cycle phase or cycle phase and Time interaction (All $F(1.40) < 1.17$, $p > 0.29$, $\eta^2 < 0.03$). However, an effect of time was significant ($F(1.40) = 34.56$, $p < 0.001$, $\eta^2 = 0.46$), reflecting more negative emotions after the white noise task (M=20.91, SD=7.53) as compared to before (M=15.36, SD=4.75).

3.2. Exploratory analyses

To explore the reported certainty, clarity, and emotional valence positive/negative of the false alarms, a 2 × 2 ANOVA was set up for each of these independent variables (mean scores) with n-back as within-subject factor and cycle phase as a between-subject factor. There was a main effect of Cycle Phase for Clarity of AHs ($F(1,40) = 5.38$, $p = 0.03$, $\eta^2 = 0.12$), where the participants tested in the early follicular phase (M=1.69, SD=1,23) reported the AHs to be more clear as compared to participants tested in the late follicular phase (M=0.92, SD=0.93). The interaction effect between Task and Cycle Phase was not found significant ($F(1,40) = 1.4$, $p = 0.26$, $\eta^2 = 0.03$). Also, no significant main effect of Cycle Phase or interaction effects were found for the variables Certainty and Emotional valence (All $F(1,40) < 3.2$, $p > 0.08$, $\eta^2 < 0.07$). Main effects of Task was found significant for two of the variables: Clarity ($F(1,40) = 5.76$, $p = 0.02$, $\eta^2 = 0.13$) and Certainty ($F(1,40) = 7.80$, $p = 0.008$, $\eta^2 = 0.16$).

4. Discussion

The current study tested hallucinatory proneness across the menstrual cycle, comparing the number of false alarms (sometimes referred to as hallucination proneness) in the low-estradiol early follicular phase and the high-estradiol late follicular phase using a white-noise paradigm. It was predicted an effect of cycle phase on reducing hallucination proneness in white noise, and that cognitive load would mediate this relationship. The main findings showed that participants tested in the early follicular phase reported more false alarms as compared to participants tested in the late follicular phase (H1; see Fig. 2). These results were supported by a multiple regression analysis showing that estradiol significantly predicted hallucination proneness across cycle phase and task load (H4; see Fig. 3). The effect of cycle phase on number of false alarms reported was not found to depend on the cognitive control (H2) manipulation (1-back vs 2-back task) or schizotypy score (H3).

4.1. Estradiol and hallucination proneness

The hypothesis (H1) that hallucination proneness would be higher in the low estradiol early follicular phase as compared to the high estradiol late follicular phase was supported by the finding of more false alarms during the early follicular phase as compared to participants tested in the late follicular phase (see Fig. 2). Exploratory analyses also showed that during the early follicular phase these hallucinations were 'heard' more clearly. There was no performance effect of menstrual cycle phase or differences in emotion induction between cycle phases (control analyses) that could account for the effect. Further, regression analysis showed that estradiol was negatively related to the number of false alarms/hallucination proneness (H4; see Fig. 3), suggesting that fluctuations in estradiol contribute to the observed cycle effect. Overall, the results converge with previous studies suggesting that positive symptoms increase with decreased levels of estradiol in people with schizophrenia (Bergemann et al., 2007; Goldstein and Link, 1988). The results are also consistent with observations of high hallucination frequencies in delusionary syndrome, a condition that typically relates to a menopausal drop in estrogen (Dubertret and Gorwood, 2001). The comparability with the current study and previous clinical findings is of course uncertain as there might be differences in underlying mechanisms between white-noise hallucinations and real hallucinations. Individuals with schizophrenia also report increased false alarms during white noise (Catalan et al., 2014) but has never been studied in relation to estradiol levels. Further, the results can be seen in relation to studies reporting altered auditory processing during the menstrual cycle (for a review see McFadden, 1998). Various studies have observed a latency change in the central (Elkind-Hirsch et al., 1991) auditory pathway, reflecting an increased latency of brainstem auditory evoked potential. Other studies report generally reduced auditory sensitivity during the early follicular phase as compared to time of ovulation (Swanson and Dengerink, 1988), more bilateral speech processing related to high levels of estradiol and progesterone (Hodgetts, Weis et al., 2015), and changes in signal to noise perception (Guimaraes et al., 2006; Sao and Jain, 2016). More specifically, Sao and Jain (2016) found that estradiol changes the signal to noise ratio as they found participants to have a more accurate discrimination between (real) voices and noise during the late follicular (ovulatory phase) as compared to the early follicular phase. Given the improved signal to noise detection this might also affect the ability to discriminate real sounds from false alarms, which could explain the reduced hallucination proneness observed in the current study during the high estradiol early follicular phase. How this plays out on the molecular level remains unknown. However, estradiol has been suggested to moderate psychotic symptoms by regulating dopamine receptor binding and reducing striatal dopamine (Owens et al., 2017), potentially by altering the sensitivity (Bédard et al., 1984; Koller et al., 1980) or the availability (Gordon et al., 1980) of these receptors. The role of dopamine for hallucinations is well known through the effect of antipsychotic drugs (Rolland et al., 2014). Similarly, Schmack et al. (2021) demonstrated, in mice, an increase in dopamine prior to experiencing false alarms, suggesting that dopamine contributes to a perceptual distortion in which individual priors/expectations are emphasized at the expense of actual sensory stimuli. An effect of estradiol on striatal dopamine levels could in this sense increase the ability to discriminate real sounds from false alarms.

4.2. Cognitive control and schizotypy

The second hypothesis of the current study was not supported. As hallucinations are thought to depend on cognitive control abilities (Laloyaux et al., 2019), and estradiol has been found to enhance cognitive control of bottom-up auditory processing (Hjelmervik et al., 2012), it was expected that the difference in false alarms between the early and late follicular phase would increase when solving the more demanding task (2-back). The analyses (ANOVA and regression) did, however, not support this as no interaction effect was found between cycle phase and N-back task. This result in isolation could indicate that the higher number of false alarms reported in the early follicular phase across task is not due to an effect of estradiol on cognitive control, but perhaps rather on bottom-up auditory processes as suggested above. Some evidence suggest that positive and cognitive symptoms do not always go hand in hand. For example, antipsychotic medication typically reduces auditory hallucinations while leaving cognitive impairment unaffected (Owens et al., 2017). Lastly, we cannot exclude that there is a methodological explanation for the lack of findings. A prerequisite for experiencing hallucinations is that the participants attend to the noise. The 2-back task might have been too challenging for some

of the participants to simultaneously keep attention on the noise (van de Ven and Merckelbach, 2003), and this might have distorted the results. This is supported by the data showing generally more false alarms during the 1-back than 2-back task – a finding that was not expected and that will be discussed in the second to last section.

The degree of schizotypy was also not found to affect the relationship between cycle phase and hallucinations during white noises. This is in contradiction to Hodgettes et al. (2015) who found increased false memory rate in participants scoring high on schizotypy during high levels of circulating estradiol. Since the current study and Hodgettes et al. (2015) study different phenotypes (symptoms), the results might however not be comparable. In general, the findings of the current study could indicate that the antipsychotic effects of estradiol observed in previous studies are not specific to schizophrenia. If the cycle effect was disease specific, one would expect individuals with high schizotypy scores to be more affected by the early follicular phase' low estradiol (but also see limitation section).

4.3. Effect of task load on hallucinations

The current study used a modified version of the paradigm presented in Laloyaux et al. (2019), who found more false alarms to be reported during the 2-back condition as compared to the 1-back condition when participants were in a negative emotional state. It was therefore surprising to find the reverse effect, namely more false alarms reported during the 1-back task. A few differences in the paradigms could explain the differences in results. First, Laloyaux et al. (2019) tested a larger sample. Second, Laloyaux et al. (2019) used a between subject design, while the current study had a within-subject design in which all participants completed both the 1-back and 2-back task, with the order of blocks being 2-back, 1-back, 2-back, and lastly 1-back task. A critical point is to keep the participants focused on the white noise. A previous study shows that if participants are directed to attend to other stimuli, the number of hallucinations goes down (Margo et al., 1981). The participants might have failed to keep the attention on the noise while simultaneously solving the challenging 2-back – this task also being the starting task makes it even more challenging, although the participants were given at least two practice trails before the real experiment began. When the 1-back task appeared, the participants were already more familiar with the task, and could perhaps better attend to the noise. In addition, the stressful nature of the 2-back task could have left the participants in a hypervigilant state, which could increase the hallucinatory proneness in the following 1-back blocks (Dodgson and Gordon, 2009). Looking into the data block by block, supports this interpretation: The number of false alarms is clearly lower during the first round of 2-back blocks as compared to the second round, suggesting that task novelty plays a role either by distracting from paying attention to the noise or by introducing the hypervigilant state.

4.4. Limitations

First, the study's between-subject design to investigate cycle phase effects poses a potential limitation of the study and is therefore discussed. It could be argued that a within-subject design involves less inter-subject variability and could have more accurately identify the variability associated with cycle phase changes. On the other hand, between-subject designs have the advantage of preventing carryover effects (e.g. Hausmann and Güntürkün, 2000) and drop out of participants. In the current study, participants were randomly allocated into groups, which reduces the risk of systematic effects of potential confounding variables. In addition, the significant hormone correlations suggest that the observed menstrual cycle effect is real. Second, limitations must be addressed in relation to the cognitive-perceptual schizotypy variable. The study lacks individuals with schizotypy scores in higher ranges, which might have effects on the strength of the correlation: While possible scores on the cognitive-perceptual factor range from 14 to 70, the current sample had scores ranging from 17 to 52. Also, the schizotypy analysis could have been underpowered as the variable was not considered in the power analysis. Given a medium effect size for the non-significant Schizotypy x Cycle phase interaction, a replication of this effect in a larger sample is warranted. Lastly, we want to comment on the procedure of cycle phase verification/ exclusion of participants based on hormone levels. This method is not absolute certain, and we cannot guarantee that there are no remaining individuals in the sample that were tested outside of the intended cycle phase.

5. Conclusion

Taken together, the current study suggests that hallucinatory proneness depend on the cycle phase in which participants are tested, and that this is caused by changes in estradiol levels across the menstrual cycle. The results suggest that higher levels of estradiol lead to better discrimination between sounds and noise, which could lower the number of false alarms. In general, the findings of the study could indicate that the antipsychotic effects observed in previous studies are side effects of estradiol's impact on neuronal processes, hence, the protective properties of estradiol are not limited to schizophrenia. Whether there exist qualitative differences in the phenomena and underlying mechanisms observed in this non-clinical sample and in psychotic patients experiencing hallucinations must however be taken into consideration.

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Declaration of Competing Interest

Authors have no conflict of interests to declare.

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