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High estradiol levels improve false memory rates and meta-memory in highly schizotypal women

Sophie Hodgetts*, Markus Hausmann, and Susanne Weis

Department of Psychology, Durham University, South Road, Durham, DH1 3LE, United Kingdom

*Corresponding Author:

Sophie Hodgetts
Department of Psychology
Durham University
South Road,
Durham DH1 3LE
United Kingdom
Phone: +44 (0) 191 33 43275
E-mail: s.l.hodgetts@dur.ac.uk

Abstract

Overconfidence in false memories is often found in patients with schizophrenia and healthy participants with high levels of schizotypy, indicating an impairment of meta-cognition within the memory domain. In general, cognitive control is suggested to be modulated by natural fluctuations in estrogen. However, whether estrogen exerts beneficial effects on meta-memory has not yet been investigated. The present study sought to provide evidence that high levels of schizotypy are associated with increased false memory rates and overconfidence in false memories, and that these processes may be modulated by natural differences in estradiol levels. Using the Deese-Roediger-McDermott paradigm, it was found that highly schizotypal participants with high estradiol produced significantly fewer false memories than those with low estradiol. No such difference was found within the low schizotypy participants. Highly schizotypal participants with high estradiol were also less confident in their false memories than those with low estradiol; low schizotypy participants with high estradiol were more confident. However, these differences only approached significance. These findings suggest that the beneficial effect of estradiol on memory and meta-memory observed in healthy participants is specific to highly schizotypal individuals and might be related to individual differences in baseline dopaminergic activity.

Keywords: Estrogen, cognitive disorganisation, knowledge corruption, false recognition

1. Introduction

Schizophrenia is a severe psychiatric disorder characterised by positive symptoms (e.g. hallucinations, delusions), negative symptoms (e.g. blunted affect, anhedonia) and cognitive deficits (e.g. cognitive disorganisation). While many aspects of cognition are impaired (Green, 1996; Lesh et al., 2011), it has been purported that memory processes in particular are severely affected (e.g. verbal memory: Toulopoulou and Murray, 2004; working memory: Manoach et al., 2000; see Aleman et al., 1999, for a meta-analysis).

Memory impairments in schizophrenia have been linked to delusions (Moritz and Woodward, 2006), that is, false beliefs characterised by implausibility, which are fixed in spite of evidence to the contrary and asserted with a high degree of confidence (e.g., grandiose delusions, persecutory delusions, paranoid delusions). While delusions are a hallmark of the diagnosis of schizophrenia, an understanding of their neurocognitive basis is still lacking (Gilleen and David, 2005). It has been suggested, though, that delusions are underpinned, at least in part, by a general susceptibility to forming false beliefs/memories with a high level of confidence (Laws and Bhatt, 2005; Moritz and Woodward, 2006). Therefore, investigating the factors influencing confidence in false memories could be of high clinical relevance by improving an understanding of the development and maintenance of delusions, and by potentially influencing individual treatment options for schizophrenia (Favrod et al., 2014; for a review, see Moritz et al., 2014).

To date, false memories in schizophrenia have received comparatively little attention, which might primarily be due to methodological problems. For example, most neurocognitive memory assessments measure recall and recognition accuracy by assessing hit rates, but neglect false recall and recognition, which can be assessed via false positive error rates (Moritz and Woodward, 2006). Those studies that have investigated false memories in

schizophrenia have mainly used the Deese-Roediger-McDermott (DRM) paradigm. In this paradigm, participants study a series of words (e.g. piano, sound, note, sing, melody, band, concert and instrument) that are semantically associated to a non-presented target word (e.g. 'music', the "critical lure", Roediger and McDermott, 1995). Participants are then required to freely recall as many words from the list as possible (recall phase), before being asked to complete a forced choice recognition test on a list comprised of previously seen words. The recognition list is comprised of the critical lure (strongest association to the study list), new words that are related to the study list (strongly associated, but less so than the critical lure), and new words that are unrelated to the study list). Typically, healthy participants falsely remember seeing the critical lure and / or new-related items ("false-positive response"; Roediger et al., 2001), during both the recall and the recognition test. Using this paradigm, it has been shown that while patients have poor recall abilities compared to healthy controls (increased forgetting, Elvevåg et al., 2004), they do not demonstrate increased false recognition (Elvevåg et al., 2004; Moritz et al., 2004). Using the same paradigm, Bhatt et al. (2010) found that patients, both with and without delusions, made more false positive responses during recognition, compared to controls. Moreover, during free recall, patients with delusions produced significantly more false positives than patients without delusions, and healthy controls (see also Brébion et al. 1999; Stirling et al., 1997). Thus, the proneness to false memories seems to be strongly related to the presence of delusions and a possible reason for the inconsistencies in present studies may be that some studies (e.g. Elvevåg et al., 2004; Moritz et al., 2004) did not differentiate between patients with and without delusions.

Considering that generally poorer memory in patients as opposed to healthy controls might confound the formation of false memories (Laws and Bhatt, 2005), an alternative avenue for research employs a non-clinical model of schizophrenia by investigating healthy participants with varying degrees of certain schizotypal personality traits (Ettinger et al., 2014; Johns and

van Os, 2001). Using the DRM paradigm, Laws and Bhatt (2005) investigated false memories in healthy participants, grouped according to their scores on the Peters et al. (2004) Delusional Inventory (PDI); during recall, high PDI scorers produced significantly more false positives compared to low PDI scorers. Saunders et al. (2012) extended these findings to determine which aspects of schizotypy are related to false memories by including a multidimensional schizotypy measure (The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE), Mason et al., 2005). The O-LIFE comprises four subscales: Unusual Experiences (i.e. perceptual aberrations and odd beliefs), Cognitive Disorganisation (i.e. attentional difficulties and thought disorganisation), Introvertive Anhedonia (i.e. blunted affect), and Impulsive Non-Conformity (i.e. antisocial behaviour). Saunders et al. (2012) found that high scorers on Unusual Experiences and/or Cognitive Disorganisation produced more false positives during recall compared to low scorers. Consequently, the authors suggest that specific subtypes of schizotypy are more susceptible to false memories, and thus might also be more delusion-prone.

The investigation of memory processes in schizophrenia and schizotypy has recently extended to acknowledge meta-cognitive processes (Bhatt et al., 2010; Moritz et al., 2002; 2003; 2004; 2005; 2006). Meta-memory refers to an individual's knowledge and awareness of their memory capabilities, and the processes of memory self-monitoring (Nelson and Narens, 1990; Pannu and Kaszniak, 2005). While many measures of meta-memory have been developed (Pannu and Kaszniak, 2005), retrospective confidence ratings are most relevant in the context of false memories and delusions. Indeed, Moritz and Woodward (2006) have argued that high confidence in false belief is a "defining feature of delusions" (p.185), and that the level of confidence one has in a (false) memory determines its impact on overt behaviour. That is, one is unlikely to act upon a memory, if one is not confident that it is correct. However, high confidence in a false memory could elicit drastic behavioural consequences.

As a meta-cognitive measure of confidence in false memories, Moritz et al. (2004) introduced the knowledge corruption index (KCI) defined as the proportion of high confidence responses that are errors. Employing the DRM paradigm, these authors found that while patients with schizophrenia and controls did not differ in number of false memories per se, patients made more high confidence errors both when forgetting items that were presented ("misses") and during false positive recognition.

With respect to meta-memory processes in healthy participants with schizotypal traits, Laws and Bhatt (2005) reported higher KCI scores for false memories in high PDI scorers, suggesting they are more confident in their errors than low PDI participants are. Corlett et al. (2009) extended these findings by including multiple schizotypy measures. In line with the findings of Moritz et al. (2004; 2006), highly schizotypal participants did not produce more false positives during recognition than those with low schizotypy. However, a positive correlation was found between schizotypy scores and confidence in false positive responses, particularly for subscales analogous to positive schizophrenic symptoms (e.g. perceptual aberrations, magical ideation). These findings provide further evidence that schizotypy provides an appropriate non-clinical model by which to investigate meta-memory impairments in schizophrenia.

A separate stream of research has shown that estrogen can act as a neuroleptic agent against the symptoms of schizophrenia (Seeman & Lang, 1990; Häfner, 2003; Riecher-Rössler et al., 1994; Kulkarni et al., 2013). Riecher-Rossler et al. (1994) directly investigated the possible neuroleptic properties of estradiol by assessing symptomology across the menstrual cycle. A significant association was found between levels of estradiol and clinical assessment scores; symptoms appeared to improve with increases in estradiol, and deteriorate when estradiol levels decreased. Further research has suggested that memory processes, including working memory (Hampson and Morley, 2013), verbal memory (Joffe et al., 2006), implicit

memory (Maki et al., 2002), and discriminability (Keenan et al., 2001) can be enhanced with increased levels of estrogen (for recent reviews see Duarte-Guterman et al., in press; Frankfurt and Luine, in press). However, it is currently unclear whether the effect of estrogen on memory occurs because of direct effects of estrogen on memory or rather via hormonal effects on memory control functions, such as meta-memory processes (Colzato et al., 2010). Indeed, it has been suggested that the enhancing effect of estrogen is particularly evident during tasks that demand a high level of (meta-) cognitive control, (Hjelmervik et al., 2012; Jacobs and D'Esposito, 2011). Given that meta-memory processes are conceptually comparable to cognitive control processes, it follows that meta-memory abilities should be enhanced under high estrogen conditions.

In summary, previous research has suggested that false memories and impaired meta-memory (indicated by overconfidence in errors) are found both in schizophrenia (potentially providing the basis for the experience of delusions in these patients) and in healthy participants scoring highly on certain schizotypy traits. Still, studies including measures of meta-memory are largely lacking. Another line of research suggests that within memory processes, especially meta-cognitive control functions in memory might be modulated by individual differences in estrogen.

In light of these previous studies, the present study employed a verbal DRM paradigm to further investigate whether or not high levels of schizotypy are characterised by increased false memory rates (indicated by a high rate of false positive responses during recognition) and with impaired meta-memory (as evidenced by high confidence in false memories). In addition, we sought to investigate whether false positive recognition rates and meta-memory abilities are affected by naturally fluctuating estradiol levels.

It was expected that participants with high levels of schizotypy would make more false positive errors than low schizotypy scorers and show overconfidence in these false memories, especially when their estradiol levels were low. Further, it was hypothesised that high levels of estradiol should have a beneficial effect, especially with respect to meta-cognitive control of false memories.

2. Method

2.1.Participants

Seventy-three healthy, normally cycling women (out of 81 tested; see hormone assessment section for exclusion details) with a mean age of 23 years (S.D. = 4.86; range: 19 – 40 years) were assigned to either the high (n = 37) or low estradiol (n = 36) group, based on saliva estradiol assays (see section 2.2.3 Hormone assays). This method of classification is based on objective quantification of estradiol levels, which are subject to both individual (inter-subject) differences and to natural (intra-subject) fluctuations across the menstrual cycle. Age did not differ significantly between the groups ($t_{(71)} = 1.21$, $p = 0.23$).

All participants were native English speakers with normal or corrected-to-normal vision. Participants did not currently, or in the previous 6 months, use hormonal contraceptives or other hormone regulating medications.

2.2. Procedure and materials

2.2.1. Schizotypy questionnaire

The short version of the O-LIFE was used to measure schizotypy (Mason et al., 2005). This scale is comprised of four factors: Unusual Experiences, Cognitive Disorganisation, Impulsive Non-conformity, and Introvertive Anhedonia. A schizotypy scale with multiple subscales was applied as the data reported here form part of a larger battery of cognitive tasks

(for each of which different subscales might be most relevant). The Cognitive Disorganisation (CD) subscale measures cognitive aspects of schizotypy such as poor attention and concentration (Mason et al., 2005). In light of previous research suggesting that CD is particularly associated with false memories (e.g. Saunders et al., 2012), this scale is the focus of the current study. Moreover, this scale contains items that directly relate to cognitive control, such as "Are you easily confused if too much happens at the same time?" and "Do you often have difficulties in controlling your own thoughts?". Given that meta-memory processes are essentially cognitive control processes and that estrogen has been shown to have an enhancing effect on cognitive control, this subscale was considered most appropriate, Participants are required to give yes/no responses, and the score is calculated as the sum of all positive answers. A median split was performed based on CD scores (Low CD = 0-4 (M = 2.39 ± 1.29), High CD = 5-11 (M = 7.11 ± 1.75; see Table 1).

2.2.2. Verbal meta-memory task

Six word lists (received and adapted from Moritz et al., (2006) unpublished companion study) comprising 12 semantically associated words each were used for the verbal meta-memory task. The study lists were associated with the following target words: laugh, funeral, road, holiday, time, and panic. The task was completed via a computer using MATLAB (R2013a, MathWorks). For the study phase, participants were presented with the study list, one immediately following another, in the centre of the screen. Each word from the list was presented individually, at a rate of two seconds per word. After all 12 words had been presented; participants were given 75 seconds to freely recall as many words from the list as possible by writing them down (recall phase). The next list was then presented. This procedure was repeated for all six lists. The recognition lists were also made up of 12 words: the critical lure, three new words that are related to the study list ("new-related items"), two new words that are unrelated to the study list ("new-unrelated items"), and six words from the

study list ("old items"). For the recognition phase, participants were presented with the recognition list, one word at a time, in a random order, in the centre of the screen. Participants were asked to indicate via button press whether they thought the item was old or new, and how confident they were in their response on a four-point scale (1-4). Words were not randomised between lists, nor was the order of lists, but the order of words within each list was randomised. There was no time restriction during the recognition phase. The recognition test is the focus of the present paper. From the recognition phase we calculated the number of false positive responses, and knowledge corruption indices ([highly confident false positives /all highly confident responses] × 100)].

2.2.3. Hormone assays

To facilitate collection of a pure saliva sample, women were asked to avoid eating, drinking, smoking and brushing teeth for 30 minutes prior to the testing session. One sample (2 ml) was collected at the beginning of the test session. The saliva was stored -20°C until completion of the study. Samples were then assayed by an independent professional hormone laboratory with commercially available hormone assays. Eight women were excluded from further analyses due to saliva sample contamination by blood, as indicated by sample discolouration and/or extremely high hormone levels out the expected range of the assay. Classification of estradiol as high or low was based on a median-split (split score: 3.4 pg/ml). Mean estradiol and progesterone levels for each group are given in Table 1.

Table 1. Saliva estradiol and progesterone levels and cognitive disorganisation scores for each group (mean±standard deviation).

	Low cognitive disorganisation		**High cognitive disorganisation**	
	Low estradiol N=15	High estradiol N=23	Low estradiol N=21	High estradiol N=14
Estradiol (pg/ml)	2.11±.82	5.37±2.70	2.04 ±.73	6.58±4.53
Progesterone (pg/ml)	77.72±77.19	158.67±111.33	76.91±45.18	130.01±101.03
Cognitive disorganisation	2.27±1.22	2.48±1.34	7.09±1.7	7.14±1.88
Age	22.20±4.39	24.21±6.01	22.38±4.66	22.79±3.40

3. Results

3.1.Salivary hormone concentrations

Estradiol and progesterone levels did not differ between the high CD and low CD subgroups within the low estradiol (LE) (both $t_{(34)} < 0.24$, n.s.) or high estradiol (HE) group (both $t_{(35)} < 1.03$, n.s.)

On the other hand, estradiol levels were significantly higher in the HE than in the LE subgroup, both within the low CD group ($t_{(36)} = 4.52$, $p = < 0.001$) and the high CD group ($t_{(33)} = 4.54$, $p < 0.001$). Similarly, progesterone levels were significantly higher in the HE than in the LE subgroup both within the low CD group ($t_{(36)} = 2.45$, $p = 0.019$) and in the high CD group ($t_{(33)} = 2.12$, $p = 0.041$).

3.2 Data analysis

2 × 2 ANCOVAs with estradiol (high, low) and cognitive disorganisation (high, low) as between-subjects factors were conducted on a variety of measures of memory and meta-memory (confidence in memory). Because progesterone has been shown to influence memory process (Ertman et al., 2011), progesterone levels were included as a covariate.

3.3. Recognition of critical lure

3.3.1. False recognition of critical lure

For the percentage of false-positive responses to the critical lure, the main effects of progesterone, CD group, estradiol group as well as the CD × Estradiol interaction did not reach significance (all $F_{(1, 68)} < 2.09$, $p \geq 0.15$).

3.3.2. Knowledge Corruption Index for false recognition of lure items

The examination of knowledge corruption indices revealed no significant main effects of progesterone, CD group, estradiol group, and the CD × Estradiol interaction did not reach significance (all $F_{(1,68)} < 0.19$, $p \geq 0.66$). Table 2 lists false positive error rates and KCIs for each group.

Table 2 False positive error rates and knowledge corruption indices to critical lure items for each group (means ± standard error).

	Low Cognitive Disorganisation		**High Cognitive Disorganisation**	
	Low estradiol N = 15	High estradiol N = 23	Low estradiol N = 21	High estradiol N = 14
False positives	54.44 ± 7.18	56.52 ± 5.21	57.14 ± 6.56	53.57 ± 4.34
Knowledge corruption index	51.22 ± 8.63	52.61 ± 7.51	58.41 ± 8.65	52.14 ± 9.72

3.4. Recognition of new-related items

3.4.1. False recognition of new-related items

The ANCOVA on the percentage of false-positive responses revealed a significant interaction between CD group and Estradiol group, ($F_{(1, 68)} = 4.72$, $p = 0.03$, $n_p^2 = 0.07$). Neither the main effects of progesterone, or CD or estradiol group were significant (all $F_{(1, 68)} < 1.28$, $p \geq 0.26$.).

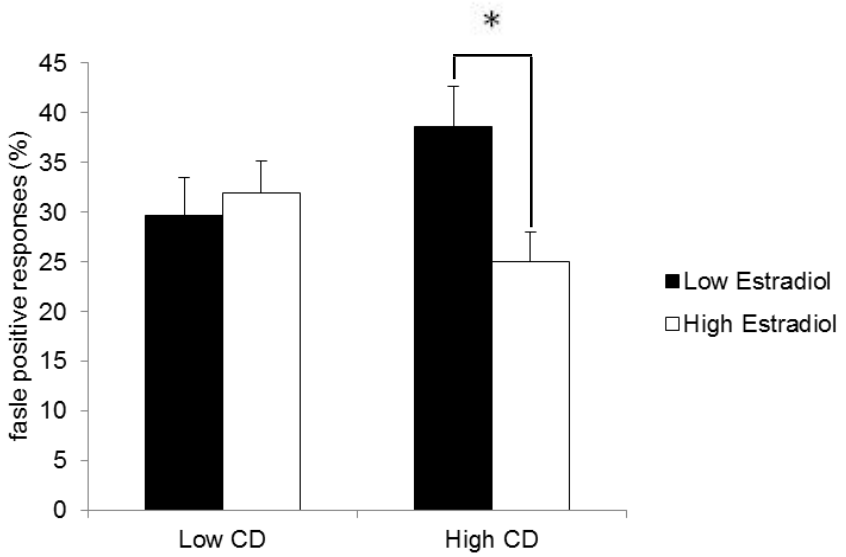

Figure. 1. The interactive effect of estradiol and cognitive disorganisation on false positive response rates for new-related items (error bars are SEMs * = $p < 0.05$).

Post-hoc t-tests (Bonferroni corrected) revealed that the significant interaction was driven by a significant difference between the HE and LE groups within the High CD group ($t_{(33)}$ = 2.48, p = 0.018; see Fig. 1).

3.4.2. Knowledge Corruption Index for false recognition of new-related items

For the knowledge corruption indices for new-related items a significant interaction between CD group and E group ($F_{(1, 68)}$ = 5.51, p = 0.02, n_p^2 = 0.08) (see Fig. 2) was found. The ANCOVA revealed that the main effects of progesterone, CD, and estradiol group were not significant (all $F_{(1, 68)} < 0.57$, $p \geq 0.45$).

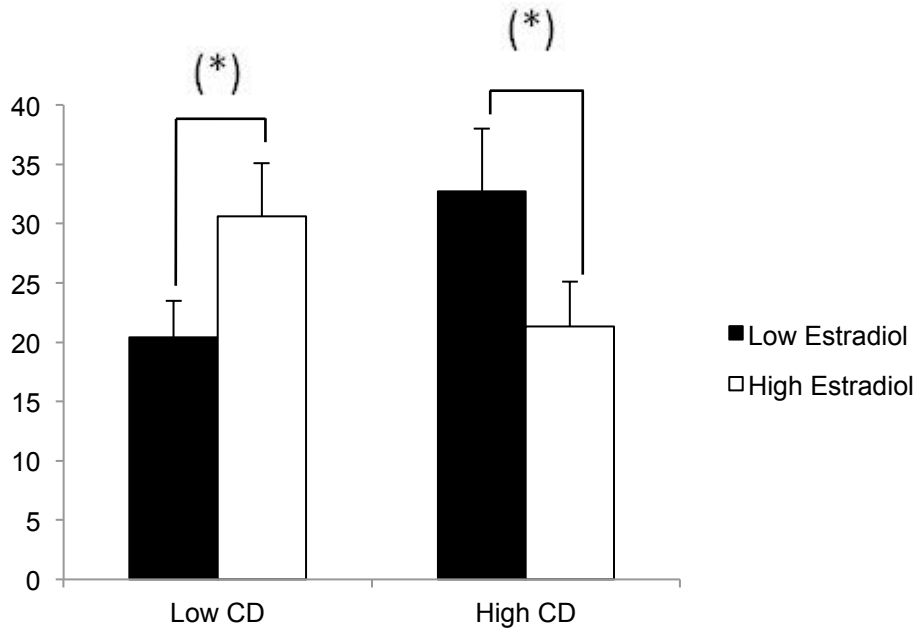

Figure. 2. The interactive effect of estradiol and cognitive disorganisation on KCI for new-related items (error bars are SEMs; (*) = $p < 0.15$).

Post-hoc t-tests (Bonferroni) were conducted within each CD group. This revealed that the difference between the HE and LE subgroups approached significance, within both the High CD ($t_{(33)} = 1.57$, $p = 0.13$) and Low CD groups ($t_{(36)} = 1.69$, $p = 0.10$) (see Fig. 2). Table 2 lists false positive error rates and KCIs for each group.

Table 3 False positive error rates and knowledge corruption indices to new-related items for each group (means ± standard error).

	Low Cognitive Disorganisation		**High Cognitive Disorganisation**	
	Low estradiol N = 15	High estradiol N = 23	Low estradiol N = 21	High estradiol N = 14
False positives	29.63 ± 3.89	31.88 ± 3.24	38.62 ± 4.01	25.00 ± 2.95
Knowledge corruption index	20.42 ± 3.07	30.64 ± 4.45	32.70 ± 5.32	21.34 ± 3.75

3.5. Recognition of old items (misses)

For the percentage of false-negative responses to old items, the main effects of progesterone, CD group, estradiol group as well as the CD × Estradiol interaction did not reach significance (all $F_{(1, 68)} < 1.22$, $p \geq 0.27$).

The examination of knowledge corruption indices also revealed no significant main effects or interactions (all $F_{(1,68)} < 0.013$, $p \geq 0.72$).

3.6. Relationship between hormones, schizotypy and meta-memory

The ANCOVA revealed an interactive effect of estradiol and cognitive disorganisation on both false memory rates and knowledge corruption for new-related items. Therefore, we conducted moderated multiple regression analyses (enter method) to investigate any linear relationship between estradiol, progesterone, cognitive disorganisation (and estradiol × CD interaction) and both dependent variables, for the new-related items, in more detail. To avoid multicolinearity, independent (predictor) variables were centered. The CD × E interaction variable was calculated as the product of estradiol and CD (both centered)

For the false memory rate, the moderated multiple regression model was not significant ($F_{(4, 68)} = 0.57$ $p = 0.69$). None of the predictors approached significance (all $\beta < 0.03$, $p \geq 0.28$).

Similarly, the moderated multiple regression model for the KCIs was not significant ($F_{(4, 68)} = 0.46$, $p = 0.77$). None of the predictors approached significance (all $\beta < 0.12$, $p \geq 0.33$).

4. Discussion

The present study aimed to examine individual differences in false memory rates and meta-memory. It was hypothesised that high levels of cognitive disorganisation would be associated with increased false memory rates and impaired meta-memory, indicated by overconfidence in false memories. Further, the present study sought to investigate whether false memories and meta-memory processes are modulated by differences in estradiol levels, which occur naturally both between and within participants due to fluctuations across the

menstrual cycle. We found that participants with high levels of cognitive disorganisation and high estradiol levels produced significantly fewer false memories than highly disorganised participants with low estradiol levels. No effect of estradiol was found in participants with low levels of cognitive disorganisation. Moreover, highly disorganised participants with high levels of estradiol were less confident in their false memories than those with low estradiol. In contrast, participants with low levels of cognitive disorganisation and high estradiol levels were more confident in their false memories than those with low estradiol levels. These findings will be discussed with respect to individual differences in the physiological processes underlying memory and meta-memory, including baseline dopaminergic activity.

Estradiol reduces false recognition in highly schizotypal women.

Investigating false positive rates for experimentally induced false memories revealed an interactive effect of schizotypy and estradiol levels. While increases in estradiol levels did not influence false memory rates in participants scoring low on cognitive disorganisation, high levels of estradiol were associated with significantly reduced false memory rates in participants high in cognitive disorganisation.

This suggests that estradiol might have a positive effect (reducing false memory rates) specifically in participants with high levels of cognitive disorganisation. While the effect of estradiol on false memories has not yet been directly examined in humans, recent animal studies have demonstrated improved object recognition memory in rats following estradiol treatment (e.g. Frye et al., 2007; Inagaki et al., 2010; Jacome et al., 2010). In contrast to previous studies investigating recognition performance, the present findings suggest that estradiol does not improve false recognition in humans in general. Rather, the effect was specific to participants scoring high on cognitive disorganisation. In addition, no such effects

were found for false negative error rates, suggesting that the effects of both estradiol and schizotypy are specific to false memories.

This finding is highly unlikely to be due to higher hormone concentrations in high CD participants, as both CD groups (within the high estradiol group) did not significantly differ in estradiol (or progesterone) levels. Instead, the present findings suggest that the estradiol effect of reducing false memory is specific to individuals with high cognitive disorganisation, and thus those especially prone to false memories.

Estradiol might influence memory via dopaminergic actions

It has recently been suggested that the effect of estrogen on cognition is dependent on individual differences in baseline dopamine function (Colzato and Hommel, 2014). These authors suggest that dopaminergic effects on cognitive tasks (including learning and working memory) follow an 'Inverted-U' function; performance improves with medium dopamine levels, but deteriorates with high/low levels. Given that estradiol is associated with higher dopamine turnover rates, Colzato and Hommel (2014) speculate that participants with low baseline dopamine levels, and thus poor cognitive performance, might benefit from high levels of estradiol and concurrent increases in dopamine. In contrast, estradiol would have detrimental effects in those with high baseline dopamine levels and good cognitive performance, as dopamine increases beyond an optimal point. Indeed, behavioural evidence suggests that schizotypy (and schizotypal personality disorder) is associated with aberrant dopamine function (e.g. Mohr et al., 2004; McClure et al., 2010). Mohr et al. (2004) demonstrated that levodopa (a dopamine agonist) improved visuo-motor performance exclusively in participants with high 'positive' schizotypy (i.e. magical ideation); low schizotypy participants showed a slight performance deterioration with levodopa. Subsequently, Mohr et al. (2004) suggest that high schizotypy is associated with a relative

hyperdopaminergia, and a better ability to adapt to higher dopamine levels. If high levels of cognitive disorganisation are associated with relative hyperdopaminergia, this might also explain the improvement in false positive error rates shown by participants high in schizotypy with high estradiol levels, while low schizotypy participants showed a slight (non-significant) impairment.

It is notable that the false memory rates seen in the higher schizotypal participants in the high estradiol group are comparable to those seen in both the low schizotypy subgroups. This might suggest that the effect of estradiol is limited not only to a specific subgroup, but also that it is not enhancing per se, rather estradiol has a 'normalising' effect on false memory rates.

False recognition of the critical lure is not influenced by estradiol or schizotypy

The analysis of responses to the critical lures revealed that neither estradiol nor cognitive disorganisation affected false positive error rates for the lures. This suggests that false memories created by the lure are different to those created by the related items, in that the stronger semantic relationship between the critical lure and the word lists might create a 'stronger' false memory trace. In this case, both schizotypy groups might susceptible to a ceiling effect; that is, the effect of estradiol might not be strong enough to exert a protective effect over false memory rates related to the critical lure. Still, our data suggests that higher levels of estradiol might help improve memory processes in those participants high in CD.

Estradiol reduces false memory confidence in highly schizotypal women

The analysis of confidence in false memories, measured by KCIs, also revealed a significant interaction. In participants scoring high in cognitive disorganisation, high estradiol levels resulted in decreased confidence in false memories, while for participants scoring low

on cognitive disorganisation, confidence in false memories was greater with higher estradiol levels. When considering meta-memory as a cognitive control process, the present data suggests that the beneficial effect of estradiol on cognitive control (Hjelmervik et al., 2012; Jacobs and D'Esposito, 2011; Keenan et al., 2001) might be specific to participants with high cognitive disorganisation, at least within the domain of memory.

Recent evidence suggests that meta-cognitive processes, like memory processes, can be influenced by dopamine. Using magnetoencephalography during a forced-choice word recognition paradigm, Joensson et al. (2015) demonstrated improved meta-cognitive ability in participants who received 100mg of L-dopa, as compared to placebo. In addition, dopamine administration was associated with increased activity of the medial prefrontal cortex.

It is notable that a similar interaction was found for both memory performance, measured by the rate of false positives, and meta-memory as measured by KCI. For both measures, participants scoring high in cognitive disorganisation benefitted from high levels of estradiol. However, this improvement was significant for the false positive error rates only, suggesting that the objective measures (false positive error rates) might be more sensitive to the effects of schizotypal traits and estradiol levels. This finding supports the notion that the inclusion of both objective (e.g. false positive error rates) and subjective measures (e.g. memory confidence) is important when investigating memory process across the schizophrenic spectrum.

The relationship between sex hormones, schizotypy and memory processes

The present study failed to demonstrate a linear relationship between the interactive effect of estradiol and schizotypy on either false positive error rates or knowledge corruption. However, it is possible that the relationship between these factors it is not linear. Indeed, findings from a recent animal study suggest that the enhancing effects of estradiol on

recognition abilities are non-linear. Inagaki et al. (2010) demonstrated that medium doses of estradiol (17α-estradiol) were most effective, while high and low doses were ineffective. An alternative explanation for the lack of a significant relationship is that the observed estrogenic effects are not directly related to estradiol but another estrogen, such as estrone. Indeed, Louzã et al. (2004) reported that schizophrenic patients given an adjunctive estrone treatment showed a trend towards greater symptom improvement than patients given an adjunctive placebo. The authors note, however, that this effect was not comparable to the significant improvements seen in patients with 17β-estradiol (e.g. Kulkarni et al., 1996; 2001). Moreover, given that estradiol is the most potent agonist of estrogen receptors (Turgeon et al., 2004), it seems unlikely that estrone is related to the current findings.

Importantly though, the present results may explain some of the inconsistent findings with respect to false memories in schizophrenia, which typically do not control for differences in the hormonal environment (e.g. menstrual cycle). Specifically, if estradiol levels are high in patients the risk of false memories might be reduced, as suggested by the high CD group of the present study. Thus, differences between patients and controls may only be apparent when estradiol levels are low in female patients, or when males dominate patient samples. For example, Bhatt et al. (2010) demonstrated elevated false positive recognition in both delusional and non-delusional schizophrenic patients compared to controls. In this study, both patient groups were male-dominated (12 men 1 woman, and 11 men, 1 woman respectively). Similarly, using a stem completion task, Stirling et al. (1997) report increased rates of false recall in patients compared to controls. This patient sample contained 22 males to 5 females. However, using a gender-balanced patient sample (18 males, 17 females) Moritz et al. (2006) found no excess of false positive error rates in patients. Although these studies also vary in task type, these results suggest that, in

conjunction with the present study; differing hormonal environments between participants may modulate differences between patients and controls (but see Moritz et al., 2004).

Conclusions

In conclusion, the present study demonstrated that high levels of estradiol resulted in reduced rates of false memories together with a reduction of an over-confidence in these memories in participants with high levels of schizotypy, specifically cognitive disorganisation. Considering that overconfidence in false memories is key to the development and maintenance of delusional symptoms, these results provide additional support for the potential role of estrogen as a neuroprotective agent against the symptoms of schizophrenia (Seeman and Lang, 1990; Riecher-Rössler et al., 1994; Kulkarni et al., 1996). Moreover, these findings lend further support to the notion that estradiol effects are dependent upon individual differences in the neurophysiology underlying cognitive processes (e.g. baseline dopamine function). For example, a relative hyperdopaminergia (at baseline) in participants with high levels of cognitive disorganisation might explain the improvement in false positive error rates shown by these participants with high estradiol levels, while low schizotypy participants demonstrated a slight impairment. Finally, in the clinical context, the present results underline the importance of taking individual differences into account when devising tailored treatment options for schizophrenia.

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