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Estradiol-related variations in top-down and bottom-up processes of cerebral lateralisation

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Abstract

Objective: Natural fluctuations of sex hormones have been shown to modulate cerebral lateralisation in dichotic listening tasks. Two recent studies presented contradictory notions regarding the mechanism of this effect. Specifically, while Hjelmervik et al. (2012) suggested that estradiol affects lateralisation by enhancing top-down processes, such as cognitive control, Hodgetts et al. (2015) suggested that the effect was due to estradiol-related variations in bottom-up aspects of lateralisation.

Method: The present study used two well-established left- and right-lateralised dichotic listening tasks (Hugdahl, 1995, 2003; Grimshaw et al., 2003; 2009), with forced-attention conditions to differentiate between these two ideas. Fifty-two naturally cycling women underwent both tasks, during either the menstrual, follicular or luteal cycle phase. Saliva estradiol and progesterone levels were determined by luminescence immunoassays.

Results: The results showed that sex hormones did not affect language lateralisation, which may be due to the larger degree of lateralisation yielded by the task, compared to that shown by Hodgetts et al. (2015). In the emotional prosody task, high levels of estradiol were marginally associated with a reduction in cognitive control; while the language task yielded no cycle effects for either top-down or bottom-up processes.

Conclusions: In sum, the current study revealed weak support for the idea that estradiol affects top-down control of lateralisation, as measured with dichotic listening tasks. Given that the task employed in the present study seemed less cognitively demanding than that used previously, it is suggested that estradiol-related inter- and intra-individual variations in lateralisation are small when task demands are low.

Keywords: Estradiol; Progesterone; Lateralisation; Dichotic listening; Cognitive control

Introduction

Sex hormones, such as estradiol and progesterone, have been shown to influence functional brain organisation. In particular, cerebral lateralisation (i.e., the differential involvement of the left or the right hemispheres in specific cognitive process) is sensitive to the fluctuations in estradiol and progesterone that occur naturally across the menstrual cycle. While lateralisation is stable in men, it fluctuates within relatively short time periods across the menstrual cycle in women (for a review, see Hausmann & Bayer, 2010). Indeed, a number of neuropsychological studies, across different modalities and cognitive processes, have demonstrated reduced lateralisation during cycle phases associated with high levels of estradiol during the follicular phase (e.g., Holländer et al., 2005; Weis et al., 2008) or high levels of both estradiol and progesterone during the luteal phase (e.g. Hausmann et al., 2002; Hausmann & Güntürkün, 2000; Hausmann, 2005; Rode et al., 1995; Alexander et al., 2002; Altemus et al., 1989; Mead & Hampson, 1996) as compared to greater lateralisation during the low-hormone menstrual phase in these studies.

The dichotic listening (DL) paradigm is commonly used to investigate language lateralisation (Hugdahl, 1995, 2003; Hugdahl et al., 2009). The paradigm involves the presentation of two auditory stimuli, usually monosyllabic words (e.g. Alexander et al., 2002; Hampson, 1990a, 1990b) or consonant-vowel syllables (e.g. Cowell et al., 2011; Sanders & Wenmoth, 1998; Wadnerkar et al., 2008). One stimulus is presented to the left ear, and the other is presented simultaneously to the right ear. Participants are required to report the syllable/word they heard the most clearly, either verbally or by button press. In healthy right-handed adults, this task typically reveals a bias towards stimuli presented to the right ear, indicative of left-hemispheric language lateralisation. The so-called right ear advantage (REA) results from several factors relating to the anatomy of auditory projections from the ear to the primary auditory cortex (Kimura, 1967). Firstly, although auditory information is relayed to both hemispheres via subcortical projections, contralateral projections are stronger than ipsilateral ones. Therefore, when both ears are stimulated simultaneously, the ipsilateral projections are suppressed in favour of processing contralateral stimuli (Hugdahl, 2003; Kimura, 1967; Pollmann et al., 2002, for a review see Westerhausen and Hugdahl, 2008). Stimuli presented to right ear have direct access to the language-dominant left hemisphere. In contrast, stimuli presented to the left ear are projected to the right hemisphere and have to be transferred via the corpus callosum for processing.

Several studies have used the DL task to investigate language lateralisation across the cycle, yielding inconsistent results. While many studies have demonstrated increased language lateralisation when levels of estradiol and/or progesterone are high (Cowell et al., 2011; Hampson, 1990a, 1990b; Sanders & Wenmoth, 1998; Wadnerkar et al., 2008), others have shown the opposite, a decreased REA during the luteal phase ("premenstrual week", Alexander et al., 2002; Altemus, et al., 1989; midluteal phase, Mead & Hampson, 1996). Moreover, two recent DL studies did not find that the menstrual cycle affected language lateralisation; the non-forced condition in Hjelmervik et al. (2012) and Can et al. (2012) (see Hodgetts et al. 2015).

Task instruction can also affect the REA and interact with menstrual cycle effects in the DL task (Hjelmervik et al., 2012; Wadnerkar et al., 2008; Hodgetts, Weis, & Hausmann, 2015). In these studies, participants are required to selectively attend to and report from either the left or the right ear, in addition to the standard non-forced attention condition in which participants are not required to allocate attention to either the left or right ear. In contrast to the non-forced attention condition, the forced-left condition requires top-down cognitive control, requiring participants to actively override the tendency to report stimuli presented to the dominant right ear (Hugdahl, 2003; Loberg et al., 1999; Hugdahl et al., 2009). While

Wadnerkar et al. (2008) pooled data across all three conditions, Hjelmervik et al. (2012) found a cycle-related change only in the condition that required participants to shift attention to stimuli presented to the left ear. In this condition, women in the high-estradiol follicular phase showed an increased left-ear advantage compared to both the menstrual and the luteal phase. As no menstrual cycle effect was observed in the non-forced condition, Hjelmervik et al. (2012) concluded that estradiol influences cognitive control as opposed to language lateralisation *per se*.

A recent study by Hodgetts et al. (2015) aimed to replicate this finding. In this study, the DL task was used in a between-subjects design. Naturally cycling women were tested only once, with all three forced-attention conditions, and hormone levels (assessed via saliva assays) were used *post-hoc* to classify women as either high or low in estradiol. In contrast to Hjelmervik et al. (2012), this study demonstrated reduced lateralisation in women with relatively high estradiol levels across all attention conditions and regardless of cognitive control demands. Consequently, it was concluded that sex hormones, and particularly estradiol, reduced the stimulus-driven, bottom-up aspect of lateralisation, while top-down cognitive control was unaffected. Given that different attention conditions were used, Hodgetts et al. (2015) argued that the observed effect was unlikely to be due to sex hormones selectively influencing one hemisphere. Moreover, it was argued that it is unlikely that sex hormones influenced the efficacy of the subcortical projections that give rise to the DL biases, as sex hormonal effects on subcortical auditory pathways are not known (Al-Mana et al., 2008). Instead, it was proposed that the observed reduction in DL biases occurred on the cortical level, perhaps by sex hormones modulating lateralisation via their neuromodulatory effects on interhemispheric inhibition (Hausmann, 2010; Hausmann & Bayer, 2010; Weis & Hausmann, 2010).

The *hypothesis of progesterone-mediated decoupling* originally proposed that high levels of progesterone reduced lateralisation by suppressing the excitatory responses of neurons to glutamate and increasing their response to GABA. In turn, this would result in a 'decoupling' of the hemispheres by reducing corticocortical transmission and interhemispheric inhibition (Hausmann & Güntürkün, 2000). This model was later revised, in light of evidence that estradiol may also modulate interhemispheric interaction and, in turn, lateralisation (Hausmann et al., 2013; Weis et al., 2008; Weis et al, 2011; Hausmann et al., 2006; Holländer et al., 2005). In line with this hypothesis, Hodgetts et al. (2015) argued that the reduced REA found in women with high estradiol levels during the non-forced and forced-right conditions may be explained by a reduction of inhibition of the subdominant right hemisphere by the dominant left. This would facilitate right hemisphere processing of stimuli presented to the left ear. Moreover, during the forced-left condition, it was suggested that the top-down control required to successfully ignore the dominant right ear in favour of the left ear results in a shift of activation from the left hemisphere to the right hemisphere. As such, the reduced LEA in the forced-left condition may be viewed as a reduction of inhibition from the right hemisphere over the left hemisphere, which subsequently facilitates left hemisphere processing of stimuli presented to the right ear, which would consequently reduce the LEA.

Given that interhemispheric inhibition is a universal process that should affect lateralisation generally, it follows that high estradiol levels should also reduce lateralisation for tasks related to the right hemisphere. Thus, the present study aims to extend these findings of Hodgetts et al. (2015) using a different DL paradigm. The present study used a DL paradigm that includes both a linguistic and an emotional prosody task. Like the DL tasks used in previous studies (Cowell et al., 2011; Hjelmervik et al., 2012; Hodgetts et al., 2015; Sanders & Wenmoth, 1998; Wadnerkar et al., 2008), this task involves the simultaneous presentation of two different words, one to the left and one to the right ear. However, unlike the tasks used in the aforementioned studies, the words presented to participants in the present study also differ in emotional prosody. Thus, participants may be asked to listen to the stimuli and respond to a specific word in the linguistic task, or they may be asked to respond to a specific emotional tone in the emotional prosody task. These tasks have been shown to produce a REA and a LEA, respectively on account of left hemispheric specialisation for language processing, and right hemispheric specialisation for emotion processing (Bryden & MacRae, 1988; Grimshaw et al., 2003; 2009; Najt et al., 2011). In addition, similar to Hjelmervik et al. (2012) and Hodgetts et al. (2015), the present study incorporated a cognitive control (top-down) element into both the linguistic and the emotional prosody task, by implementing two forced-attention conditions and asking participants to respond only to targets presented to the left or right ear. This experiment was designed to differentiate between two contradicting ideas claiming that estradiol can affect lateralisation by modulating (improving) the top-down (Hjelmervik et al., 2012) or bottom-up aspects of cerebral lateralisation (Hodgetts et al., 2015). If estradiol affects the bottom-up aspects of lateralisation, reduced DL biases should be found in both tasks, regardless of the forced attention condition, when estradiol levels are high. In contrast, if estradiol affects cognitive control, increased DL biases should be found in the forced-left and forced-right conditions of the linguistic and emotional tasks, respectively.

Method

Participants

Fifty-two healthy, normally cycling women (out of 55 tested; see Hormone Assessment section for exclusion details) with a mean age of 25.15 years (*SD* = 6.60, range: 19-41 years) were tested either during the menstrual (cycle days 2 - 5), follicular (cycle days 8 - 12), or luteal cycle phase (cycle days 20 - 22). All participants were native English speakers and were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). The laterality quotient (LQ) provided by this hand preference measure is calculated as [(R – L) / (R + L)] × 100, resulting in values between –100 and +100, indicating consistent sinistrality and dextrality, respectively. The mean LQ was 78.79 (*SD* = 19.82). There was no difference in age ($F_{(2, 49)} = 0.49$, $p = .62$) or handedness ($F_{(2, 49)} = 0.12$, $p = .88$) between the groups. Mean age and handedness are given in Table 1. This study was approved by the Durham University Psychology Department Ethics Committee.

Table 1. Estradiol, progesterone, handedness and age (mean ± standard deviation and range) for all women in each cycle phase.

	Menstrual (n = 17) M ± SD (range)	**Follicular (n = 18)** M ± SD (range)	**Luteal (n = 17)** M ± SD (range)
Estradiol (pg/ml)	2.73 ± 2.45 (0.30 – 8.80)	4.45 ± 3.66 (1.40 – 16.80)	4.42 ± 4.34 (0.40 – 20.10)
Progesterone (pg/ml)	101.41 ± 34.00 (46.00 – 177.00)	130.89 ± 62.77 (52.00 – 283.00)	281.94 ±109.96 (73.00 – 510)
Handedness LQ	77.02 ± 23.91 (20.00 – 100)	78.87 ± 18.53 (37.50 – 100)	80.46 ± 17.59 (47.37 – 100)
Age	24.29 ± 6.27 (19.00 – 41.00)	26.39 ± 6.42 (20.00 – 39.00)	24.71 ± 7.29 (19.00 – 41.00)

All participants reported no current/previous psychiatric or neurological illness. Participants were not pregnant and did not currently, or in the previous 6 months, use hormonal contraceptives or other hormone regulating medications.

Hormone assays

Two saliva samples were collected during each session, one before the dichotic listening tasks, and one after (2 × 1 ml). To facilitate the collection of the samples, all participants were asked to avoid eating, drinking, smoking, chewing gum or brushing their teeth for 30 minutes prior to the test session. The saliva was stored at -20°C until completion of the study. Samples were assayed by an independent, professional hormone laboratory with commercially available luminescence immunoassays for estradiol and progesterone. The analysis was completed on an average amount of the two samples. The sensitivity of the estradiol assay was 0.3 pg/ml, the sensitivity of the progesterone was 2.6 pg/ml. Intra-assay coefficients for estradiol and progesterone were 13.3% and 6%, respectively.

Three women were excluded from further analyses due to progesterone levels exceeding the range of the assay (> 1000 pg/ml), or contamination by blood.

The linguistic and prosodic dichotic listening task

The DL task consisted of a linguistic (target word identification) and a prosodic task (target emotional tone identification). The stimulus set for both tasks consisted for four, two-syllable words: “bower”, “dower”, “power” and “tower” spoken in angry, happy, sad and neutral tones of voices by a New Zealand male voice (Grimshaw et al., 2003; 2009). The stimuli were presented in blocks of 144 trials, consisting of all possible pairings of words and emotions, with the constraint that a different word/emotion combination was presented to each ear on each trial (e.g. “bower” in a sad tone to the left ear, “tower” in a happy tone to the right ear).

Participants were instructed to monitor for either word target or to a tone of voice target, and provide a single response on each trial. During the linguistic task, participants were asked to monitor for the word “bower”, while in the prosodic task participants were required to monitor for the sad tone of voice. These particular targets were chosen so as to elicit the strongest REA and LEAs respectively (Grimshaw et al., 2003). Participants were required to indicate, as quickly and accurately as possible, whether the target was present or absent. Responses were given by pressing one of two keyboard buttons (one for “target present”, one for “target absent”). During each block and for both tasks, the target was present in 50% of trials (25% in the left ear, 25% in the right ear). The stimuli were delivered using E-Prime (Psychology Tools Inc., Pittsburgh, PA) on a laptop (Lenovo 4233, Morrisville, NC) and supra-aural headphones (K271, AKG Acoustics, Vienna, Austria).

For each task, participants completed three blocks (see Figure 1). Each block of trials began with a different instruction, in line with the three different attention conditions. All participants began with the non-forced attention condition, the order of the forced-attention conditions was randomised and counterbalanced between participants. In the non-forced condition, participants were asked to monitor for the target, and indicate whether the target was present or absent on each trial, regardless of which ear the target was presented to. In the forced-attention conditions, participants were asked to monitor for the target being presented to a particular ear, and respond with "present" only if the target was presented to that ear. If the target was presented to the non-attended ear, they were to ignore it (i.e. respond "absent"). Task order (linguistic or prosodic task first) and was randomised and counterbalanced between participants. Orientation of the headphones (normal or reversed) was also randomised and counterbalanced between participants, in order to control for potential mechanical differences between channels. In addition, participants used both hands to respond, with half beginning each block with their right hand and half beginning each block with their left hand, with all participants swapping hand half way through each block.

For each task and each condition, the number of times the target (word/emotion) was identified in each ear was recorded. This was used to calculate both the directional laterality quotients, using the following formula: $[(RE - LE) \div (RE + LE) \times 100]$, and the absolute laterality quotients, based on dominant (D) ÷ non-dominant (ND) ears, using the following formula: $[(D – ND) \div (D + ND) \times 100]$.

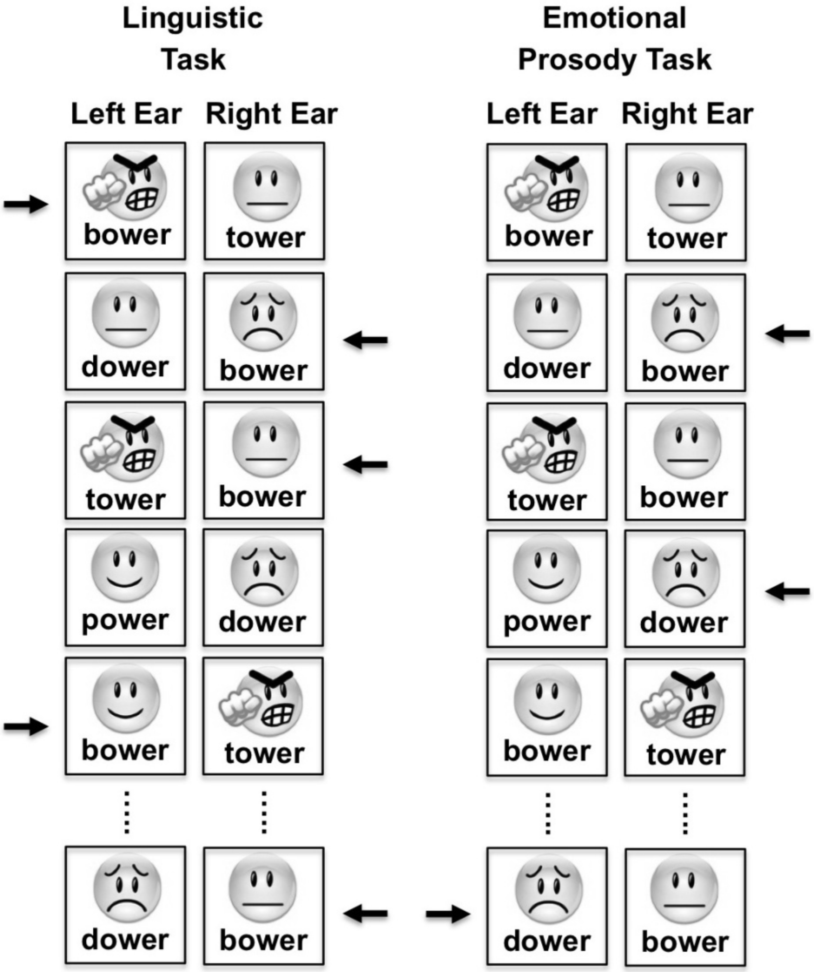

Figure 1. Schematic figures of the linguistic and emotional prosody dichotic listening tasks. In the non-forced condition, participants are required to pay attention to both ears at the same time and indicate, via button press, whether the target word/tone was present or absent. This condition was always presented first to avoid biasing participants' responses in the forced attention conditions. In the forced attention conditions, participants were required to selectively attend to, and report from, either the left or the right ear. The order of the forced attention conditions was counterbalanced between participants. The arrows indicate correct responses across trials for each task (i.e., target word ('bower') in the linguistic task and target emotion ('sad intonation') in the emotional prosody task).

Data analysis

Non-parametric tests were used where assumptions of normality were not met.

Greenhouse-Geisser adjustments were used whenever sphericity was violated.

Results

Salivary hormone concentrations

The mean saliva estradiol and progesterone levels are given in Table 1. Although mean estradiol levels were numerically higher in the follicular and luteal groups compared to the menstrual group, there was no main effect of Cycle Phase on estradiol levels ($F_{(2,\ 49)} = 1.29$, $p = .28$, $\eta_p^2 = .050$). A significant effect of Cycle Phase was found for progesterone ($F_{(2,\ 49)} = 28.15$, $p < .001$, $\eta_p^2 = .054$), and post-hoc tests (Bonferroni) revealed significantly higher progesterone levels in the luteal group as compared to both the menstrual ($d = 2.22$) and follicular groups ($d = 1.69$, both $p < .001$). There was no difference in progesterone levels between the menstrual and follicular groups ($d = 0.58$, $p = .761$).

Dichotic listening tasks

The laterality quotients were subjected to a 2 × 3 × 3 mixed model ANOVA, with Task (emotional, linguistic) and Condition (non-forced, forced-right, forced-left) as the within-subjects factors, and Cycle Phase (menstrual, follicular, luteal) as the between-subjects factor. The main effect of Task was significant ($F_{(1,\ 49)} = 46.42$, $p < .001$, $\eta_p^2 = .49$), indicating an expected overall REA (mean LQ ± *SD*: 13.88 ± 14.02) for the linguistic task and LEA (-4.29 ± 11.02) for the prosody task. The main effect of Condition was also significant ($F_{(1.75,\ 85.66)} = 988.77$, $p < .001$, $\eta_p^2 = .95$), indicating a greater REA (83.66 ± 17.02) in the forced-right condition, as compared to both the non-forced and forced-left conditions across both tasks (both $p < .001$), and a significant LEA in the forced-left condition, as compared to both the non-forced and forced-right conditions across both tasks (both $p < .001$). Moreover, there was a significant Task × Condition interaction ($F_{(1.69,\ 82.69)} = 13.42$, $p < .001$, $\eta_p^2 = .22$). This interaction as followed up by two repeated measures ANOVAs, one for each task, with condition as the within-subjects factor. For both the emotional and the linguistic tasks, the main effect of Condition was significant ($F_{(1.47,\ 74.73)} = 421.38$, $p < .001$,

η_p^2 = .89; $F_{(2,\ 102)}$ = 904.55, p < .001; η_p^2 = .95 respectively). Mean laterality quotients for each condition in each task are depicted in Figure 2. For both tasks, post-hoc tests (Bonferroni) revealed significant differences between the non-forced and forced-right conditions, the non-forced and forced-left conditions, and the forced-right and forced-left conditions (all p < .001). Taken together, the interaction shows that, across cycle phases, participants were able to shift their attention according to the task instructions in both tasks. There was no Condition × Cycle Phase interaction ($F_{(3.49,\ 85.66)}$ = 0.68, p = .61, η_p^2 = .027), no Task × Cycle Phase interaction ($F_{(2,\ 49)}$ = 0.005, p = .99, η_p^2 < .001), and no between-subjects effect of Cycle Phase ($F_{(2,\ 49)}$ = 0.41, p = .66, η_p^2 = .017).

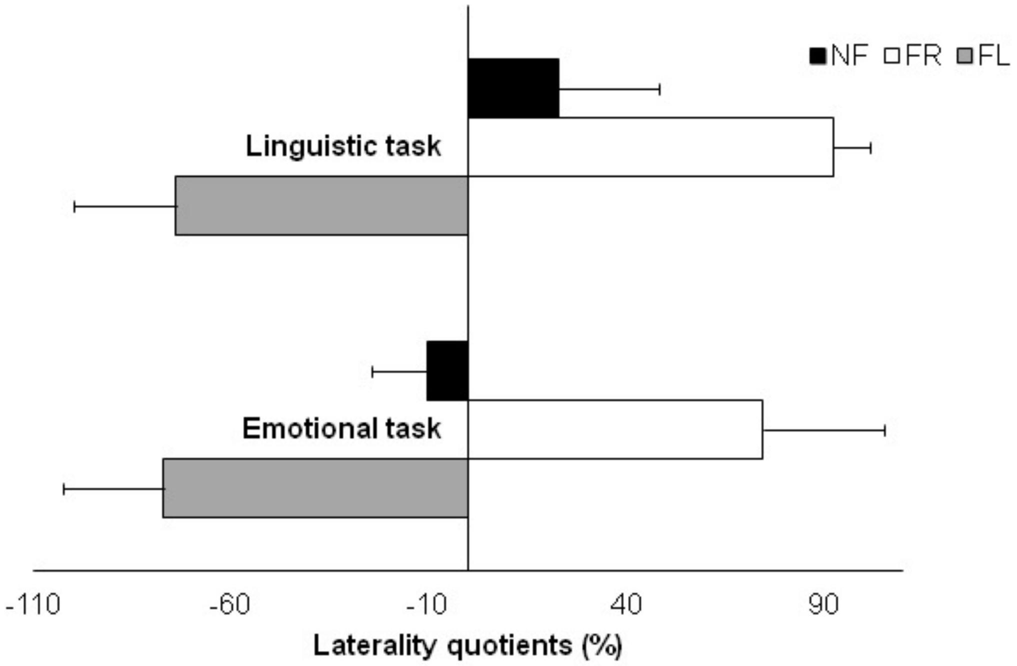

Figure 2. Laterality quotients for each attention condition (non-forced, NF, forced-right FR, forced-left, FL) in both tasks, across all cycle phases. Error bars are standard deviations. One-sample t-tests revealed laterality quotients in both tasks to be significantly different from zero across all conditions (all p < .0001).

Critically, the Task × Condition × Cycle Phase interaction was significant ($F_{(3.38,\ 82.69)}$ = 2.69, p < .05, η_p^2= .099; see Table 3). The interaction was followed up by two mixed-model ANOVAs, one for each task with Cycle Phase as the between-subjects factor, and Condition as the within-subjects factor. For the Linguistic task, the Condition × Cycle Phase interaction was not significant ($F_{(4,\ 98)} = 0.34$, $p = .85$, $\eta_p^2 = .01$), whereas in the Emotional task, the Condition × Cycle Phase interaction approached significance ($F_{(3.00,\ 73.58)} = 2.13$, $p = .10$, $\eta_p^2 = .08$), which appeared to be driven by a reduction in lateralisation in the follicular phase, as compared the menstrual and luteal phases, in the forced-attention conditions of the emotional task only (see Table 3). However, three one-way ANOVAs (one for each attention condition) yielded no significant main effects of Cycle Phase (all $F < 2.07$, n.s., $\eta_p^2 < .08$).

Table 3. Laterality quotients (LQ) and standard deviations for each attention condition of both the emotional and linguistic dichotic listening tasks, according to cycle phase.

	Emotional prosody task			**Linguistic task**		
	Non-Forced M ± SD	**Forced-Right** M ± SD	**Forced-Left** M ± SD	**Non-Forced** M ± SD	**Forced-Right** M ± SD	**Forced-Left** M ± SD
Menstrual	-8.70 ± 13.83	82.44 ± 26.20	-82.63 ± 22.70	26.14 ± 21.56	91.41 ± 9.23	-71.93 ± 23.59
Follicular	-12.06 ± 16.86	63.21 ± 32.98	-68.35 ± 27.63	22.25 ± 28.12	93.78 ± 70.53	-77.72 ± 21.02
Luteal	-10.38 ± 11.30	76.35 ± 30.81	-81.28 ± 24.71	20.66 ± 26.20	92.34 ± 11.05	-71.83 ± 33.30

In order to increase the group difference in estradiol levels (as estradiol levels did not significantly differ between the cycle phases), the data were re-analysed according to an estradiol median split (split score = 3.25 pg/ml) instead of cycle phase, as in the previous study (Hodgetts et al., 2015). The median split divided the sample into a high and low estradiol group which differed significantly in estradiol levels ($t_{(27.33)} = 5.09$ $p < .001$, $d = 1.41$). However, the median split analysis of the dichotic listening data neither revealed a significant main effect of Group ($F_{(1,\ 50)} = .09$, $p = .76$, $\eta_p^2 = .002$), nor any interaction with Group approached significance (all $F < = 0.693$, n.s., $\eta_p^2 < 0.014$).

Similar to Hodgetts et al. (2015), and in order to investigate differences in the degree of lateralisation between the tasks, absolute LQs were also subjected to a 2 × 3 × 3 mixed model ANOVA, with Task (emotional, linguistic) and Condition (non-forced, forced-right, forced-left) as the within-subjects factors, and Cycle Phase (menstrual, follicular, luteal) as the between-subjects factor. The main effect of Task was significant ($F_{(1,\ 49)} = 13.81$, $p < .001$, $\eta_p^2 = .22$), indicating that the absolute LQ in the linguistic task ($M = 65.02$, $SD = 9.24$) was significantly greater than those in the emotional task ($M = 55.40$, $SD = 16.69$). There was also a main effect of condition, ($F_{(2,\ 98)} = 314.64$, $p < .001$, $\eta_p^2 = .87$), as across both tasks, the non-forced conditions yielded smaller absolute LQs compared to the forced-left ($d = 4.01$) and forced-right conditions ($d = 4.54$, both $p < .001$). The absolute LQ for the forced-right condition was also larger than that for the forced-left condition ($d = 0.45$, $p < .05$). The Task × Condition interaction was also significant ($F_{(2,\ 98)} = 7.15$, $p < .001$, $\eta_p^2 = 13$, see Table 4). This interaction reflects the generally larger degree of bias in the linguistic DL task, particularly in the forced-right condition, compared to the emotional prosody task. None of the remaining effects were significant (all $F < 2.51$, $\eta_p^2 < 0.093$ n.s.).

Table 4. Absolute laterality quotients (mean ± standard deviation and range) for each attention condition in both tasks, across all cycle phases.

	Non-forced	**Forced-right**	**Forced-left**
	M ± SD (range)	M ± SD (range)	M ± SD (range)
Emotional task	14.01 ± 10.35 (0 – 41.67)	74.95 ± 30.40 (0 – 100)	77.24 ± 25.51(0 – 100)
Linguistic task	27.02 ± 20.62 (0 – 76.92)	92.54 ± 9.22 (63.64 – 100)	75.49 ± 20.87 (2.86 – 100)

Relationship between laterality quotients and sex hormones

Since the ANOVA results revealed a significant effect of the Task × Condition × Cycle Phase interaction on dichotic listening biases, we expected estradiol and/or progesterone levels to be significantly related to the laterality quotients in the forced attention conditions of the emotional prosody task. To investigate the relationship between sex hormone levels and dichotic listening biases, we conducted a series of stepwise multiple regression analyses. Absolute levels of estradiol and progesterone were entered as predictors, and standard laterality quotients from each condition of each task were the dependent variables.

This analysis revealed a significant model for the forced-right condition of the emotional prosody condition only ($F_{(1,\ 50)} = 5.96$, $p = .01$, $R^2 = .11$, $f^2 = 1.12$). Estradiol was the only significant predictor in this model ($\beta = -.33$, $p = .01$). In line with the ANOVA results, the regression model suggests a negative relationship between estradiol level and lateralisation, specifically in the forced-right (cognitive control) condition of the emotional task. However, the relationship was driven by two participants with considerably high estradiol levels (see Figure 3). Re-running the analysis with these participants excluded resulted in a non-significant model ($F_{(2,\ 47)} = 1.09$, $p = .35$, $R^2 = .04$, $f^2 = 1.04$).

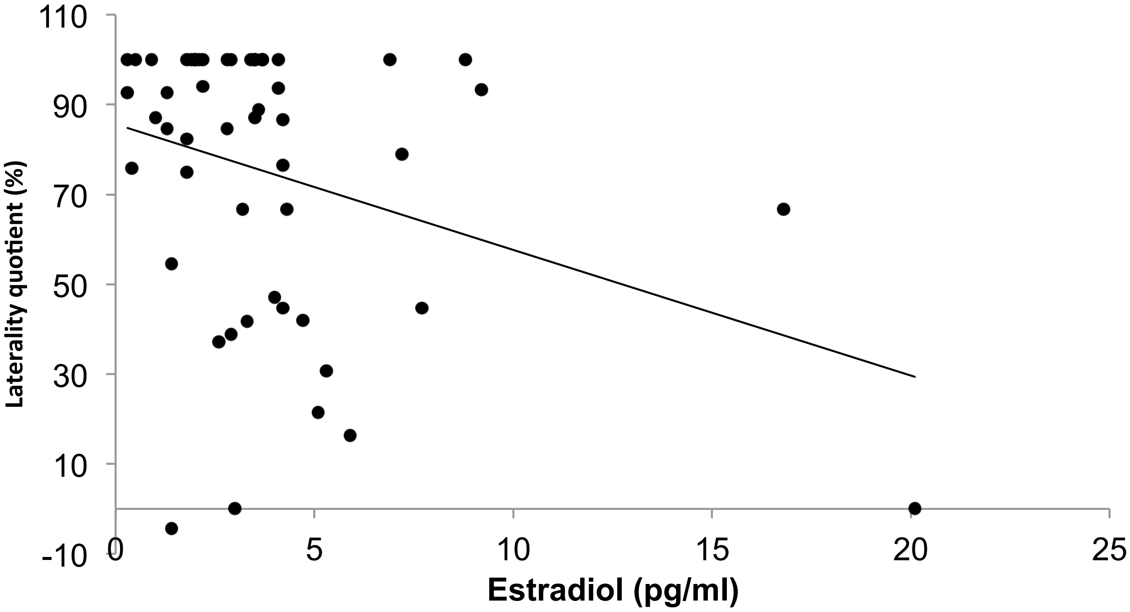

Figure 3. Scatterplot of the relationship between estradiol levels and the laterality quotients of the forced-right condition of the emotional prosody task.

Discussion

The present study demonstrated a significant three-way interaction between task, attention condition, and cycle phase, suggesting that the cycle-related effects on lateralisation in the forced attention conditions were task-specific. In the emotional prosody based DL task, lateralisation in the forced-right condition was slightly reduced during the follicular phase of the menstrual cycle. The results suggest that high levels of estradiol, typical of the follicular phase, are related to a reduction in cognitive control, as measured by the forced-attention conditions of the (emotional) DL task. The effects were in contrast to those of Hjelmervik et al. (2012), who reported a significant increase in lateralisation during the forced-left condition of a linguistic DL paradigm in the follicular phase. The authors interpreted this finding as an estradiol-related improvement in cognitive control. However, the apparent reduction in cognitive control in the present study was only small ($\eta_p^2 = .078$) and the significant negative relationship between LQs and estradiol levels in the forced-right condition was driven by a small number of participants with particularly high estradiol levels (Fig 3). Sex hormones did not affect lateralisation in any of the conditions in the linguistic DL task. The findings from the present study were also different to those previously presented by Hodgetts et al. (2015). In the previous study, a high level of estradiol-reduced language lateralisation, as measured by dichotic listening, was found regardless of attention condition.

Hodgetts et al. (2015), Hjelmervik et al. (2012) and the present study investigated normally cycling women with a linguistic DL paradigm, though stimuli were consonant-vowel syllables in the previous studies, and two-syllable words in the present study. However, while Hodgetts et al. (2015) and Hjelmervik et al. (2012) investigated groups *with* significant differences in estradiol levels, the present study was unable to demonstrate significant, cycle-phase related differences in estradiol. Consequently, previous studies may have been more likely to detect estradiol-related changes in lateralisation. However, the lack of such an effect in the present study is surprising, given that numerically, the mean estradiol levels of the women in the present study were comparable to those reported previously. Moreover, the median-split analysis, which resulted in groups that *did* differ significantly in estradiol, also did not show hormone-related changes in either language or emotional prosody processing lateralisation. This makes it rather unlikely, that different findings of the present study, compared to previous studies (Hodgetts et al., 2015; Hjelmervik et al., 2012) result from differences in estradiol levels between the studies.

One of the main differences between the current and previous studies (Hodgetts et al., 2015; Hjelmervik et al., 2012) is the degree of lateralisation. The laterality quotients in the linguistic task of the present study are substantially larger than those seen in previous studies, which used consonant-vowel DL tasks (e.g. Cowell et al., 2011; Hodgetts et al., 2015; Hjelmervik et al., 2012; Wadnerkar et al., 2008) rather than a DL task that required participants to detect a target, as used in the current study. For example, in the non-forced condition of the previous study (Hodgetts et al., 2015) the mean LQ was 14.71. In contrast, the mean LQs for the linguistic non-forced condition in the present study was 23.01. The difference in the strength of lateralisation generated by the task used in the present study becomes even clearer when the forced attention conditions are considered. For example, in the forced-right condition, the previous sample yielded mean LQs of 44.19. However, in the present study, the mean LQ from the linguistic forced-right condition was 92.54. This is more than double that seen in the previous study, indicating that almost all targets were detected on the forced-attention side in combination with only a very small number of detection errors on the unattended side (the maximum LQ is 100). The large biases demonstrated in the present study are due to the very high target-detection rates observed in almost all participants. Specifically, across both tasks and all conditions, between 40% and 63% of targets where correctly identified (when considering the total number of targets detected across both ears). Consequently, there is little variation in laterality that remains to be explained by variations in sex hormones. This might also explain some of the inconsistencies in the literature investigating cycle phase-related fluctuations in lateralisation (e.g. Can et al., 2012; Bibawi et al., 1995). For example, Can et al. (2012) also failed to demonstrate sex hormone effects in a DL task (comparable to that used by both Hjelmervik et al., 2012, and Hodgetts et al., 2015) which revealed considerably larger LQs than those reported previously (average LQ of 47% across cycle phases), despite a larger group difference in estradiol levels than that reported in the current study. In other words, the large DL biases might reflect ceiling effects in target-detection rates that estradiol was unable to further improve.

The generally high target-detection rates and considerably large degree of lateralisation even in the non-forced conditions of the present study, compared to those reported previously, suggests that the task might have been very easy and consequently resulted in very large laterality biases. This stimulus-driven effect might have been so strong that potentially smaller sex hormone-related modulations of cerebral lateralisation were covered. This might be particularly true in the present study, as the cycle-related changes in estradiol levels were only small ($\eta_p^2 = .050$). The largest detection rates and DL biases were found in the forced-left and forced-right conditions of the linguistic and emotional prosody task, respectively, which were also least sensitive to hormone-related fluctuations. The only condition to show an estradiol-related trend was the cognitive control condition (forced-right) of the emotional task, which also revealed the lowest target detection rates and smallest bias of all forced-attention conditions. These findings suggest that high target-detection rates and large DL biases are less susceptible to sex-hormonal variations. Although the relatively low cognitive demands of the present task resulted in only a small estradiol-related effect, the results also revealed that, in principle, sex hormones are capable of influencing top-down processes in both left (Hjelmervik et al., 2012) and right lateralised tasks (current study).

The suggestion that task-related factors might influence the detection of sex hormonal effects on lateralisation may shed light on some of the inconsistencies in the current literature. A number of studies of language lateralisation have used visual half-field (VHF) tasks, such as word-matching or lexical decision tasks, to investigate sex hormonal effects of lateralisation. Like different DL tasks, different VHF tasks also differ in difficulty and the amount of cognitive control required. For example word-matching tasks require the participant to decide whether two subsequently presented words are the same, while lexical decision tasks require the participant to discriminate between words and non-words. Although both tasks are performance-based, word-matching tasks are likely more difficult than lexical decision tasks, as participants have to engage working memory processes in order to successfully complete the task. Moreover, in line with the present DL study, the literature suggests that visual half-field studies that are more cognitively demanding (i.e. word-matching tasks) are more likely to demonstrate sex hormonal effects on lateralisation (Chiarello et al., 1989; Weekes & Zaidel, 1996; Weis et al., 2008).

High levels of estradiol were marginally associated with a reduction in lateralisation in the cognitive control condition for the emotional prosody task. This suggests that, unlike the previous study (Hodgetts et al., 2015), the present study is demonstrating a hormonal effect on a specific cognitive (top-down) mechanism, separate to the general (bottom-up) aspect of emotional processing lateralisation. However, this finding should be interpreted with caution because the regression was weak and due to a small number of participants with very high estradiol levels. Also, it should be noted that the regression suggests that high levels estradiol lead to a reduction in cognitive control, which is in direct contrast to

Hjelmervik et al. (2012), who demonstrated an estradiol-driven improvement in cognitive control. Critically, the present study showed an estradiol-related reduction in cognitive control specifically in an emotional prosody task. In contrast, Hjelmervik et al. (2012) demonstrated improved cognitive control in a linguistic task only. While this might be due to differences between the tasks used in each study (i.e., target detection as compared to reporting stimuli), an alternative suggestion is that the effect of estradiol on cognitive control is beneficial to linguistic-based tasks, provided they are not strongly lateralised, but detrimental to emotion-based tasks. There is some evidence in the literature that suggests a conflict with some studies reporting estradiol-related improvements in cognitive control functions (Joffe et al., 2006; Krug et al., 2006; Duff & Hampson, 2000) and others suggesting that estradiol is detrimental to cognitive control (Colzato et al., 2010; Gasbarri et al., 2008; Hatta & Nagaya, 2009). While, these studies do not provide an explanation as to why estradiol might be beneficial to some tasks and not others, the present study suggests that if the tasks employed in these studies vary in their cognitive demands and difficulty, this may explain some inconsistencies in the results.

It is also noteworthy that there is a significant methodological difference between the present study and that presented previously (Hodgetts et al., 2015). Firstly, while the previous study investigated sex hormone effects using an estradiol-based median split, the present study chose to focus on menstrual cycle phases. Critically, analysing the present data according to an estradiol-based median split resulted in no significant group differences or interactions. However, unlike the previous study, the hormone profiles of participants in the present study appeared to be in concurrence with the participants' self-reported cycle phase. This is likely due to the application of more stringent criteria regarding the cycle days on which participants were tested. For example, in this study, the luteal phase was defined as cycle days 20-22, while the previous study defined this phase as cycle days 15-23. As a result, conducting a median split on the present results in a substantially different hormone profile, as compared to the previous sample. Specifically, across both groups, the present sample yields a higher progesterone level (mean progesterone across both groups = 170.64 pg/ml). Given that progesterone has a predominantly inhibitory effect on neural activity, via GABAergic interactions, it is possible that the higher level of progesterone in the High estradiol group of the present sample was sufficient to counteract any influence of estradiol on cognitive control. This is in line with an earlier notion purported by Smith (1994), who suggested that the excitatory effect of estradiol is dependent on the presence of other steroids in the "background milieu" (p. 67) of hormones

In conclusion, in contrast to previous studies (Hodgetts et al., 2015; Hjelmervik et al., 2012; Cowell et al., 2011; Sanders and Wenmoth, 1998; Wadnerkar et al., 2008), the present study did not demonstrate an effect of sex hormones on language lateralisation per se. Instead, the results revealed a significant interaction between sex hormones, task, and attention condition. As such, the present study suggests that tasks with low task demands, resulting in a large degree of lateralisation in the current study, are less sensitive to the effects of sex hormones. This difference in sensitivity might be due to a strong stimulus-driven (bottom-up) effect, resulting in a pronounced difference in activity between the two hemispheres that cannot be modulated by small changes in estradiol. In addition, it should be noted that estradiol levels were only marginally different between the groups in the present study. This might suggest that strongly lateralised tasks require larger group differences in estradiol in order for asymmetries to show cycle-based effects. The lack of a significant difference in estradiol between the groups also highlights the importance of direct, objective hormone measures in menstrual cycle studies. Moreover, for the emotional prosody task, the present study revealed a trend which suggested that estradiol might reduce cognitive control. However, the present study suggested an estradiol-related reduction in cognitive control in an emotional prosody task, as opposed to a linguistic task. This finding suggests that the effect of estradiol on cognitive control may be task-dependent. Consequently, the present study might imply that differences in task type between studies can account for some of the inconsistencies in the literature regarding sex hormonal effects on lateralisation, and cognitive control. This finding is particularly relevant, given the significant amount of inconsistency in the literature sex hormones and lateralisation.

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