Sex hormones modulate sex differences and relate to hemispheric asymmetries in a divided visual field Navon task

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ABSTRACT

Sex differences in functional hemispheric asymmetries (FHA) have been hypothesized as a fundamental mechanism behind sex differences in global-local processing. So far, it has not been assessed how interactive effects of sex and hemifield presentation influence common indicators of global precedence. The current study is the first to investigate the involvement of FHAs by using a divided visual field Navon paradigm and controlling for sex hormone status. Moreover, various factors that have previously shown a reliable influence on global-local processing performance are verified within the context of unilateral presentation. 39 men and 39 naturally cycling women in their luteal cycle phase completed a divided visual field Navon task with the instruction to detect targets either at any level (divided attention) or only at the global or local level (selective attention) in three different spacing conditions. The obtained evidence reveals significant sex differences in the global advantage effect (faster reaction to global vs. local level targets) for densely spaced letter stimuli, as well as significant sex differences in global-local level interference, with findings on both measures being mediated by testosterone. Also, estradiol showed different relationships to the global advantage effect in men and women together with a positive relationship to global advantage for the selective attention condition. Behavioural reaction time results were mirrored by accuracy measures but presented significantly higher global-over local-level accuracy in women compared to men for the divided attention condition. Our results did not show significant sex differences in FHAs but indicate differential relationships between progesterone and FHAs in men and women. In conclusion, sex hormones emerged as central mediators of sex differences in global precedence and possible moderators of hemispheric asymmetries.

1. Introduction

Visual scenes are hierarchically composed of multiple objects or surfaces in a specific spatial configuration. Whether the perceptual system is decomposing a scene from its global structure to its local components or rather building it up vice versa, is traditionally assessed with attention tasks using hierarchical visual stimuli, i.e. global level structures made up of smaller local level parts. Target detection is requested at either both levels (global and local; divided attention paradigm) or only one level while ignoring the other (global or local; selective attention paradigm).

Early research employing the Navon-Task [1–3] delivered accumulating evidence in favor of global processing precedence established by measures like the global advantage effect (GA), i.e. faster reaction times to global targets compared to local targets, as well as global-to-local interference (GLI), i.e. slower rejection of global targets compared to non-targets, when asked to focus on local targets, along with the absence of local-to-global interference (LGI), i.e. slower rejection of local targets compared to non-targets, when asked to focus on global targets. However, the idea of global precedence as a universal phenomenon has been challenged, as more recent research suggests effect sizes of global precedence to vary in respect of numerous factors, including task-dependent features like spacing, attention condition, presentation mode or stimulus material [3,5–8], as well as interindividual differences like sex and menstrual cycle phase [6,7,9], all with functional hemispheric asymmetries (FHA) as a key underlying factor.

FHAs describe an advantage or dominance of one hemisphere over the other for the processing of specific information, traditionally explored with behavioral methods or neuroimaging techniques like EEG, fMRI, or PET [10–14]. Conclusions about asymmetries are drawn by comparing both hemisphere’s activation patterns (lateralization), or by taking behavioral approaches like divided visual field paradigms, where

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lateralization is induced to one hemisphere at a time through unilateral stimulation, and asymmetries are inferred from differences in response-time or accuracy measures. Particularly relevant in global-local research, the right hemisphere is commonly related to an advantage in global or low spatial frequency processing [15–18], with a bias towards non-verbal material such as shapes [19], whereas the left hemisphere is related to an advantage in local or high spatial frequency processing, with a bias towards verbal content, including letters and numbers [20,21]. Therefore, although global processing appears to outperform local processing in both hemispheres [8,15], GA is generally larger for stimuli processed in the right hemisphere compared to stimuli processed in the left hemisphere [21,22].

The impact of sex on FHAs has consistently been proven in numerous tasks including Navon [7,23–25], and is supposed to originate from organizational and activational effects of sex hormones. First, testosterone levels in early brain organization are promoting development towards callosal asymmetry and structural lateralization in favor of the right hemisphere [26,27]. Hence, compared to women, men typically show stronger asymmetric processing in a variety of tasks [see (28) for a review] along with superior right lateralized and inferior left-lateralized brain functions. Second, behavioral and neuroimaging studies report activational effects of sex hormones on interhemispheric connectivity and occipital lateralization of brain activity [29].

When performing global-local tasks, a general right-hemispheric specialization for visual attention [30,31] is commonly followed by negative right-to-left interhemispheric connectivity, i.e. inhibition of the non-dominant left hemisphere [32], for both global and local targets [29]. Thus, lateralization of information to the left hemisphere as well as left-hemispheric processing speed is reduced, accounting for an amplification of global precedence in hierarchical letter tasks. The degree to which inhibition of the non-dominant hemisphere affects behavioral outcomes and by association possible sex differences in effect sizes is further affiliated to modulating effects of sex hormones [7]. According to the Hypothesis of Sex Hormone-modulated Cortical Interaction [33], cognitive asymmetries are influenced by both, progesterone and estradiol. While interhemispheric decoupling is supposedly driven by inter-active effects of progesterone and estradiol [34,35] causing suppression of inter-hemispheric inhibition, estradiol might also play an important role in asymmetry reduction by particularly increasing cortical activation in the non-dominant hemisphere [34,36]. As a result, sex differences in global-local processing might become especially apparent during the luteal cycle phase, where progesterone and estradiol concentrations are both high, which is supported by previous results obtained from bilateral presentation [6]. However, interhemispheric decoupling is only one of several models to explain activating effects of sex hormones on hemispheric asymmetries as findings turn out to be rather controversial. For instance, some studies report reduced FHAs only during the follicular cycle phase while others show lowest asymmetry during menstruation (see [34] for a review). Moreover, the way in which sex hormones affect lateralization-patterns turns out to be highly task-specific, and the precise mechanisms involved in the supposed hormonal interactions are not fully understood.

Concerning androgens, a recent fMRI analysis on global-local processing provides implications on an activating role in the modulation of FHAs, as increased levels of testosterone were linked to reduced occipital lateralization of brain activity. Also, a positive relationship between interhemispheric inhibition and lateralization was increased with higher levels of testosterone in men, whereas opposite in women. As a consequence, women already showed stronger occipital lateralization by default, which then again impacted the consecutive parietal lateralization, restricting the traditional lateralization-by-inhibition model [23], i.e. right-hemispheric lateralization as an exclusive consequence of left-hemispheric inhibition, to observations from male participants [29,32].

It is thereby important to note, that a majority of prior work may have failed to spot possible sex differences since the impact of sex steroids and the consequences of hormonal contraceptives have barely been controlled for in global precedence research.

As for behavioral results, an impact of local-letter spacing on global precedence has been demonstrated, as a decline in GA was associated with an increase in sparsity [3,8,37] (but see [38]). Also, despite overall global precedence in both hemispheres [8,15], visual hemifield studies show a right-hemispheric preference for global and left-hemispheric preference for local processing, with larger GA for presentation in the left visual field (right hemisphere: LVF-RH) compared to the right visual field (left hemisphere: RVF-LH) [5,39].

With respect to attention condition, GA is usually larger for selective compared to divided attention conditions in neurotypical [6,29] as well as clinical samples [40,41]. Since divided attention conditions are considered to require an interplay between hemispheres for the parallel processing of both hierarchical levels within the respective specialized side, inhibitory mechanisms are hypothesized to primarily take place and affect processing during selective attention conditions. This idea is also supported by the common finding of weak progesterone and testosterone influence on divided attention performance [6,29]. Therefore, induced lateralization through hemifield presentation should be more predictive and sex differences in global precedence based on FHAs should be more apparent for conditions fostering unilateral processing, i.e. the selective attention condition.

Regarding sex, GA is typically stronger in men compared to naturally cycling women with hierarchical letter stimuli [6,7,9]. While some earlier studies revealed significant sex differences for samples including a large percentage of Asian participants, this could not be replicated by a more recent fMRI study involving a Caucasian Central European sample. Still, sex differences in processing styles, as well as a negative relationship between progesterone and GA, were confirmed for all samples. Unlike GA, only few studies have investigated sex differences in interference. Besides differences in hemispheric asymmetries [42], they suggest a trend towards higher GLI in men compared to luteal phase women, but no significant difference between both groups. Still, GA and GLI were positively related to testosterone levels in men and women during their follicular phase, whereas GA and LGI were negatively related to testosterone in luteal phase women. By contrast, a relationship to GA or interference could not be confirmed for estradiol [6].

Yet, influences of sex and sex hormones on global precedence have not been directly tested for the divided visual field Navon paradigm and there is only limited evidence on whether induced lateralization predicts sex differences in global precedence. Conceptually associated findings from number comparison tasks indicate advanced local processing with RVF-LH presentation, for both sexes [43] and in women compared to men [44], stressing the idea of left-hemispheric dominance in local processing. Also, while numerous studies give reason to expect sex differences in hemispheric asymmetries, this was not confirmed for divided visual field number comparison [44]. ERP-results showing differences in hemispheric asymmetries only for central, but not lateral presentation [22], are further challenging transferability of the involved mechanisms. It should thereby especially be called into question if lateralization by hemifield presentation comes to conflict with the assumed processes of hormone-mediated lateralization in bilateral paradigms.

In trying to extend the existing body of evidence on sex differences in global precedence and their underlying hemispheric asymmetries, the current study aims to investigate the interactive relationships between hemifield presentation and sex, while taking various attention conditions and stimulus spacings into account and controlling for sex hormone status. Based on established findings concerning sex differences in global-local-processing, we hypothesize stronger global precedence (GA and GLI-LGI-difference)

(i) for narrow compared to sparse spacing
(ii) for left compared to right hemifield presentation
(iii) for the selective compared to the divided attention condition
(iv) in men compared to women
Furthermore, we hypothesize

(v) stronger hemispheric asymmetries in global precedence in men compared to women

Finally, we intend to explore the modulatory role of sex hormones and if visual hemifield is a stronger predictor for global precedence in the selective compared to the divided attention condition.

2. Material and methods

2.1. Participants

A total of 87 participants (40 men, 47 women) were recruited for the current study. Eligibility requirements were met if participants were between 18 and 35 years old, right-handed, did not suffer from any physical, mental, or endocrinological disorders, and did not use hormonal contraception or medication. All of these criteria, including handedness, were indicated by participant’s self-reports in a general screening-questionnaire before the experiment. Female participants needed to have a regular menstrual cycle between 21 and 35 days [45] and were tested during luteal cycle phase, which was confirmed by respective hormone levels and the onset of next menses. Hormone levels were required to fall within three standard deviations from the group mean and progesterone levels, in particular, were expected to lie within a normal range for the luteal cycle phase (compare Hormone Analysis).

All participants gave their informed written consent to participate in the study. All methods conform to the code of ethics constituted by the Declaration of Helsinki (2014). The institutional guidelines of the University of Salzburg (Statutes of the University of Salzburg) state in §145 (1) that it is necessary to seek ethical approval for research on human subjects if the physical or psychological integrity is affected, the right for privacy or other important rights or interests of the subjects or their dependents are confounded. Paragraph §145 (2) states that it is the decision and responsibility of the PI to decide, whether (1) applies to a study or not. Therefore, no ethical approval for this study was sought out. Non-invasive methods were used on healthy adult volunteers, who willingly gave their informed consent to participate. Accordingly, (1) did not apply. Data were processed in anonymized/de-identified form. Participants were assigned a subject ID (v001, v002, etc.), when physically present at the lab, which was used throughout the study.

One woman and one man were excluded for hormone levels exceeding the group mean by more than three standard deviations. One woman was excluded due to a cycle length above 35 days. Another six women had to be excluded, as they could not be assigned to the luteal cycle phase, with progesterone levels falling below the required threshold of 43 pg/mL (compare Hormone analysis). The remaining sample of 39 women (mean age 22.13, SD = 2.61, range 18–31 years) and 39 men (mean age 23.95, SD = 3.24, range 19-34 years) was included in statistical analysis. Age ranged from 18 to 34 with a significant differences between both groups (t_{172.71} = −2.76, p = 0.008).

All women reported a natural menstrual cycle of a regular duration between 23 and 35 days (mean cycle length: 29 days, SD = 2.5, range = 23–35) and a mean cycle day of 20.5 (SD = 4.09, range = 14–30). Raven’s APM Intelligence Screening revealed no significant differences between both groups, t_{187} = −0.71, p = 0.48. All participants received course credits or proportionate monetary compensation for their participation.

2.2. Navon task

Global and local processing was assessed by presenting traditional Navon letter stimuli (Navon 1977; Fig. 1) in two different hemifield-(left visual field – right hemisphere: LVF-RH; right visual field – left hemisphere: RVF-LH) and three different spacing-conditions (dense, average, sparse). Stimuli were constructed from the letters “C”, “D”, “O”, “U”, and “V”, resulting in 20 possible letter combinations Oc, Od, Ov, Cv, Co, Cd, Cu, Cv, Do, Dc, Du, Dv, Uo, Uc, Ud, Uv, Vo, Vc, Vd, and Vv. Upper case letters represent the global letter, lower case letters represent the local letter. There were no combinations presenting the letters at both levels (e.g. Cc, Dd), assuring a distinct measure of preference from one level over the other. Distance between local letters was approximately 3% of the global letter size for dense-, 7% for average and 15 % for sparse-spacing.

Stimuli were presented for 150 ms, preceded by a fixation cross at the center of the screen for 500 ms and followed by an inter-stimulus interval (ISI) of 1500 ms. Participants were assigned one target with the task to identify the target either at any level (divided attention condition) or only at the instructed level (global or local, selective attention condition). Participants performed a total of 972 trials separated into three blocks (324 trials for each, divided attention, selective attention global instruction, and selective attention local instruction). Stimuli were displayed with Presentation software Version 18 (2014, Neurobehavioral Systems Inc., Albany, CA, USA) on a 19-inch pc monitor.

To ensure a constant viewing distance, seats were fixated centrally according to a viewing distance of 45 cm, and participants were instructed to keep an upright sitting position and avoid head-movements throughout the experiment, which was monitored by trained instructors. Moreover, to ensure unilateral processing, participants were urged to focus on a central fixation cross during all trials. To avoid fatigue-related deviations from instructions, sufficient rest time between presentation blocks was provided. Since stimuli were presented for less than 200 ms and stimulus presentation side was fully randomized, effects of responsive or anticipatory eye movements should not come into effect.

Reaction times over correctly solved items (RTs) and error rates (ERs) were recorded. In line with previous examinations on hemifield effects in the Navon paradigm [46–48], all participants responded with their dominant (right) hand by pressing a key (left yes, right no) on a computer mouse. While one-handed response protocols are generally uncommon in divided visual field tasks as they hold an inherent risk of systematic response biases in favor of the ipsilateral presentation side, we did not see the necessity of a counter-balanced protocol for the current study. Since we compare reaction-time differences between global and local level stimuli within each hemisphere rather than total reaction times to global or local stimuli between hemispheres, we do not expect measures of global precedence to be skewed by such effects, as responses to both hierarchical levels should be equally delayed for LVF-RH presentation. Based on the essential prerequisite of unilateral processing in divided visual field paradigms, differences between both global- and local-level measures should be comparable across hemifields and should therefore not affect interpretability regarding lateralization.

2.3. Hormone analysis

Testosterone, progesterone, and estradiol levels were analyzed from saliva samples using ELISA kits by DeMediTec. To obtain average hormone levels over the course of the experiment, samples taken before and after the experiment were merged. Samples were stored at ~20 °C and centrifuged twice at 3000 rpm for 15 and 10 min before analyzing.

In line with the DeMediTec kit instructions, cut-off values for the luteal cycle phase were based on an unrelated sample of 60 women tested in three menstrual cycle phases (compare Pletzer et al., 2018), confirming their individual progesterone peak value. None of the women displayed a luteal progesterone value below 48 pg/mL. Considering the assay sensitivity of 5 pg/mL, a progesterone cutoff of 43 pg/mL was established for the luteal phase.

In addition, hormone levels deviating more than 3 SD from the population mean were excluded.
estradiol, progesterone, and testosterone levels were compared between men and women during luteal cycle phase using one-way ANOVAs (all F > 159.5, all p < 0.001, all 1d702;2 > 0.10). Estradiol and progesterone levels were significantly higher in luteal women compared to men, whereas testosterone levels were significantly higher in men (compare Table 1).

2.4. Statistical analyses

For each participant, only conditions performed with at least 50% accuracy (above chance) were added to the final analysis. Several linear mixed-effects models with random intercepts and fixed slopes were fitted to data by using the lmer function of the lme4 package [49] in R version 3.6.1, with global advantage effect (GA) and Interference effects (GLI, LGI) as dependent variables (DV) and participant number as a random effect in each model. In order to evaluate sex differences and their modulation by task-related factors, the following baseline models were fitted: For GA, attention, spacing, hemifield, and sex as well as their respective interactions were entered as fixed effects [model (1): GA ~ 1 | PNr + attention*spacing*hemifield*sex]. For Interference, instruction, spacing, hemifield, and sex, as well as their respective interactions, were entered as fixed effects [model (2): Int. ~ 1 | PNr + instruction*spacing*hemifield*sex]. Final models were determined by removing non-significant interactions through backwards elimination using the step function of the lmerTest package [50] (see Appendix for a detailed overview). Degrees of freedom were evaluated using Satterthwaite’s approximation. P-values were rounded to three decimal places and values below 0.05 were viewed as significant.

In order to evaluate the mediating and moderating effects of sex hormones, estradiol, progesterone, and testosterone were added to models (1) and (2) respectively. Again, final models were determined by removing non-significant interactions through backwards elimination using the step function of the lmerTest package [50] (see Appendix for a detailed overview). If in the final model, the effect of sex did not survive, while the effect of a hormone did, the hormone was considered a mediator of sex differences, indicating that sex differences are likely explained by different sex hormone levels in men and women. If on the other hand, a sex-hormone interaction emerged, the hormone was considered a moderator, indicating that the relationship between the hormone and the dependent variable differed between men and women.

Data and scripts are openly available at http://webapps.ccns.sbg.ac.at/OpenData/.

3. Results

3.1. Sex differences and hemispheric asymmetries in the Global Advantage Effect (GA)

3.1.1. Reaction times

GA_{RT} represents faster reaction times to global targets compared to local targets. Overall, responses to global targets were significantly faster (M = 519.04 ms, SD = 102.26 ms) than responses to local targets (M = 561.13 ms, SD = 98.39 ms; t(860) = -15.76, p < 0.001, d = 0.54).

Regarding task effects, there was a significant negative relationship between GA_{RT} and spacing (main effect of spacing: b = -0.31, SE b = 0.03, t(803.06) = -10.32, p < 0.001), indicating a larger global advantage effect for increased local-letter density. GA_{RT} was significantly larger for LVF-RH compared to RVF-LH presentation (main effect hemifield: b = -0.20, SE b = 0.05, t(800.02) = -4.05, p < 0.001) and significantly larger for the selective compared to the divided attention condition (main effect of attention condition: b = 0.37, SE b = 0.05, t(801.56) = 7.71, p < 0.001). Furthermore, there was a significant interaction between attention condition and hemifield (b = -0.22, SE b = 0.07, t(799.67) = -3.16, p = 0.002), revealing a stronger hemifield effect for the selective compared to the divided attention condition (Supplementary Fig. 1).

Regarding sex differences, there was no significant main effect of sex (b = 0.12, SE b = 0.08, t(74.96) = 1.53, p = 0.131), but a significant interaction between sex and spacing on GA_{RT} (b = -0.10, SE b = 0.04, t(801.97) = -2.41, p = 0.016, Fig. 2). Separate analyses by spacing revealed significantly higher GA_{RT} in men compared to women for dense spacing (b = 0.21, SE b = 0.10, t(71.42) = 2.14, p = 0.036), while average spacing showed a significant interaction between attention condition and sex (b = 0.27, SE b = 0.12, t(219.53) = 2.28, p = 0.024). Accordingly, with average spacing, there was a moderate non-significant sex difference for the selective attention condition (b = 0.24, SE b = 0.12, t(75.57) = 1.99, p = 0.050), but not for the divided attention condition (b = -0.01, SE b = 0.10, t(69.65) = -0.08, p = 0.936). GA did not differ between sexes for sparse spacing (b = 0.03, SE b = 0.08, t(74.96) = 0.31, p = 0.758).

### Table 1

Hormone levels. Sign. larger compared to the other group: ***p < 0.001.

|        | Estradiol   | Progesterone | Testosterone |
|--------|-------------|--------------|--------------|
| g      | 3.52 pg/ml ± 1.20*** | 211.74 pg/ml ± 127.91*** | 63.83 pg/ml ± 25.49 |
| d      | 2.67 pg/ml ± 0.69 | 77.21 pg/ml ± 46.62 | 152.85 pg/ml ± 62.11*** |

Fig. 1. Example trials composed of a 1500 ms inter-stimulus-interval (ISI) followed by 500 ms central fixation and 150 ms right visual field (RVF-LH) or left visual field (LVF-RH) stimulus presentation featuring dense, average or sparse Navon-letter spacings.
3.1.2. Accuracy

GA(A) represents a higher response accuracy for global targets compared to local targets. Overall, response accuracy was significantly higher for global targets (M = 89.16 % ± 11.81) compared to local targets (M = 86.49 % ± 12.96; t(860) = 5.41, p < 0.001, d = 0.18).

Regarding task effects, GA(A) was negatively related to spacing (main effect of spacing: b = −4.42, SEb = 0.71, t(795.48) = −6.26, p < 0.001), indicating a higher GA(A) for increased local-letter density. GA(A) did not differ between LVF-RH and RVF-LH presentation (main effect of hemifield: b = −1.43, SEb = 1.19, t(795.20) = −1.20, p = 0.229), but was significantly larger for the divided compared to the selective attention condition (main effect of attention condition: b = −3.45, SEb = 1.42, t(795.29) = −2.43, p = 0.015). Moreover, there was a significant interaction between attention condition and hemifield on GA(A) (b = −3.96, SEb = 1.65, t(795.56) = −2.40, p = 0.017). While GA(A) was significantly lower for RVF-LH compared to LVF-RH presentation for the selective attention condition (b = −5.37, SEb = 1.06, t(374.91) = −5.05, p < 0.001), there was no hemifield difference in GA(A) for the divided attention condition (b = −1.49, SEb = 1.15, t(345.81) = −1.29, p = 0.197, Supplementary Fig. 1). In addition, there was also a significant interaction between spacing and hemifield (b = −3.49, SEb = 1.01, t(795.79) = −3.44, p < 0.001). While GA(A) was significantly lower with RVF-LH compared to LVF-RH presentation for sparse spaced stimuli (b = −5.39, SEb = 2.00, t(215.82) = −2.70, p = 0.008), there was no evidence for differences in GA(A) between hemifield presentation sides for average spaced stimuli (b = −2.76, SEb = 2.00, t(217.53) = −1.38, p = 0.168) and dense spaced stimuli (b = 3.46, SEb = 2.10, t(209.27) = 1.65, p = 0.101).

Regarding sex differences, we observed higher GA(A) in women compared to men (main effect of sex: b = −4.97, SEb = 1.69, t(127.34) = −2.95, p = 0.004) as well as a significant interaction between attention condition and sex (b = 4.90, SEb = 1.66, t(804.69) = 2.96, p = 0.003, Fig. 2). While women showed significantly higher GA(A) compared to men for the divided attention condition (b = −5.58, SEb = 1.85, t(666.68) = −3.01, p = 0.004), there was no sex difference for the selective attention condition (b = 0.09, SEb = 1.90, t(74.21) = 0.05, p = 0.96).

3.2. Sex differences and hemispheric asymmetries in Interference effects

3.2.1. Reaction times

GLI(RT) represents a slower rejection of global targets compared to non-targets when instructed to focus on local targets. GLI(RT) represents a slower rejection of local targets compared to non-targets when instructed to focus on global targets. As expected by the concept of global precedence, interference in reaction times was significantly higher for the local compared to the global instruction (main effect of instruction: b = 0.18, SEb = 0.04, t(826.62) = 5.10, p < 0.001). The main effect of instruction did not interact with spacing or hemifield across men and women. However, we observed a significant interaction between instruction and sex (b = 0.10, SEb = 0.05, t(824.34) = 2.06, p = 0.040), as well as a significant three-way interaction between instruction, sex and spacing (b = −0.13, SEb = 0.06, t(825.42) = −2.03, p = 0.043, Fig. 3). Separate analyses for each spacing revealed larger sex differences in global precedence, the higher the local letter density. There was a modest, non-significant interaction between instruction and sex for dense spaced stimuli (b = 0.19, SEb = 0.10, t(823.31) = 1.93, p = 0.055) and a significant interaction between instruction and sex for average spaced stimuli (b = 0.19, SEb = 0.09, t(226.67) = 2.14, p = 0.034), suggesting that the sex differences in the effect of instruction are larger in denser spacings. For sparse spaced stimuli, no significant interaction between instruction and sex became apparent (b = −0.07, SEb = 0.08, t(230.98) = −0.82, p = 0.412).

3.2.2. Accuracy

GLI(A) represents a lower response accuracy in the presence of global targets compared to non-targets when instructed to focus on local targets. GLI(A) represents a lower response accuracy in the presence of local targets compared to non-targets when instructed to focus on global targets. As expected by the concept of global precedence, interference in response accuracy was significantly higher for the local compared to the global instruction (main effect of instruction: b = 1.97, SEb = 0.88, t(826.15) = 2.24, p = 0.025). This effect of instruction was modulated by spacing and hemifield as indicated by a three-way interaction between instruction, hemifield and spacing (b = −3.18, SEb = 1.25, t(825.51) = −2.56, p = 0.011, Supplementary Fig. 2). Separate analyses by spacing suggest that GLI(A) increased with local-letter density in the LVF-RH, but not in the RVF-LH. While GLI(A) was significantly higher than LGI(A) for LVF-RH presentation (b = 2.53, SEb = 1.07, t(373.76) = 2.38, p < 0.018), there was a significant two-way interaction between instruction and spacing for RVF-LH presentation (b = −4.76, SEb = 0.85, t(373.73) = −5.61, p < 0.001). Accordingly, for RVF-LH presentation, GLI(A) was significantly higher compared to LGI(A) for densely spaced stimuli (b = 7.60, SEb = 1.89, t(273.56) = 4.05, p < 0.001) and average spaced stimuli (b = −1.18, SEb = 1.34, t(72.93) = −0.89, p = 0.378) and by trend smaller compared to LGI(A) for sparsely spaced stimuli (b = −2.99, SEb = 1.68, t(69.37) = −1.78, p = 0.080).

Regarding sex differences, we observed a significant interaction between instruction and sex (b = 2.98, SEb = 1.02, t(826.62) = 2.92, p = 0.004), indicating a stronger effect of instruction in men than women (Fig. 3).

Fig. 2. Global advantage in reaction times (GA [RT]) and accuracy (GA [%]) in the selective compared to the divided attention condition for dense, average, and sparse letter spacing in men compared to women. GA [RT] was significantly higher in men compared to women for densely spaced stimuli. GA [%] was significantly higher in women compared to men for the divided attention condition. Error bars represent standard errors.

t(77.30) = 3.28, p = 0.748).
3.3. Relation of global advantage to sex hormones

To evaluate relationships between sex hormones and global precedence (GA, Interference) and control for mediating effects, mixed-effects models were applied with each hormone added to previous baseline models as independent factors.

3.3.1. Reaction times

When adding testosterone to model (1), sex was no longer included in the final model, but instead, a significant interaction between spacing and testosterone emerged (b = −0.06, SE_b = 0.02, t(802.18) = −2.91, p = 0.004, Supplementary Fig. 3). Just like the sex difference, the positive relationship between testosterone and GA_{RT} was stronger for dense (r_{76} = 0.22, p = 0.057) compared to average (r_{76} = 0.14, p = 0.234) and sparse spacing (r_{76} = −0.03, p = 0.791). As a result, sex differences in GA_{RT} for dense spaced letters were mediated by testosterone.

When adding estradiol to model (1), we observed a significant interaction between estradiol and attention condition (b = 0.10, SE_b = 0.04, t(804.97) = 2.77, p = 0.006), as well as a significant interaction between estradiol and sex on GA_{RT} (b = −0.20, SE_b = 0.10, t(72.83) = −2.10, p = 0.039), indicating a differential relationship between estradiol and GA_{RT} in men and women. Separate analyses by sex showed that in men, there was a trend towards a negative relationship between estradiol and GA_{RT} (r_{37} = −0.16, p = 0.346), while estradiol shows a positive relationship to GA_{RT} in women (r_{37} = 0.39, p = 0.013) (Fig. 4). As suggested by the significant interaction between estradiol and attention condition, in women, this association was furthermore modulated by attention condition, with a stronger association for selective attention (r_{37} = 0.39, p = 0.015) than for divided attention (r_{37} = 0.21, p = 0.200).

When adding progesterone to model (1), a significant three-way interaction occurred between sex, hemifield and progesterone (b = −0.37, SE_b = 0.14, t(799.18) = −2.74, p = 0.006). While there was no significant interaction between hemifield and progesterone in women (b = 0.03, SE_b = 0.04, t(396.19) = 0.63, p = 0.532), the interaction was significant in men (b = −0.13, SE_b = 0.05, t(400.07) = −2.50, p = 0.013). This indicates a stronger hemifield effect, i.e. higher GA_{RT} with LVF-LH presentation, for increasing levels of progesterone in men (r_{37} = 0.31, p = 0.055), but not in women (r_{37} = −0.13, p = 0.419) (Fig. 5a).

3.3.2. Accuracy

Testosterone and progesterone did not show any significant associations to the GA effect in accuracy. When adding estradiol to model (1), a significant four-way interaction between hemifield, attention condition, sex, and estradiol emerged (b = −11.46, SE_b = 4.29, t(786.44) = −2.67, p = 0.008). This interaction could be traced back to a highly significant association between the hemifield effect and estradiol in the selective attention condition in men (r_{36} = 0.44, p = 0.006; results not shown).

3.4. Relation of interference to sex hormones

3.4.1. Reaction times

Testosterone and estradiol did not show any significant associations to interference. When adding progesterone to model (2), we observed a significant interaction between spacing and progesterone (b = −0.04, SE_b = 0.02, t(825.46) = −2.14, p = 0.033). However, while the directionality of associations between interference and progesterone differed across spacings, the association was non-significant for all spacings (dense: r_{75} = 0.05, p = 0.662, average: r_{76} = −0.07, p = 0.558, sparse: r_{76} = −0.18, p = 0.119; results not shown).

3.4.2. Accuracy

When adding testosterone to model (2), the interaction between instruction and sex was replaced by a significant interaction between instruction and testosterone (b = 1.82, SE_b = 0.51, t(831.78) = 3.60, p < 0.001). While GLI(A) showed a significant positive relationship to testosterone (r_{75} = 0.23, p = 0.042), LGI(A) was negatively related to testosterone (r_{75} = −0.25, p = 0.026). Furthermore, a significant interaction between sex and testosterone on LGI(A) (b = 2.94, SE_b = 1.27, t(72.40) = 2.32, p = 0.023) is indicating a differential impact of
testosterone on LGI(A) in men and women. While there was no relationship between testosterone and LGI(A) in men ($t_{36} = -0.02, p = 0.906$), there was a negative relationship in women ($t_{37} = -0.38, p = 0.016$). In consequence, sex differences in GLI(A) - LGI(A) show a mediation by testosterone.

While estradiol showed no associations to interference, there was a significant interaction between sex, hemifield and progesterone ($b = -4.24, SE = 1.94, t_{37} = -2.18, p = 0.029$) as well as sex, spacing and progesterone ($b = -3.16, SE = 1.19, t_{37} = -2.66, p = 0.008$). In men, the hemifield effect was larger, the higher the progesterone levels ($t_{37} = 0.34, p = 0.037$), while no such association was observed in women ($t_{37} = -0.05, p = 0.743$) (Fig. 5b).

In addition, men showed a significant interaction between spacing and progesterone ($b = -1.32, SE = 0.44, t_{40.86} = -3.04, p = 0.003$). As for RT, the associations between interference and progesterone ran in different directions for each spacing, but were non significant in all spacings (dense: $t_{36} = 0.29, p = 0.090$, average: $t_{36} = -0.24, p = 0.141$, sparse: $t_{37} = -0.17, p = 0.313$; results not shown).

4. Discussion

To investigate hemispheric asymmetries in global-local processing, we employed a divided visual field Navon paradigm, while controlling for sex, sex steroid concentration, attention condition, and spacing. According to Navon (1977), global precedence is consistent with (a) global advantage (GA) and (b) stronger interference of global level distractors with local level processing(GLI) compared to interference of local level distractors with global level processing (LGI). We hypothesized stronger global precedence (i) for stimuli presented in the left hemifield, (ii) for the selective compared to the divided attention condition, (iii) for dense compared to average compared to sparse spacing, (iv) and for men compared to women. Furthermore, we hypothesized stronger hemispheric asymmetries in global precedence for men compared to women (iv), indexed by a significant interaction between sex and hemifield on GA/Interference. Finally, we intended to explore a possible modulatory role of sex hormones in global-local processing and if hemifield presentation serves as a stronger predictor for global precedence in the selective compared to the divided attention condition.

4.1. Task-dependent effects on global precedence

Regarding task-dependent influences, our results indicate the following. As expected, we observed higher global precedence, i.e. higher GA and higher GLI as opposed to LGI, in both, RT and accuracy for smaller spacing between letters. This is conceivably explained by an increasing distortion of the overall global letter-gestalt for increasing space between local elements. Similar findings have previously been reported for central presentation [3,8,37].

Regarding the hemifield effect, we obtained evidence for the hypothesis of higher global precedence with LVF-RH compared to CVF-LH presentation from RT data in GA and from accuracy data in interference. In line with earlier findings, both hemifields showed a bias towards the global level [5], but the right hemisphere showed a higher GA in RT and stronger GLI as opposed to LGI in accuracy compared to the left hemisphere, suggesting a right-hemispheric specialization for global and a left-hemispheric specialization for local processing [15-17]. Furthermore in line with previous studies, for both, RT and accuracy, the hemifield effect regarding GA was significantly stronger for the selective attention condition compared to the divided attention condition. As portrayed in studies on the concept of bilateral advantage, the cooperation of cerebral hemispheres facilitates performance in complex tasks, whereas unilateral processing is most efficient for simple tasks [51,52]. This may very well resemble the differences in processing strategies between both attention paradigms. Since divided attention tasks are more challenging [42], processing might be distributed to both hemispheres, even if the initial stimulation is unilateral. However, this interpretation must be treated very cautiously, as the possibility of bilateral processing violates general assumptions of the divided visual field task.

Finally, while RT data support the idea of higher GA for the selective compared to the divided attention condition, the opposite effect was observed for accuracy. While RT data are in line with previous results [6, 29,40,41], a comparison of GA in the divided and selective attention condition has not been previously conducted regarding accuracy data. The fact that opposite results are observed for RT and accuracy is indicative of a speed-accuracy trade-off in the divided attention condition. While for global targets speed seems to be emphasized over accuracy, for local targets accuracy seems to be emphasized over speed. As will be discussed below, this effect is particularly apparent in female participants.

4.2. Sex differences in global precedence

Regarding sex differences, most results obtained during the current study support the idea of stronger global precedence in men compared to women. The difference between global-to-local interference and local-to-global interference was larger in men compared to women for both RT and accuracy data. Likewise, GA in RT was larger in men compared to women. However, as for the effect of attention condition, results on
GA run in opposite directions for RT and accuracy in terms of sex differences. These findings may result from a speed-accuracy trade-off for local elements in women. Particularly, in the divided attention condition, women seem to emphasize speed over accuracy for local elements, resulting in a smaller GA effect in RT, but a larger GA effect regarding accuracy. This observation has the potential to change previous interpretations of sex differences in GA. While it was previously assumed that local elements are perceived faster by women, the observation that this is at the expense of accuracy, partially questions this interpretation. It is conceivable that women respond to local elements before a complete perception is formed. However, the dissociation between RT and accuracy results is particularly apparent in the divided attention condition, where global and local elements have to be processed in parallel, while no sex differences in GA regarding accuracy emerged in the selective attention condition. On the contrary, sex differences in RT seem to particularly concern the selective attention condition, as indicated by results of the current study as well as previous findings [5]. Likewise, interference results obtained during the selective attention condition also strongly support the idea of a stronger global precedence in men. This suggests that emphasizing speedy responses to local elements in women, is only a problem for accuracy, if global elements also need to be attended to. This observation fits several studies suggesting a male advantage in divided attention paradigms [53,54].

Furthermore, sex differences appear to increase, the more densely spaced the local elements are, particularly in RT. Both, sex differences in GA and GLI are larger in denser spaced stimuli. It is possible that women perceive even densely packed local elements as independent forms. This modulation of sex differences by the spacing of local elements may explain previous inconsistencies regarding sex differences in GA [7,9,55] since different studies use stimulus material with different spacings.

Interestingly, we did not observe any sex differences in hemispheric asymmetries during this task. This result is somewhat surprising since several studies on verbal and spatial processing suggest stronger lateralization in men compared to women (see [34] for a review). Please note, however, that these studies did not consider a distinction between the lateralization of different stimulus aspects, but rather the lateralization of stimuli as a whole. These previous results thus suggest that men tend to more unilateral processing during cognitive tasks, which, however, could simply result from men emphasizing global processing more strongly during cognitive tasks. In line with this idea, an association of global precedence to cognitive processing has repeatedly been suggested [43,56–58]. Results of the current study suggest that in tasks where global and local processing have to be balanced, men and women do not differ significantly in how they distribute processing across hemispheres, but men process global information faster. This finding is in line with results from divided field number comparison [43,44]. However, similar to number comparison [43], we discovered sex differences within hormonal effects on cognitive asymmetries.

4.3. Relationship of sex hormones to global precedence

Regarding sex hormonal influences, testosterone emerged as a mediator of sex differences in both, GA and interference, suggesting that higher testosterone levels in men account for sex differences in global precedence. This observation is in line with previous investigations demonstrating positive associations between testosterone and GA [5].

Similarly, estradiol showed a positive relationship to GA for the selective attention condition. As estradiol can be derived from testosterone through the enzyme aromatase, the observed similarities in testosterone and estradiol effects might stem from testosterone-related effects on GA being mediated via estradiol-receptors.

Also, for estradiol, we obtained significant evidence for a differential influence on GA in men and women. While there was a tendency towards a positive relationship between estradiol and GA in women, the relationship appeared to be negative in men. Since men and women differed in default estradiol levels, the relationship between estradiol and GA could follow a u-shaped function. However, more generally speaking, sex differences in the relationship between cognition and sex hormones, like in this case, estradiol, might be subject to various underlying biological mechanisms. While sex differences in hormone receptor expression might create different thresholds for hormonal modulation, differences in the male and female neurotransmitter system [59,60] represent differential starting points for sex hormonal modulation. Also, respective primary reproductive hormones are produced in different locations for both sexes and are therefore also assumed to exert different functions in men and women [61], which is in line with the observed relations to estradiol but also with differential modulatory effects of progesterone on cognitive asymmetries in men and women as discussed in the following paragraph.

While testosterone was an important mediator of sex differences, progesterone emerged as an important modulator of hemispheric asymmetries in both GA and interference. Progesterone was positively related to increased hemispheric asymmetries in men, but we could not replicate a relation to FHAs in women, as previously observed for a variety of cognitive tasks [23,28,43,62]. This restriction of a progesterone-dependent modulation of hemispheric asymmetries may be explained by a hormonal ceiling effect in women since all women were tested in their luteal cycle phase when their progesterone levels peaked. The results in men do however support the accumulating evidence that progesterone modulates hemispheric asymmetries in a variety of cognitive tasks.

4.4. Limitations

First, like in previous hemifield studies of the Navon paradigm [5,39], fixation control was implemented by instructing participants to fixate a central marker without the use of eye-tracking. While this does not control for the accuracy of the initial fixation, presentation time lasted less than 200 ms, which supposedly rules out the possibility of saccadic eye movements. Still, a deviation from central fixation may lead to bilateral representations, and results on asymmetries may be skewed. Similarly, there was no application of chin- or headrest devices that would have provided a constant viewing perspective. Although chairs were fixated and participants were monitored and instructed to avoid any head or body-movements throughout the experiment, a lack of such devices leaves room for error and again may skew results on asymmetries. Second, manual responses were exclusively given right-handed, with a left or right mouse click. Since only visual field presentation, but not the side of responding was counter-balanced across participants, crossover effects leading to a RVF-LH bias might influence the current results [63]. However, since we did not compare total reaction times, but reaction time differences for various stimulus modalities between visual fields, we do not expect this bias to influence the interpretability of our data, provided that stimulus processing is isolated to the contralateral presentation side.

Third, women were only tested in one cycle phase, which does restrict our results on sex differences to the luteal cycle phase and our results on sex hormones to inter-individual variation in sex hormone levels, while no conclusions on intra-individual changes in sex hormone levels are possible. Furthermore, while sex differences are likely largest in the luteal cycle phase, testing women at the time of their progesterone peak may have resulted in a ceiling effect regarding progesterone associations.

5. Conclusion

The current investigation is the first to explore the impact of sex differences in functional hemispheric asymmetries on global-local processing performance by employing a divided visual field Navon paradigm. Overall, it replicates common findings on the effects of spacing, hemifield and attention condition on global-local processing from central presentation paradigms but extends these findings to global-local
interference. Furthermore, the current study matches a number of previous investigations, that were either able to spot significant sex differences in global precedence [6,7,9,56,64] or did, at least, show modest, non-significant evidence in favor of a difference [29,55]. By comparing RT and accuracy data, we were also able to shed some light on the finding that sex differences emerge primarily when participants are instructed to focus on a particular level (selective attention condition) as opposed to when both levels are processed simultaneously.

Most importantly, we present evidence for mediating and moderating effects of sex hormones on sex differences in global precedence and hemispheric asymmetries. While testosterone emerged as a mediator of sex differences in global precedence, progesterone was related to hemispheric asymmetries in both global advantage and interference.

Author statement

Tobias Hausinger: Formal analysis, Writing – Original Draft, Visualization.

Belinda Pletzer: Conceptualization, Methodology, Validation, Investigation, Resources, Writing – Review and Editing, Supervision, Project Administration, Funding Acquisition.

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Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

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