



Testosterone influences volitional, but not reflexive orienting of attention in human males



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ARTICLE INFO

Keywords:

Visual orienting
Visual attention
Testosterone (T)
Inhibition
Facilitation
IOR

ABSTRACT

The impact of testosterone (T) on the exogenous (Experiment 1) and endogenous (Experiment 2) orienting of visual attention in males was examined. Sixteen male participants completed both an exogenous and an endogenous cuing task on two separate days. About 2–3 h prior to testing, either a placebo or a dose of T was administered. The inhibition of return (IOR) phenomenon was observed during the exogenous cuing task, but IOR was not influenced by T. During the endogenous task, participants demonstrated the expected cuing effects on both days. However, longer reaction time to invalid target locations was observed following T-administration. The manipulation of T-levels in males provides converging evidence of dissociation between reflexive and volitional orienting of attention.

1. Introduction

A growing body of literature indicates an influence of sex hormones on visual processing (see [28]). Although results are equivocal, gonadal hormones influence behavioral measures of neurocognitive processing on a variety of tasks when hormone levels are measured (e.g., [1,4,10,15,21,30,31,37,43,45,46]) or when hormones are administered [2,9,16,17,20,49]. One aspect of visual processing where it appears that sex hormones have an influence is selective attention (e.g., [3,10,34]).

A common paradigm used to evaluate selective attention mechanisms is the Posner cuing paradigm [39,40]. The Posner cuing paradigm is used extensively to investigate the facilitation and inhibitory processing generated by an environmental cue as measured by the time to identify and respond to relevant targets (e.g., [39,40]). There are two versions of the paradigm. The first examines reflexive attention or bottom-up processes by using exogenous cues that draw attention to a potential target location. The second paradigm examines more volitional or top-down processes by using endogenous cues, typically arrows presented at a central location, that inform the participant about the potential location of a target.

Exogenous versions of the paradigm involve the cue appearing at one of two potential target locations and then the target appearing equally often at the cued or opposite location. In this case, attention is described as being reflexively “pulled” to the target location (i.e., stimulus-driven orientation of attention). The attention processes are said to be more reflexive as the association between cue and target are

direct because the cues are presented at the potential target locations. In exogenous Posner paradigms, the reaction time pattern is biphasic (e.g., [33,39]). Specifically, there is a facilitation of reaction time with cue-target stimulus onset asynchronies (SOA) below 300 ms, followed by an inhibition of reaction time with an SOA above 300 ms. This specific lengthening of responses back to the cued location has become known as inhibition of return (IOR). The function of the IOR phenomenon is purported to be to facilitate environmental searches by supporting the search for targets in novel locations as opposed to the previously searched locations [26].

In endogenous versions of the paradigm, a directional cue at the fixation “pushes” attention to the potential target in a more volitional manner once the cue's content is determined (i.e., attention is oriented based on expectations, prior knowledge, or an understanding of task goals). The cues reflect the probability of a target occurring at the cued location (e.g., 80%). The endogenous Posner cuing paradigm reaction time pattern is characterized by shorter reaction time to targets at validly cued locations and longer reaction time to targets at invalidly cued locations. This version of the paradigm is also known as the cost-benefit paradigm leading to the prediction outcome effect because the task involves determining the probability of the central cue being valid or invalid. If the cue is invalid (e.g., the central arrow pointed left, but the target appeared on the right) then there is an added cost associated with responding incorrectly (i.e., pushing the left button) or a temporal cost associated with rejecting the original left response and reprogramming a correct movement to the right button. In contrast, if the cue is

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valid then there is a temporal benefit to responding to the target indicated by the cue.

Although they appear similar, exogenous and endogenous orienting are unique and distinct mechanisms of attention (e.g., [6,23,25]) and neuroimaging studies have affirmed the notion that the two processes follow distinct neural subsystems (see [18,22]). Increased blood oxygenated level-dependent (BOLD) responses associated with exogenous cues have been observed in the bilateral temporoparietal junction, anterior and posterior insula, right precentral gyrus, bilateral fusiform gyri, lingual gyri, cingulate gyrus, and cuneus. In comparison, BOLD responses associated with endogenous stimuli have been observed in the left intraparietal sulcus, inferior and superior parietal lobule, bilateral precuneus, middle frontal gyri, and middle occipital gyri [18]. The IOR phenomenon occurs across a spectrum of paradigms including those involving different neural systems (i.e., between-person or joint-action IOR; e.g., [19,52]), different sensory-modalities of cue-target pairings [29,47], populations with physical or mental challenges (e.g., [44,53]), and different head orientations (e.g., [32]). These paradigms are ideal for examining the influence of hormones on orienting of attention given the reliable nature of the IOR phenomenon (see [24] for a review of IOR) and endogenous cost-benefit paradigm (i.e., [40]). In this study, the stimuli and SOA were selected because they reliably elicit robust exogenous and endogenous cuing effects (e.g., [32,33,39]). Therefore, our intention was to examine the influence of T-administration on attention rather than examining the pattern of responses to different time-courses of SOA or inter-stimulus intervals.

In previous research examining visual selective attention, Bayliss et al. [3] and Merritt et al. [34] used variations of the Posner cuing paradigms to investigate sex-differences. Both sets of researchers found that males and females responded similarly to exogenous cues, but differently to centrally-presented endogenous cues such as arrows. Specifically, females demonstrated a larger cuing effect in response to invalid cues. However, these previous studies were completed without monitoring naturally occurring hormone levels or administering hormones (e.g., [3,34]). Although the studies of Merritt et al. [34] and Bayliss et al. [3] contribute to the understanding of sex differences by directly comparing male and female performances on spatial cuing tasks, the lack of information regarding the hormonal status of the participants prevents a mechanistic interpretation beyond implications involving hormonal activation or structural organization of the neurological systems. Given inconsistencies in both methodology and findings of previous literature, it is important to establish causal relationships between gonadal hormones and visual-spatial behaviors.

This study was designed to investigate the influence of heightened T-levels in human males on the inhibitory mechanisms of visual attention under exogenous and endogenous cuing paradigms. Increased T-levels were predicted to influence generalized inhibitory mechanisms, revealing larger cuing effects during both paradigms. However, should the provision of T only affect volitional control then a larger cuing effect would only occur during endogenous cuing. To our knowledge, this is the first investigation of the influence of T-administration on selective attention in human males.

2. Methods

2.1. Participants

Sixteen males were recruited (mean = 21.85 ± 2.14 years). Participants were a subgroup from a larger protocol ($n = 30$; [8,51]). Eligibility was determined before enrollment. Exclusion occurred if applicants were receiving prescription medication affecting hormone concentrations, were diagnosed with psychiatric disorders or heart conditions, or were members of an organization restricting exogenous-T.

Participants provided informed consent on an orientation day. They consented to blood draws and having their T-levels temporarily

modified. All had normal or corrected to normal vision. Participants completed Experiments 1 and 2 on two testing days in a counter-balanced manner. There were no main effects or significant interactions involving experiment order. The University's ethics board approved this protocol (#14-06-09) and the guidelines of the declaration of Helsinki were followed.

2.2. Testosterone and placebo administration (Experiments 1 & 2)

Participants completed a repeated measures, double blind, placebo controlled paradigm. On both testing days, a registered nurse, who was female, drew 10 cc of blood and then a male research assistant administered 150 mg of Androgel® (a drug used to treat hypogonadal men) or an equivalent amount of placebo onto the shoulders and upper arms. The placebo was a mixture of Carbomer 940 NF, Alcohol 95% w/v, Purified Water, Sodium Hydroxide, and Isopropyl Myristate NF. Additional blood samples were drawn at 60 and 120 min post-administration. After the 120 min draw, participants completed a series of computer-based experiments as part of the larger protocol. Other experiments examined decision making abilities, facial preferences, social perceptions, and cognition. The current experiments occurred approximately 2 h and 44 min (± 6 min) following gel administration. Including the instructions, each experiment lasted approximately 8 min. Pharmacokinetic research indicates that T-concentrations begin to rise within 2 h and peak concentrations occur within 3 h [14]. A single T-administration can modulate brain function within 45–90 min (see [16,50]).

Day 2 occurred 2-weeks after Day 1. Day 2 was identical except that the opposite substance was administered (Androgel® or placebo). After testing, participants were asked to guess which day they had received T. A binomial test indicated guessing at chance ($p = 0.23$).

2.3. Hormone assays & hormone concentrations

Commercially available enzyme immunoassay kits (DRG international) were used to estimate total T-concentrations. Blood samples were assayed in duplicate and mean T-concentrations were analyzed. Intra- and inter-assay coefficients of variation were below 5%.

Hormone concentrations were submitted to a 2-Hormone Condition (Testosterone, Placebo) by 3-Time (Baseline, 60 min, & 120 min) repeated measures ANOVA. Follow-up Tukey's HSD post-hoc tests were used ($\alpha = 0.05$). Analysis revealed main effects of Hormone Condition, $F(1,15) = 39.75$, $p < 0.001$, $\eta_p^2 = 0.726$, Time, $F(2,30) = 43.10$, $p < 0.001$, $\eta_p^2 = 0.742$, and a significant interaction of Hormone Condition and Time, $F(2,30) = 39.86$, $p < 0.001$, $\eta_p^2 = 0.727$. In the placebo condition, total-T remained at the same amount across the three time periods (Baseline = 4.26 ± 0.88 ng/ml, 60 min = 4.60 ± 1.35 ng/ml, & 120 min = 4.58 ± 1.48 ng/ml). As expected, total-T at baseline before administration (4.07 ± 0.85 ng/ml) was at the same level as the placebo ($p > 0.948$). Post-T-administration, total-T was higher at 60 min (6.84 ± 1.96 ng/ml) and remained higher at 120 min (6.53 ± 1.63 ng/ml) when compared to baseline ($p < 0.001$ & $p < 0.001$) and any time-period under placebo ($p < 0.001$).

2.4. Experiment 1: exogenous cuing

2.4.1. Apparatus

White stimuli were presented on a black background (22-inch monitor; refresh rate = 75 Hz). Responses were made on the “f” and “j” keys of a keyboard. An E-Prime 2.0 program (Psychology Software Tools Inc., Pittsburgh, PA) controlled stimulus presentation and recorded responses.

2.4.2. Procedure

Participants sat 45 cm from the screen. Trials began with a 1000 ms

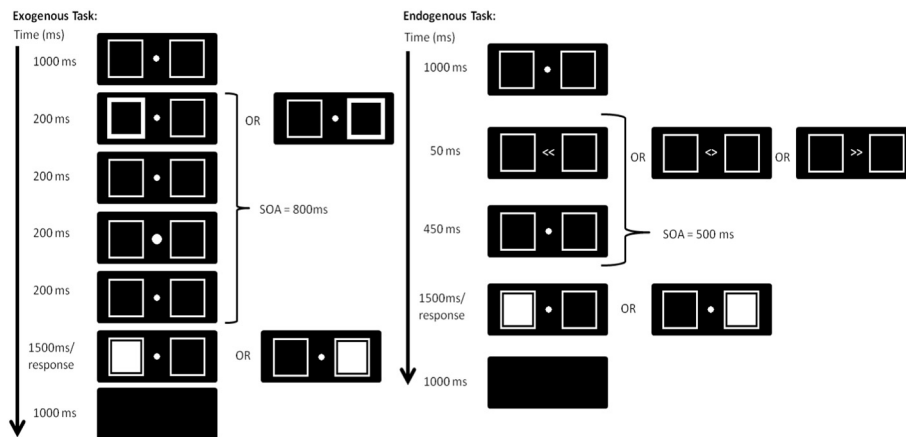


Fig. 1. Illustration of the trial sequence for the exogenous (Experiment 1) and endogenous (Experiment 2) tasks.

presentation of two square outlines ($1^\circ \times 1^\circ$) on the horizontal meridian at a distance of 5° to the left and right of a filled fixation dot (0.2° diameter; see Fig. 1). The cue was then presented. It was the border of one of the squares expanding to 1.1° for 200 ms. The original two squares were then presented for 200 ms. Subsequently, the fixation dot expanded by 0.5° for 200 ms. Afterwards, the original squares were presented for 200 ms. Finally, the target appeared as a filled-in white square ($0.7^\circ \times 0.7^\circ$) within one of the squares. Therefore, the stimulus onset asynchrony (SOA) was 800 ms. The target remained until response or 1500 ms elapsed. Participants were requested to avoid responding during catch trials (20%) where a target failed to appear. Catch trials were inserted in order to prevent anticipatory responses. A blank screen was presented for 1000 ms following response or after 1500 ms elapsed.

Participants were requested to maintain fixation and respond as quickly and as accurately as possible. Participants were informed that the cue was non-predictive. Trials where the cue was presented in the same location as the target were labeled “cued”. Trials where the cue was presented in the opposite location from the target were labeled “uncued”. Participants performed 60 trials each day (24 cued, 24 uncued, and 12 catch-trials). Half of the trials had the cue on the left.

2.4.3. Data reduction & statistical analysis

Mean reaction time (RT) from errorless trials were subjected to a 2-Hormone Condition (Testosterone, Placebo) by 2-Cue Type (Cued, Uncued) by 2-Target Side (Left, Right) repeated measures ANOVA. Errors were defined as trials with incorrect responses, RT above 1500 ms or below 100 ms. Errors occurred on $< 1.1\%$ of trials.

2.4.4. Results & discussion

Analysis revealed a main effect of Cue Type, $F(1,15) = 39.05$, $p < 0.001$, $\eta_p^2 = 0.722$ s. Participants responded faster to uncued (359 ± 71 ms) compared to cued targets (380 ± 69 ms; $p < 0.001$). This is the typical IOR effect. However, analysis failed to reveal the main effect of Hormone Condition, $F(1,15) = 0.17$, $p = 0.687$, $\eta_p^2 = 0.011$, the interactions of Hormone Condition and Cue Type, $F(1,15) = 1.33$, $p = 0.266$, $\eta_p^2 = 0.082$, Hormone Condition and Target Side, $F(1,15) = 0.15$, $p = 0.704$, $\eta_p^2 = 0.010$, or the three way-interaction, $F(1,15) = 0.96$, $p = 0.343$, $\eta_p^2 = 0.060$.

Our findings failed to reveal an effect of T on inhibitory mechanisms in males during reflexive orienting of attention with an SOA of 800 ms. However, the possibility of an influence on endogenous orienting remained.

2.5. Experiment 2: endogenous cuing

2.5.1. Apparatus & procedure

The apparatus was identical to Experiment 1. However, the cue was

presented centrally and the SOA changed. Trials began with the outline of two squares and fixation dot appearing for 1000 ms and then the cue appeared for 50 ms. The cue replaced the dot. The cue was two arrowheads facing left (“<<”), right (“>>”), or one left and one right (“< >” i.e., neutral). The cue disappeared and was replaced by the fixation dot for an additional 450 ms. Subsequently, the target appeared as the filled-in white square inside one of the two squares (SOA = 500 ms). The target remained until the response or 1500 ms elapsed. A blank screen was then presented for 1000 ms (see Fig. 1). Again, participants were requested to maintain fixation and press the “f” or “j” key. Participants were informed the cues were 80% predictive.

Trials where the cue indicated the target location were labeled “valid”. Trials where the cue indicated the opposite location were labeled “invalid”. Trials where the cue was non-predictive were termed “neutral”. Each day, participants completed 60 trials (40 valid, 10 invalid, and 10 neutral).

2.5.2. Data reduction & statistical analysis

Mean RT from errorless trials were subjected to a 2-Hormone Condition (Testosterone, Placebo) by 3-Cue Type (Valid, Neutral, and Invalid) by 2-Target Side (Left, Right) repeated measures ANOVA. Errors occurred on $< 1.4\%$ of trials. Tukey’s HSD post-hoc tests were used ($\alpha = 0.05$).

3. Results

Analysis revealed a main effect of Cue Type, $F(2,30) = 25.50$, $p < 0.001$, $\eta_p^2 = 0.630$, and a significant interaction of Hormone Condition and Cue Type, $F(2,30) = 5.65$, $p < 0.008$, $\eta_p^2 = 0.274$. RT to validly cued targets (315 ± 47 ms) was shorter than to neutral targets (335 ± 47 ms; $p = 0.004$). RT to neutral targets was shorter than to invalidly cued targets (355 ± 66 ms; $p = 0.003$). RT to validly cued targets was shorter than to invalidly cued targets ($p < 0.001$).

RT increased from the valid to the neutral condition ($p = 0.008$) and from the neutral to the invalid condition with T-administration ($p < 0.001$). Without T, RT increased from the valid to the neutral condition ($p = 0.049$), but remained at similar levels for the neutral and invalid conditions ($p > 0.525$). For both hormone conditions, RT was longer in the invalid condition compared to the valid condition ($p < 0.001$ for both hormone conditions). However, RT was similar in the invalid condition with or without T ($p > 0.063$). Therefore, the interaction was driven by an increase in RT from the neutral to the invalid condition with T, but remained at a statistically similar level between the neutral and invalid condition without T (see Table 1).

4. Discussion & conclusion

T-administration to males failed to influence reflexive orienting of

Table 1

Mean reaction time (ms) with SD for Experiments 1 (exogenous) and 2 (endogenous) as a function of Cuing Condition and Hormone Condition (Testosterone or Placebo). Negative values represent facilitation.

Exogenous	Cued	Uncued	Cuing effect	
Testosterone	379 (67)	354 (64)	25 (19)	
Placebo	381 (71)	363 (78)	18 (17)	

Endogenous	Valid	Invalid	Cuing effect	Neutral cue
Testosterone	311 (44)	364 (80)	– 53 (38)	333 (47)
Placebo	320 (50)	347 (48)	– 27 (23)	337 (51)

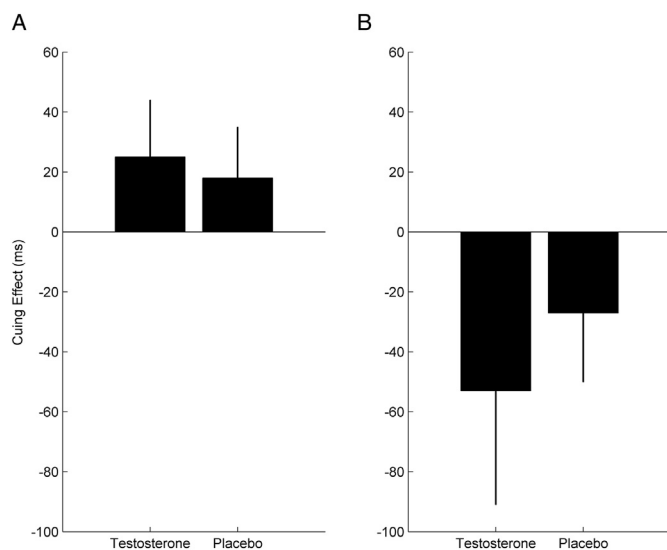


Fig. 2. Cuing effects (ms) with standard deviations for the exogenous (A) and endogenous (B) cuing paradigms as a function of Hormone Condition (Testosterone versus Placebo). Negative values represent facilitation of responding to a validly cued target.

visual attention, but led to larger cuing effects under volitional orienting (see Fig. 2). These results are consistent with the notion that reflexive and volitional orienting are functionally distinct mechanisms [6,23,25,32]. Specifically, increased-T only influenced endogenous orienting. However, we failed to detect an effect of increased T-levels upon the magnitude of IOR measured 800 ms after a peripheral cue. In this context, the larger effects associated with endogenous cues and increased-T was due to longer RT to invalid cues in comparison to neutral cues. Specifically, participants took longer to disengage the previously cued location when administered-T, indicating inefficient processes that could mediate the detection of the target when presented elsewhere. The latter effect can have negative consequences for action behaviors that require visual reorienting to novel targets, or during visual searches for relevant targets. Specifically, an individual with high T-levels could fail to perceive threat information or a more valuable resource at a new location because they failed to disengage their attention from the original (i.e., previously cued) location. More importantly, they could be more deceived by specific endogenous cues such as another individual's movements (e.g., a fake) or eye gaze direction (e.g., [3]). The latter effect leads to poor performance in tasks such as the endogenous Posner cuing paradigm. In contrast, this lack of distractibility from the original location can contribute to positive task outcomes in situations requiring sustained attention such as in “Go”/“No-Go” paradigms where an individual responds to a central target while ignoring irrelevant peripheral flankers (e.g., [48]). In this case, high T-levels would lead to increased task performance. Overall, gonadal hormone levels influence the visual inhibitory processes, but the impact of the changes to the inhibitory processes on behavioral

outcomes may also depend on the nature of the task being completed.

In regards to orienting of attention, investigations involving individuals with Parkinson Disease indicate that the neural mechanisms associated with responding to exogenous and endogenous cues are distinct [54]. Specifically, a compromised dopaminergic system was associated with reduced response efficiency during volitional orienting, but had limited impact upon reflexive orienting. Dopamine (DA) plays a key role in regulating motor and limbic functions throughout the lifespan [12,35] and is implicated in the regulation of IOR (e.g., [38]). Testosterone (T) is linked to DA metabolism within the rat brain [13,41,42]. In human males, T impacts DA driven cognitive functions such as verbal memory [9,36], working memory in older men [20], visual discriminations [1], stimulus identification [17], and decision making [4,7]. These links between gonadal hormone concentrations and cognitive function highlight the importance of considering baseline hormones when investigating attention [11]. Given the links between T and DA (e.g., [41]), the subsequent influence of DA on cognition [35], and processing of endogenous cues [54], it follows that increased-T could lead to modified inhibitory control during tasks involving voluntary, but not reflexive orienting of attention in males. However, this possibility remains speculative because DA levels were not measured during the current study.

Our results are consistent with those of Bayliss et al. [3] and Merritt et al. [34]. Specifically, reflexive orienting was similar for males and females in their studies, while reflexive orienting appeared to be independent of sex hormone status in our study. In contrast, there were larger cuing effects for the females and different patterns of response between males and females for their endogenous tasks. Although these outcomes fail to discount either activational (i.e., rate of activation differences between males and females) or neural organizational differences (i.e., different physical sizes of the structures or different connections between the structures between males and females; e.g., [27]) as an effect locus of sex differences in visual selective attention, our results indicate an important role of T in the functioning of volitional selective attention in males.

Although our data indicate that T modulates volitional, but not reflexive attentional processes, there are some limitations. First, a standard dose of 150 mg of Androgel® was used to increase T-concentrations to the “high-normal” physiological range. A higher dose could impact reflexive attentional processes. Second, the effects of T may be time-dependent. Previous T-administration experiments conducted with women indicate a time-lag (3.5–4 h) between peak-T and effects on social, cognitive, and behavioral processes (see [5] for review). Thus, a longer time-lag may yield effects of T on reflexive orienting. Third, although the design of the current study included within-participant comparisons, the total number of participants was low. This was because of the associated costs of the T-administration, and hormone assaying. Thus, perhaps the lack of an effect of T in the exogenous cuing task may be due to a lack of statistical power to detect small-to-medium effect sizes associated with the T-administration. Having said that, the cuing paradigms used in this study produce reliable and robust findings and effect sizes regardless of practice or exposure to the tasks (see [25]; e.g., [44,47]). Finally, although it was not the main impetus of this study, the use of more cue-target onset asynchronies will allow for the examination of the time-course of the influence of T on the maintenance of exogenous and endogenous orienting. Future studies from our lab will examine the time-course of the influence of gonadal hormones on visual selective attention.

Our results help clarify the role of sex hormones in modifying visual selective attention. Specifically, increased T-levels may contribute to the impairment of inhibitory processes during endogenous cuing tasks. Overall, the results support the notion that inhibitory control during visual selective attention tasks is state dependent (e.g., [10]), but we cannot discount the potential additional influence of neural-structural contributions to individual differences in performance (e.g., [27]).

Funding

This research was supported through funds from the Natural Sciences and Engineering Research Council of Canada (RGPIN-2014-06676) and Northern Ontario Heritage Fund Corporation grants awarded to J. M. Carré and funds awarded to S. Hansen from the Canada Foundation for Innovation.

Conflicts of interest

All of the authors declare that they have no conflicts of interests.

Acknowledgments

The authors would like to thank undergraduate and graduate students Brian Bird, Brandy Labine, Benjamin Moreau, Nathan Olmstead, Triana Ortiz, Erika Ruddick, and Sara Taylor for their assistance during data collection.

The authors would also like to thank Algonquin Pharmasave, and in particular, Meghan Heinz and Jen Zhou, for help preparing the testosterone and placebo gels. The authors would also like to thank Mrs Terri Moreau for help with the blood draws.

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