Testosterone Reduces Unconscious Fear but Not Consciously Experienced Anxiety: Implications for the Disorders of Fear and Anxiety

Jack van Honk, Jiska S. Peper, and Dennis J.L.G. Schutter

Background: *The fear-reducing properties of testosterone have been firmly established in animals but not in humans. However, human data on the relation between testosterone, fear, and anxiety have predominantly involved questionnaires that index cortically executed conscious appraisal of anxious mood. Animal studies, on the other hand, indicate that the effects of testosterone on motivation and emotion are of subcortical origin and of unconscious nature. Presently, it was hypothesized that a single testosterone administration to humans would reduce unconscious fear but not consciously experienced anxiety.*

Methods: *In a placebo-controlled, double-blind crossover design, a single dose of testosterone (.5 mg) or placebo was administered to 16 healthy female volunteers. Afterward, a masked emotional Stroop task measured unconscious emotional responses to fearful faces, while multiple self-reports of mood indexed consciously experienced anxiety.*

Results: *As hypothesized, the habitual vigilant emotional response to the masked fearful face observed in the placebo condition was significantly reduced after testosterone was administered, while the self-reported measures of anxiety remained unaffected.*

Conclusions: *These data provide the first direct evidence for fear-reducing properties of testosterone in humans. Furthermore, by dissociating specific aspects of fear and anxiety in humans, this outcome highlights that testosterone's effects on motivation and emotion concern the subcortical affective pathways of the brain.*

Key Words: Testosterone, emotional facial expressions, motivated attention, fear, anxiety, conscious and unconscious processing

Fear is a life-saving emotional state that serves anticipation and adaptation to danger (Gallagher and Holland 1994). However, through a multiplicity of genetic, developmental, and environmental factors, fear's adaptive properties can go awry (Charney 2004; Gross and Hen 2004). The destructive value of excess fear has been emphasized in both animal and human models of psychopathology (LeDoux 1996; Lang et al 2000). Overgeneralized, exaggerated behavioral and autonomic responses to threat and novelty are observed when pathological fear sets in (Rosen and Schulkin 1998). This happens when fear circuits of the brain have become hyperexcitable, the core of abnormality in most disorders of fear and anxiety (Coplan and Lydiard 1998; Tillfors et al 2001). A neurobiological mechanism argued to be importantly involved in these hyperexcitable fear circuits is the endocrine-neuroendocrine amygdala cascade. Heightened levels of the steroid hormone cortisol exaggerate and sustain fearfulness by facilitating corticotropin-releasing hormone (CRH) gene expression at the amygdala (Corodimas et al 1994; Schulkin et al 1998).

Contrariwise, one of the most replicated findings in research on the relationship between steroid hormones and emotional behavior involves reductions in fear after treatment with the steroid hormone testosterone. This phenomenon has been demonstrated in a large variety of species using an excessive range of behavioral assessment paradigms (e.g., Boissy and Bouissou 1994; Bouissou and Vandenheede 1996; Frye and Seliga 2001; Aikey et al 2002). However, although there is evidence for antidepressant effects in hypogonadal depressive patients after testosterone treatment (Burris et al 1992; Wang et al 1996; Pope et al 2003), clear-cut reductions in fear after testosterone administration or treatment have not been reported in humans up until now.

Here we would like to defend the notion that this contradiction is largely rooted in an operationalization confound. The tests of fear in animals predominantly involved behavioral or physiological reactions to innate or conditioned affective stimuli, whereas the tests of fear in humans mostly involved mood questionnaires or interviews that factually assessed cognitively attributed facets of anxiety (Boissy and Bouissou 1994; Mazur and Booth 1998). Although fear and anxiety have been discussed as being identical (Zuckerman 1991), they are clearly distinct (Barlow 1988; Gray 1987; Davis 1998). Mathews and Mackintosh (1999) regard fear as the basic emotion arising from the operation of a phylogenetically older amygdala-centered limbic system subserving detection and reactions to danger, whereas human anxiety, in particular, entails more complex cognitive processing and (linguistic) symbolic representations of potential danger wherein the prefrontal cortex is crucially implicated. This seems in disagreement with the influential rodent model of fear and anxiety from Davis (1998), which suggests that the central nucleus of the amygdala is responsible for the fear-induced flight activation, while the bed nucleus of the stria terminals (BNST) or extended amygdala is importantly involved in the conditioned forms of anxiety. It should, however, be noted that Mathews and Mackintosh's (1999) conceptualization relates to the human model, and encephalization, the physical expansion of the human neocortex throughout evolution, has clearly induced a spread upward for the emotions into the prefrontal cortex (PFC) (Berridge 2003). In humans, fear remains mediated by the phylogenetically older subcortical structures, but anxiety has become more strongly associated with cortical processes which provide for complex, cognitively oriented, linguistically based forms of affect (Ketter et al 2003).

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Interestingly, data from animal research indicate that testosterone predominantly acts on motivation and emotion by binding to steroid receptive neurons that occupy the amygdaloid-centered nuclei in the limbic system (Wood 1996; Schulkin 2003). Human research even so suggests a crucial role for the amygdala in the effects of testosterone on emotional processing. In healthy volunteers, a single administration of testosterone induces cardiac accelerative responses to angry facial expressions (van Honk et al 2001), and it is the central nucleus of the amygdala which innervates brain stem centers controlling heart rate that are crucially involved in motivated attention (Kling and Brothers 1992). In further agreement, vigilant attentional responses to angry faces relate positively to levels of testosterone in males as well as in females (van Honk et al 1999), and recent functional magnetic resonance imaging (fMRI) research has demonstrated that single testosterone administrations to healthy volunteers indeed activate the amygdala in response to angry facial expressions (Hermans et al 2004).

Given the unmistakable aggression-potentiating properties of testosterone (Dabbs et al 1987; Dabbs and Morris 1990; Dabbs and Hargrove 1997; Soler et al 2000) and the provoking socially threatening nature of the angry face (van Honk et al 1999), vigilant emotional responses to angry facial expressions after testosterone administration defensibly indicate an increased proneness for aggression (van Honk et al 2001). The androgenic steroid, however, possesses dual-sided, aggression-increasing and fear-reducing, motivational properties. Fearfulness or anxiousness can be indexed in humans by way of vigilant responses to fearful facial expressions (Whalen et al 1998; Rauch et al 2000; van Honk et al 2002b). The fearful face functions as a danger signal that induces amygdala activation (Whalen 1998). In defense, exaggerated amygdala activation to masked fearful faces has been demonstrated in posttraumatic stress disorder (PTSD) (Rauch et al 2000), and anxiety-disordered children show exaggerated amygdala responses to unmasked fearful faces (Thomas et al 2001).

In sum, testosterone may increase the emotional response to the angry facial expression but it should, given its fear-reducing properties, also reduce the emotional response to the fearful facial expressions.

Presently, unconscious fear was indexed using an emotional Stroop task that applied the backward masking technique and used fearful, happy, and neutral faces as stimuli (Esteves and Öhman 1993; van Honk et al 2001, 2002b). The backward masking technique has elucidated the role of the amygdala in unconscious processing of fearful facial expressions in fMRI research (Whalen et al 1998; Rauch et al 2000) and highlights subcortical aspects of affective processing through its capability of circumventing higher-order cortical processes (Morris et al 1999; van Honk et al 2000; Putman et al 2004). These higher-order cortical processes, in the form of consciously experienced anxiety, were presently measured using self-reports of mood and behavioral inhibition (Shacham 1983; Spielberger 1988; Carver and White 1994), which have not been influenced by single testosterone administration experiments until now (Tuiten et al 2002; van Honk et al 2001, 2004; Schutter and van Honk 2004; Schutter et al, in press) except in hours-long priming conditions (Tuiten et al 2000). Based on theoretical notions and experimental data above, it was hypothesized that in healthy volunteers, a single administration of testosterone compared with placebo would reduce the unconscious emotional response of fear without affecting consciously experienced measures of anxiety.

Methods and Materials

Subjects

Participants were 16 right-handed, healthy young women, ranging in age from 19 to 26 years. Only women were recruited because the parameters (quantity and time course) for inducing effects in men after a single sublingual administration of testosterone are unknown (cf. Tuiten et al 2000). The testosterone-placebo testing days were run 2 days apart but both in the early follicular phase of the menstrual cycle when endogenous levels of hormones are low and most stable (Bjork et al 2001). The women were medication-free but used oral contraceptives. Standardized interviews revealed that the women did not have pituitary or endocrine diseases or a history of substance abuse, psychiatric illness, or neurologic illness. They received a single dose of either testosterone or placebo in a double-blind, randomly assigned, crossover, and within-subject design. Drug samples consisted of either .5 mg of testosterone with cyclodextrins as carrier or placebo (see Tuiten et al 2000 for details). Subjects were unaware of the aim of the study and received payment for participation. Informed consent was given, and the protocol was approved by the Medical Ethics Committee of the University Medical Center Utrecht in accordance with the Helsinki amendments.

Testosterone Administration

Experimental studies in our laboratory have earlier established the time course of a single sublingual administration of .5 mg testosterone on blood levels and physiological responsivity. Without exception, a tenfold increase in total testosterone was observed (with no changes in plasma globulin) 15 minutes after intake, returning to baseline within 90 minutes. Crucially, however, in these studies, it was repeatedly shown that this single administration of testosterone significantly elevated vaginal pulse amplitude in healthy young women after about 4 hours (Tuiten et al 2000; Tuiten et al 1998, unpublished data; see also van Honk et al 1999 for the extension of this time course to a salivary testosterone sampling design).

Thus, physiological effects after single sublingual administration of .5 mg testosterone peak 2.5 hours after the testosterone level in the blood has returned to baseline. Note that vaginal pulse amplitude is the only physiological index having a nonhabitual nature, thus allowing multiple measures throughout the day (Tuiten et al 2000). We have successfully used this time course of effects of testosterone assessed by vaginal pulse amplitude (Tuiten et al 2000) in human cognitive and emotional research (Postma et al 2000; Tuiten et al 2002; van Honk et al 2001, 2004; Aleman et al 2004; Schutter and van Honk 2004, 2005). Presently, the delay of 4 hours between testosterone-placebo administration and measurement of mood and emotional Stroop performance was therefore again applied.

Statistics

Data were analyzed using nonparametric statistics and binomial tests. The hypotheses were directly tested (Cohen 1988) using Wilcoxon signed rank tests for related samples. For all tests, a significance level of .05, two-tailed, was applied. One subject was not capable of finishing the second session of the experiment because of insomnia the night before and her data were removed from statistical analyses.

Masked Emotional Stroop Task

A masked emotional Stroop task was employed to index the attentional response to the unseen fearful face. In this task, the

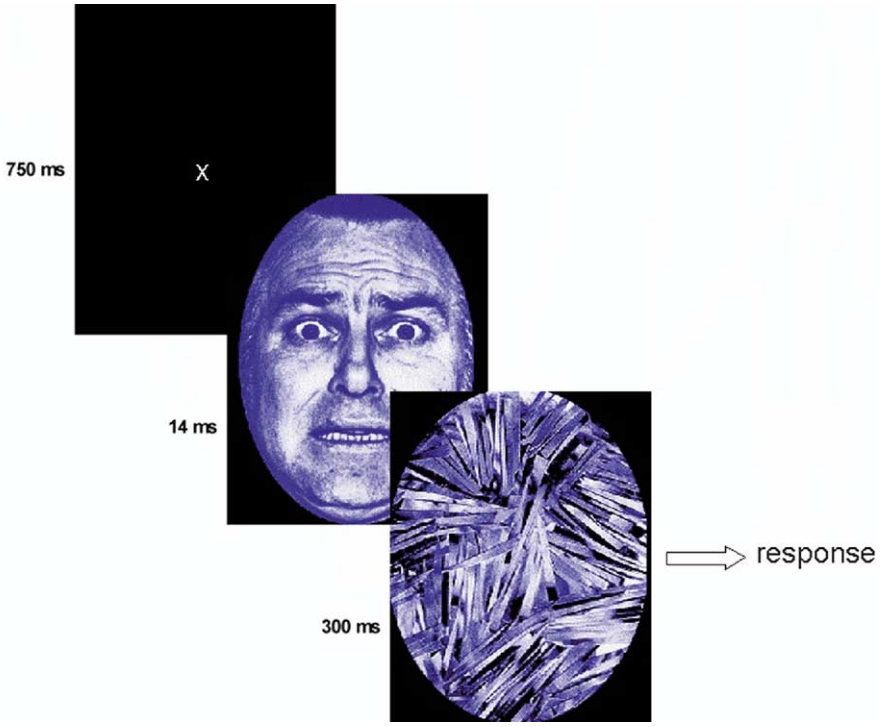

Figure 1. The sequence of stimulus presentations and their presentation times in the masked Stroop task.

masked neutral face is used as reference (van Honk et al 1998, 2002b), and with respect to the unseen happy faces, it was explored whether testosterone might negatively influence their attentional processing, since reversed correlations between testosterone and positive facial expressions have been found using electromyography (Dabbs 1997) and in observer-rated natural conditions (Cashdan 1995). The present emotional Stroop task requires participants to name as quickly as possible the color of pictures of fearful, happy, and neutral facial expressions. Our stimuli were taken from the Ekman and Friesen (1976) *Pictures of Facial Affect*. In the applied masked emotional Stroop task, a fixation point is shown for 750 milliseconds, followed by the target stimulus (a neutral, happy, or fearful face) presented for 14 milliseconds, before being replaced by a masking stimulus, with target and masked both colored red, green, or blue and presented on a 70 Hz computer screen at a distance of 110 cm at eye level. Masking stimuli were randomly cut, reassembled, and re-photographed pictures of faces. For optimizing stress-related workload, a fast externally paced version of the task (Renaud and Blondin 1997) was used with a termination of mask display after 300 milliseconds, approximating the minimum in observed vocal response initiations in this task (see Figure 1). Forty neutral, 40 happy, and 40 fearful faces were presented in random order with the restriction that the same color was never repeated more than twice consecutively. The intertrial interval randomly varied between 1500 and 2500 milliseconds.

Dependent measures in the task are attentional bias scores (i.e., the mean individual color-naming latencies of fearful or happy faces minus the individual mean color-naming latencies on neutral faces) (van Honk et al 2002b). Positive attentional bias scores result from slower color-naming responses to emotional compared with neutral stimuli and indicate a vigilant emotional response, whereas the negative attentional bias score results from faster color-naming responses to emotional faces compared with neutral stimuli and indicate an avoidant emotional response (Williams et al 1996). Finally, cognitive performance in terms of overall task performance can be computed by collapsing all data into total color-naming scores independent of expression (van Honk et al 2000, 2003a).

Threshold Control

Subliminal thresholds were controlled by subjective and objective awareness checks. Both these checks were performed after each session. The subjective check was a simple interview asking the subjects whether they had recognized the emotional valence of the faces that were displayed before the masks (cf. Whalen et al 1998; Sheline et al 2001). The objective check was a three-alternative forced-choice (3AFC) fear-happy-neutral recognition check, using the fearful, happy, and neutral facial expressions. In this 3AFC, a random set of 60 masked faces was shown to the subjects. In advance, subjects were explicitly told that the set contained 20 neutral, 20 happy, and 20 fearful faces and were instructed to indicate (or guess), by pushing a button, whether the presented picture was a fearful, happy, or neutral emotional expression (see Kemp-Wheeler and Hill 1988 for the rationale behind this instruction). Note that both these subjective and objective checks control for awareness of crucial stimulus quality in the emotional Stroop task: emotional valence (Van Selst and Merikle 1993). Moreover, since emotion is the stimulus quality most easily processed, the presently applied 3AFC check is the most conservative awareness check conceivable (Wells and Mathews 1994).

Anxiety Questionnaires

For indexing a broad spectrum of self-experienced anxiety, three different questionnaires were used. These included a five-item measure of cognitive anxiety drawn from the Spielberger State-Trait Anxiety Inventory (STAI) (Schutter et al 2001; Spielberger 1988) and the tension-anxiety measure taken from the shortened Profile of Mood States (POMS) (Shacham 1983). Since slight but pertinent changes in mood in normal subjects may be concealed when using standard scales (Bond and Lader

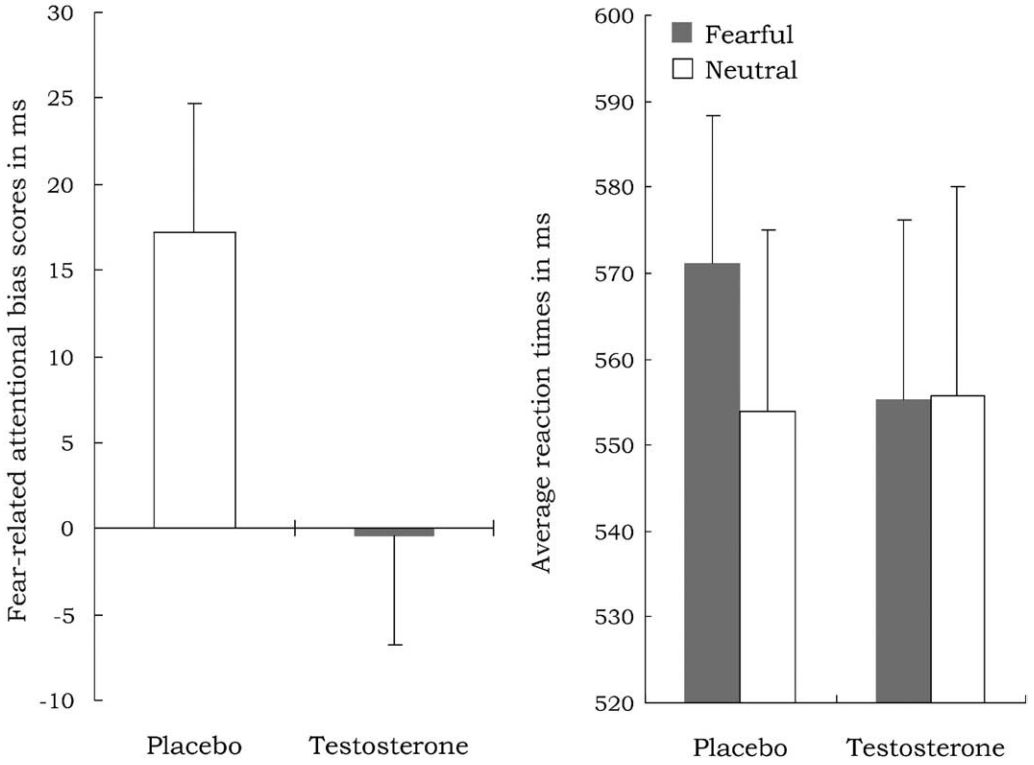

Figure 2. Mean attentional bias scores (i.e., response latencies for the masked fearful faces minus response latencies for masked neutral faces) and SEM in milliseconds (ms) differ significantly between the testosterone and the placebo conditions ($p = .015$) **(A)** and raw response latencies show that the vigilant attentional response to unconscious fear in the placebo condition (i.e., higher response latencies to masked fearful as compared with masked neutral faces in milliseconds; $p < .03$) completely disappear after testosterone is administered **(B)**.

1974; Norris 1971), for the cognitive and the tension anxiety measures, visual analogue scales were used to enhance sensitivity (Schutter et al 2001; van Honk et al 1999, 2003a). Finally, to assess possible short-term changes in Gray's (1987) anxiety paradigm of behavioral inhibition, a state version of Carver and White (1994) Behavioral Inhibition Scale (BIS) was administered.

Results

Awareness Checks

There was no evidence of recognition of emotional valence during masked presentation by subjective check. For analyzing subjects' performance on the objective check, we initially scrutinized possible effects of Order and Drug to see whether repeated measuring or testosterone had influenced perceptual thresholds in any way. There was no evidence for Order [$Z(1,15) = -.22$; ns] and Drug [$Z(1,15) = -.13$; ns] having the slightest effect on perceptual performance. This allowed us to collapse the performance measures of the subjects over both occasions and run binomial tests over 120 trials to reduce the chance of type 2 errors. Although subjectively reporting no awareness, two individuals' level of recognition on the objective tests reached significance ($p = .015$; 43% correct, and $p = .035$; 41% correct), against the chance performance of 33.3% on the 3AFC. These subjects were removed from further analyses.

Unconscious Fear

Data Reduction Emotional Stroop Task. Attentional bias scores were computed by subtracting the individual mean color naming latencies for neutral faces from the individual mean color naming latencies for both emotional faces (van Honk et al 2002b). Next, the crucial hypothesis was tested by comparing the resulting bias scores for fearful expressions between the placebo and the testosterone conditions by means of Wilcoxon signed rank tests, followed by the same analysis for the happy expressions.

Masked Fearful Facial Expression. The crucial placebo-testosterone comparison for the attentional bias scores of the unseen fearful facial expressions was significant [$Z(1,13) = -2.4$; $p = .015$]. To further scrutinize these findings, we looked into the raw color naming latencies for fearful and neutral faces. In the placebo condition, a significant bias in attention was observed for the unseen fearful facial expression [$Z(1,13) = 2.13$; $p < .03$], which completely disappeared after testosterone administration [$Z(1,13) = -.10$; ns]. This testosterone-induced loss of attentional bias for masked facial threat illustrates the reduction in unconscious fear that concurs to our primary hypothesis (see Figure 2A for the effect on basis of attentional bias scores and Figure 2B for how this relates to the raw color naming scores).

Masked Happy Facial Expression. As can be seen from Figure 3, the attentional bias scores for the unseen happy facial expressions were somewhat reduced after testosterone administration (compared with placebo); this change was in no way significant [$Z(1,13) = -.73$; ns]. Furthermore, neither in the placebo nor in the testosterone condition was there significant biased attention for the unseen happy faces when these were compared with the neutral faces [$Z(1,13) = 1.57$; ns] and [$Z(1,13) = .66$; ns].

Cognitive Performance. Figure 4 shows that overall performance (i.e., independent of emotional valence) did not differ between the drug (557 milliseconds) and the placebo conditions

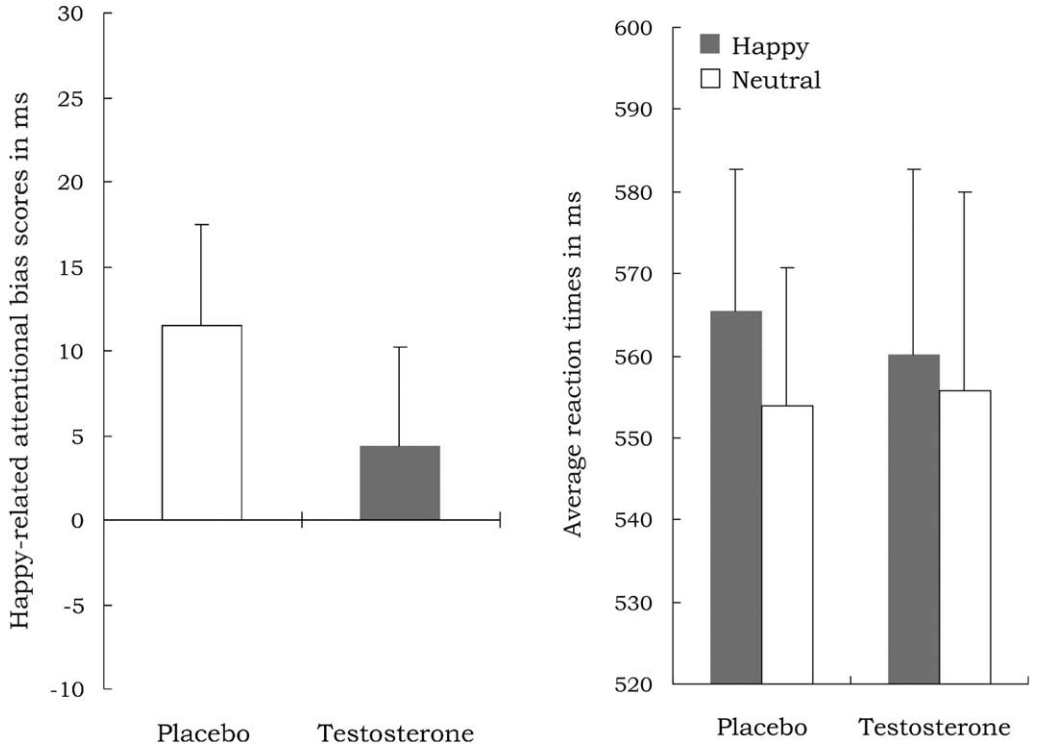

Figure 3. Mean attentional bias scores (i.e., response latencies for the masked happy faces minus response latencies for masked neutral faces) and SEM in milliseconds (ms) for the testosterone and the placebo conditions **(A)** and raw response latencies for neutral and happy faces in milliseconds (ms) in the placebo and the testosterone conditions **(B)**.

(564 milliseconds) [$Z(1,13) = -.35$; ns]. This strongly argues for the present drug-induced changes in attentional bias scores for fearful faces being motivationally driven, because cognitively driven changes in these attentional bias scores involve conscious countercontrol mechanisms that work by effortful suppression and are usually accompanied by an overall increase in color-naming speed (see van Honk and De Haan 2001; Williams et al 1996).

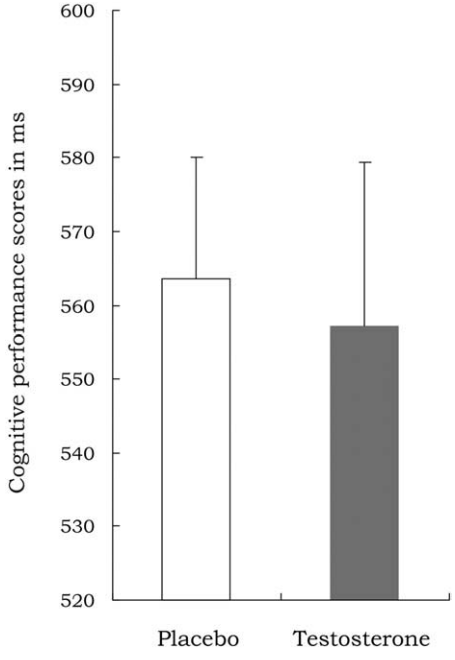

Figure 4. Overall raw response latencies (i.e., neutral, happy, and fearful faces collapsed) in milliseconds (ms) do not differ between the placebo and the testosterone conditions.

Consciously Experienced Anxiety

Behavioral Inhibition. There were no differences in self-reported behavioral inhibition between the placebo and the testosterone conditions [$Z(1,13) = -1.0$; ns].

Tension Anxiety. The POMS subscale for tension-anxiety also did not differ significantly between the placebo and the testosterone conditions [$Z(1,13) = -1.4$; ns].

Cognitive Anxiety. The analysis for the selected items of cognitive anxiety from the STAI showed no differences [$Z(1,13) = -.17$; ns] between the placebo and the testosterone conditions. Figure 5 shows the findings on self-reported anxiety and behavioral inhibition in the testosterone and the placebo conditions.

Discussion

The present study investigated the effects of testosterone on emotional responses to unconsciously processed fearful faces and consciously experienced states of anxiety. Concurring with fMRI and repetitive transcranial magnetic stimulation (rTMS) findings in healthy volunteers that involved emotional responses to unseen facial threat (Whalen et al 1998; van Honk et al 2002a), a vigilant emotional response to the masked fearful facial expression was observed after placebo administration (Figure 2B). Crucially, however, as hypothesized, testosterone significantly decreased the unconscious emotional response to fear (Figure 2A) without influencing the conscious measures of anxiety (Figure 5). The observation of reduced attention to fearful danger

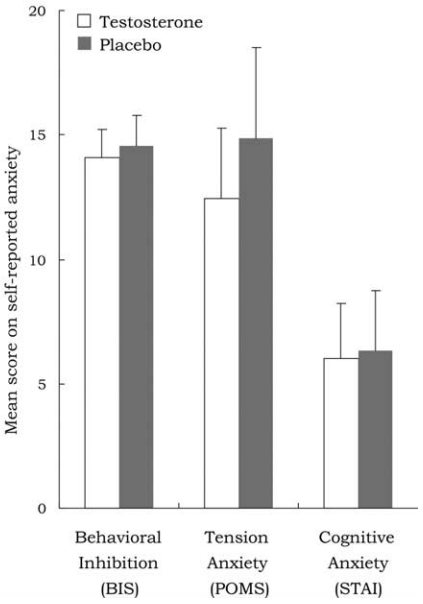

Figure 5. The consciously experienced measures of anxiety after testosterone and placebo administration (all effects nonsignificant).

signals fits the dual-sided motivational properties of testosterone mentioned in the introduction, because it not only suggests reductions in the fear paradigm of punishment sensitivity but also points at a more risky behavioral strategy that leaves room for attending to rewarding aspects of the environment (Arnett 1997; Boissy and Bouissou 1994; van Honk et al 2004; van Honk and Schutter, in press-a). Furthermore, the motivational change corroborates with recent testosterone-induced changes in decision-making strategies on the Iowa Gambling Task, which clearly indicates a shift from punishment toward reward sensitivity (van Honk et al 2004). Given the characteristics of the Iowa Gambling Task (see Bechara et al 1994), a shift from punishment to reward sensitivity leads to more risky disadvantageous decisions. Since our earlier work indicated that the steroid hormone cortisol has motivational properties opposite to testosterone on measurements of punishment and reward (van Honk and De Haan 2001), it was hypothesized that elevated levels of cortisol would be associated with more *advantageous* decisions on the Iowa Gambling Task, which was confirmed (van Honk et al 2003b).

The mutually antagonistic properties of the hormones cortisol and testosterone have been observed not only on the psychobiological but also on the neurobiological level. This starts off with the mutually inhibitory functional connection between the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes (Viau 2002). Cortisol suppresses the activity of the HPG axis at all its levels, diminishes the production of testosterone, and inhibits the action of testosterone at the target tissues (Johnson et al 1992; Tilbrook et al 2000). Testosterone, in its turn, inhibits the stress-induced activation of the HPA axis at the level of the hypothalamus (Viau and Meaney 1996; Viau 2002). Crucially, in one of their core action mechanisms, these steroid hormones bind to amygdala-centered, steroid-responsive neuronal networks (Wood 1996) that regulate and facilitate neuropeptide gene expression. On the behavioral level, animal data show that testosterone elevates vasopressin gene expression at the amygdala, thereby increasing the likelihood for behavioral approach (Schulkin 2003). Cortisol, on the other hand, increases amygdaloid CRH gene expression, which promotes behavioral withdrawal (Thompson et al 2004). Human neuroimaging data are in concordance with the above by showing increased amygdala activation after testosterone administration in healthy volunteers when confronted with the angry facial expression (Hermans et al 2004), indicating an enhanced tendency for aggressive approach (van Honk et al 2001) that probably involves a reward-associated, testosterone-vasopressin endocrine-neuroendocrine cascade (Schulkin 2003).

The predominantly unconscious affective processing properties of cortisol and testosterone (van Honk et al 1998, 2000, 2003a, 2004; Schutter et al, in press) seem to find their conscious manifestation when one applies single sessions of rTMS over the left and the right PFC in healthy volunteers. Repetitive transcranial magnetic stimulation is a technique capable of changing emotional processing by targeting cortical primary sites (Wassermann and Lisanby 2001), and transient changes in affective processing after rTMS over left and right PFC have repeatedly been evidenced in our laboratory for conscious but not unconscious measures of emotion (D'Alfonso et al 2000; Schutter et al 2001; van Honk and De Haan 2001; van Honk et al 2002a).

It should be noted that the presently proposed rather strict division between unconscious and conscious emotional processing levels primarily functions as a heuristic framework (van Honk and De Haan 2001; van Honk and Schutter, in press-a) that adds explanatory value to recommendations for clinical applications that combine cortical/top-down and subcortical/bottom-up approach in the treatment of psychopathology (Mayberg et al 1999; Goldapple et al 2004). Furthermore, the labeling of the presently applied unconscious and conscious measures as fear and anxiety restricts itself to the specific measures taken, since unconscious and conscious processes do not define fear and anxiety in an absolute manner. Also, these findings do not imply that testosterone reduces fear and not anxiety but only that testosterone's effects dissociate between the unconditioned response to the masked fear face and self-reported anxiety. Research in our laboratory that applies effects of testosterone on the fear-potentiated startle (Grillion and Baas 2004) may provide for further insights into which aspects of fear and anxiety are influenced by testosterone.

Interestingly, a recently proposed endocrine dual-systems approach (Viau 2002) may, in particular, be suitable for establishing balanced motivation and emotion in a bottom-up manner. This dual-systems approach works by monitoring, manipulating, and controling the activity of the HPA and the HPG axes under the assumption that manipulation of one of the endocrine axes influences the other (Viau and Meaney 1996; Viau 2002) and that they constitute a unitary motivational-emotional system in quest for emotional homeostasis (van Honk and Schutter, in press-a, in press-b). Furthermore, in the light of the present observation that testosterone-induced reductions in unconscious fear do not need to be related to changes in consciously experienced anxiety, the clinical efficacy of this dual-systems approach may depend on the combined application with treatment approaches that target the PFC as primary site, cognitive behavior therapy (CBT), or rTMS (Goldapple et al 2004; Wassermann and Lisanby 2001).

In conclusion, the present data provide the first direct evidence for fear-reducing effects of testosterone in humans. Given the null findings on consciously reported anxiety, this finding provides further support for the notion that, at the outset, testosterone influences unconscious but not conscious aspects of approach- and withdrawal-related emotion (Tuiten et al 2002; Schutter et al, in press; Schutter and van Honk 2004; van Honk et al 2001, 2004; Hermans et al 2004). Considering the causal

evidence now gathered by endocrine and rTMS research, the thesis that consciously appraised emotion depends predominantly on the cortically implemented cognitive brain circuits, whereas unconscious emotion relies on the densely hormonally innervated subcortical affective pathways of the brain, seems all but indisputable (for reviews see McClelland et al 1989; van Honk and De Haan 2001; van Honk et al 2004; van Honk and Schutter, in press-a).

Destructive top-down biases have been emphasized in extreme forms of anxiety, while dysfunctional fear seems related to attentional biases for threat that have been primed bottom-up in very early states of information processing (Berntson et al 2003). Future research needs to establish whether Viau's (2002) bottom-up dual-systems approach with respect to the HPA and HPG axes might have clinical applicability in the psychopathologies of fear and anxiety, in particular when combined with top-down cortically based approaches such as CBT and rTMS.

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