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INVITED REVIEW

The social neuroendocrinology of human aggression

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Summary Testosterone concentrations fluctuate rapidly in response to competitive and aggressive interactions, suggesting that changes in testosterone rather than baseline differences shape ongoing and/or future competitive and aggressive behaviors. Although recent experiments in animal models provide compelling empirical support for this idea, studies in humans have focused largely on how competitive interactions drive changes in testosterone concentrations and not how these changes influence subsequent behavior. In this paper, we provide a review of the literature on testosterone and human aggression with a main focus on the role of testosterone dynamics in modulating reactive aggression. We also speculate on one putative neural mechanism through which testosterone may bias human aggressive behavior. Finally, we conclude by highlighting important questions that should be addressed in future research.

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1. Introduction

Traditionally, human research on the neuroendocrine basis of aggressive behavior has taken a unidirectional approach focusing on testosterone's role in promoting aggression. However, testosterone concentrations fluctuate rapidly in response to and in anticipation of competitive and aggressive interactions (for reviews see Wingfield et al., 1990; Mazur and Booth, 1998; Archer, 2006; Oliveira, 2009). These observations have led some researchers to speculate that acute fluctuations in testosterone (rather than baseline concentrations) may be more relevant to our understanding of individual differences in aggressive behaviors (McGlothlin et al., 2007). Here, we provide a brief review of the main theoretical models guiding current research on the relationship between competition-induced testosterone dynamics and aggressive behavior, with examples from both animal models and human studies. Next, we highlight research examining the potential functional role of competition-induced fluctuations in testosterone. Finally, based on human neuroimaging-neuroendocrinology findings, we speculate on one potential neural mechanism through which acute fluctuations in testosterone may bias human aggression.

2. Baseline testosterone and human aggression

Aggression has been defined as ''any form of behavior directed toward the goal of harming or injuring another living being who is motivated to avoid such treatment'' (Baron and Richardson, 1994, p. 7). Researchers typically have classified aggressive behavior as either reactive or proactive. Reactive aggression, also referred to as hostile aggression, is a defensive response to perceived or actual provocation and involves retaliation (Dodge and Coie, 1987). Commonly referred to as 'hot-blooded', reactive aggression is characterized by anger and impulsivity and is often accompanied by disinhibition, affective instability, and high levels of bodily arousal. In contrast, proactive aggression, also referred to as instrumental aggression, occurs in the absence of direct provocation and is a goal-oriented behavior aimed at the acquisition of a valued resource (Dodge and Coie, 1987). In contrast to reactive aggression, proactive aggression is a 'cold-blooded' expression of aggression characterized by low physiological arousal. Although the proactive form receives widespread media attention (e.g., serial killings, assassinations, genocide), the reactive form likely accounts for most societal problems associated with aggression (Nelson and Trainor, 2007).

In contrast to the animal literature, the relationship between individual differences in testosterone and human aggression is relatively weak (see Archer et al., 2005 for review). There are several potential reasons for the weaker effects observed in human studies. First, in contrast to animal studies that obtain direct objective assessments of aggression, most human studies are based on self-report measures that are only weakly correlated with actual aggression (Bushman and Wells, 1998). Also problematic is that researchers have typically failed to differentiate between reactive and proactive aggression when assessing the relationship between baseline testosterone concentrations and self-report aggression. Another limitation is that these questionnaires assess general behavioral tendencies across situations (i.e., trait aggression). This issue is especially problematic given that studies in non-human animals indicate that the relationship between testosterone and aggressive behavior is highly context dependent (e.g., Wingfield et al., 1990).

In addition to self-report measures, other studies have compared testosterone concentrations from prisoners convicted of violent versus non-violent crimes. These studies typically report that men and women convicted of violent crimes have higher testosterone concentrations relative to those convicted of non-violent crimes (see Dabbs, 1993 for review). The main limitation to these studies is that they are based on correlations between current testosterone concentrations and previous aggressive behaviors. Implicit in this research strategy is that testosterone concentrations are stable across time and that current testosterone concentrations should reflect testosterone concentrations at the time of the crime. Although baseline testosterone concentrations are relatively stable across days, weeks, and months, testosterone concentrations also fluctuate in response to social interactions, including aggressive behaviors (reviewed in the next section). This finding presents a problem in interpreting data from prison populations. Specifically, it is not possible to determine whether elevated testosterone predispose men and women to commit aggressive crimes, or whether aggressive behavior while in prison produces elevated testosterone concentrations.

Other studies have examined the relationship between baseline testosterone concentrations and aggressive behavior as measured in the laboratory. For instance, several studies have utilized laboratory paradigms such as the Taylor Aggression Paradigm, Ultimatum Game, and the Point Subtraction Aggression Paradigm. The Taylor Aggression Paradigm (TAP) is a laboratory task in which participants compete against a fictitious opponent on a reaction time task. Before each trial, participants are required to set a shock (or noise blast) intensity, which will be administered to their fictitious opponent if he/she loses the trial. The number of trials that are won or lost can be manipulated by the researcher. Aggressive behavior in this task is defined as the average shock (or noise blast) intensity that participants deliver to their opponent on win trials (Giancola and Parrott, 2008). Berman et al. (1993) reported that individual differences in baseline testosterone concentrations were positively correlated with aggression in men tested on the TAP. Other research has used behavior during the Ultimatum Game (UG) as a proxy for reactive aggression. The UG is a behavioral economics task whereby a 'proposer' is given a sum of money (e.g., $10), and has the opportunity to offer as much, or as little money to a 'receiver.' Once the offer is made, the 'receiver' has the choice to either accept or reject the offer. If the offer is accepted, both participants receive their split of the money. If the 'receiver' rejects the offer, both participants leave with no money. Standard economic theory predicts that 'receivers' should accept any offer greater than zero — after all, some money is better than no money. However, years of behavioral economics research indicates that proposals that are below 20% of the sum (e.g., $2) are generally rejected (Camerer and Thaler, 1995). Rejection behavior on the UG can be considered a form of aggressive

behavior as it is committed with the intent to cause harm (i.e., financial) to another individual, who, in turn, is motivated to avoid such treatment. Two studies have reported that individuals with relatively higher baseline testosterone concentrations are more likely to reject unfair offers (Burnham, 2007; Mehta and Beer, 2010). Other work indicates that testosterone administration is associated with increased rejections of unfair offers in men (Zak et al., 2009), but not women (Eisenegger et al., 2009).

The Point Subtraction Aggression Paradigm (PSAP) has also been used to assess relationships between baseline testosterone concentrations and aggressive behavior. During the PSAP, participants are paired with a fictitious opponent (actually a computer program), with the goal to earn as many points as possible, which are later exchanged for money. During the task, participants have points taken from them by their fictitious opponent. In addition to earning points by pressing Button 1, participants are able to take away points from their opponent by pressing Button 2. However, participants are told that they do not keep stolen points. Thus, stealing money from the fictitious competitor is considered aggressive because, like the TAP and UG, this represents an intent to cause harm (Baron and Richardson, 1994). Given that participants are provoked during the task (i.e., points are stolen from them), aggression on the PSAP is considered reactive. Also, participants can select a third option (Button 3), which they are told will protect their points for a variable amount of time. Several studies have demonstrated that the PSAP is a valid laboratory measure of aggressive behavior. For example, male and female violent offenders select the aggressive response option (but not the reward or protection options) more frequently than nonviolent offenders. Also, self-report measures of aggression are moderately correlated with aggressive behavior on the PSAP. In addition, acutely reducing serotonin, whose concentrations are typically inversely correlated with aggressive behavior, is associated with increased aggressive but not reward or protection responses on the PSAP (see Cherek et al., 2006 for review). In a randomized, placebo-controlled, cross over study, Pope et al. (2000) reported that 6 weeks of testosterone administration, which effectively increased baseline testosterone concentrations, produced an increase in aggressive responses in healthy men tested on the PSAP. Although this experiment is limited by the use of supraphysiological doses of testosterone, the results suggest that behavioral measures of aggression may be more sensitive than self-report measures to detect testosterone—aggression relationships in humans.

Aside from methodological limitations, another plausible explanation for the weaker effects observed in humans is that aggression might be much less under the control of testosterone as it might be the case for other species. For instance, while the relative size of brain regions (such as the neocortex) concerned with higher-order cognitive capacities increase across phylogenies, those brain regions involved in regulating the hormonal control of primary motivated behaviors (e.g., sex, parental behavior, aggression) have decreased in relative size (e.g., hypothalamus, septum; Curley and Keverne, 2005). Thus, perhaps the link between testosterone and human aggression is less robust because human behavior is relatively liberated from the constraints of the neuroendocrine system (Curley and Keverne, 2005). These limitations notwithstanding, it is increasingly apparent that testosterone concentrations are not static, but rather, fluctuate rapidly during competitive interactions. These findings suggest that testosterone dynamics may play an important role in modulating ongoing and/or future aggressive behavior. In the next section, we present the 'Challenge Hypothesis' and 'Biosocial Model of Status', two of the most influential theoretical models concerning the context dependent relationship between testosterone and aggressive behavior.

3. Challenge Hypothesis

The 'Challenge Hypothesis' was originally developed to explain intra- and inter-species variation of testosterone secretion in birds. Wingfield et al. (1990) noted that testosterone concentrations fluctuate around three levels during the season: Level A, constitutive baseline; Level B, breeding baseline; and Level C, physiological maximum. In monogamous males that provide paternal care, testosterone concentrations remain low at Level A during the non-breeding season. Concentrations increase to Level B at the start of the breeding season as a means to initiate spermatogenesis, expression of secondary sex characteristics and the full display of male reproductive behavior. Lastly, concentrations may further increase to Level C in response to male-to-male competitive interactions as a means to facilitate aggressive behavior. When inter-male competition decreases, testosterone concentrations also decrease to Level A promoting paternal care. Thus, in male birds that provide paternal care, there is a trade-off between mating and paternal efforts, which appears to be mediated by testosterone concentrations (Wingfield et al., 1990). It has been proposed that the costs associated with maintaining elevated testosterone concentrations throughout the season (e.g., decreased paternal care, increased risk for physical injury/death, depressed immune function, increased energetic demands) may have led to a highly flexible endocrine system capable of modulating testosterone concentrations in response to changes in the social environment (Wingfield et al., 2001). Although the 'Challenge Hypothesis' was originally proposed to account for hormone—behavior relationships in birds, its main hypotheses have received support in a wide range of taxa including fish, non-human primates, humans, and insects (see Archer, 2006; Oliveira, 2009 for reviews).

4. Biosocial model of status

The 'Biosocial Model of Status' (Mazur, 1985) is a conceptually similar theoretical model to the 'Challenge Hypothesis'. One important difference between the 'Challenge Hypothesis' and the 'Biosocial Model of Status' is that the latter makes the specific prediction that testosterone concentrations during competition will vary as a function of the outcome of the competitive interaction: winners will experience an increase in testosterone, whereas losers will experience a decrease. Mazur (1985) hypothesized that winners of competitive interactions may face additional challenges for status and that the increase in testosterone serves to promote competitive and aggressive behaviors aimed at defending one's status. In contrast, the decrease in testosterone in

response to defeat serves to promote submissive behaviors aimed at avoiding further loss of status and/or physical injury. Although there is support for the effect of competition outcome on testosterone release (see Archer, 2006 for meta-analysis), few studies have examined Mazur's (1985) critical hypothesis that competition-induced changes in testosterone serves to modulate future social behavior.

A limitation to both theoretical models is that they do not make specific predictions concerning individual differences in testosterone responses to competitive interactions. In other words, neither model predicts how variability in testosterone responses to competitive interactions maps onto individual differences in aggressive behavior. Recently, a study in male dark-eyed juncos found that individual differences in testosterone responses to competitive interactions were positively correlated with variation in aggressive behavior (McGlothlin et al., 2007). The same research group found that variation in testosterone responses to a gonadotropin releasing hormone challenge (which is correlated with natural fluctuations in testosterone during social challenges) predicted enhanced survival and reproductive fitness (McGlothlin et al., 2010). In human work, not all winners and losers demonstrate the typical pattern of testosterone response to competition (i.e., some winners decrease in testosterone and some losers increase). In this case, it is perhaps not the average testosterone response to victory or defeat that is important, but instead individual variability in testosterone response to competition that may be most relevant to the prediction of behavioral outcomes.

5. Competition-induced testosterone dynamics and aggressive behavior

A key prediction of both models is that competition-induced fluctuations in testosterone are adaptive, possibly enabling organisms to rapidly adjust current and/or future social behavior according to changes in the environment (Mazur, 1985; Wingfield et al., 1990; Oliveira, 2009). There are only a handful of published investigations in humans. In one experiment, Mehta and Josephs (2006) had men participate against each other in a rigged laboratory competition in which half were randomly assigned to a 'loss' condition and half to a 'win' condition. After the competition, participants were asked whether they wanted to compete again against the same opponent on the same task, or whether they would prefer to fill out a questionnaire on food, music and entertainment preferences (i.e., a measure of willingness to compete). Although the authors found no differences in mean testosterone responses between winners and losers, they reported that among men assigned to the 'loss' condition, a rise in testosterone predicted willingness to choose the competitive option, whereas a decrease in testosterone predicted willingness to choose the non-competitive option. Thus, the authors found evidence that competition outcome moderated the effect of testosterone dynamics on subsequent willingness to compete (Mehta and Josephs, 2006).

In another experiment, Klinesmith et al. (2006) randomly assigned men to one of two experimental conditions: interact with a toy gun or with a board game. The authors hypothesized that interacting with a toy gun would represent a 'challenge' and that in accordance with research on the effects of social challenge this would produce an increase in testosterone concentrations (e.g., Wingfield et al., 1990; Archer, 2006). After providing their second saliva sample (the first was provided before the interaction), participants were given a cup of water and were instructed to add as much, or little hot sauce to the cup, which would later be consumed by another participant. The amount of hot sauce placed in the cup served as the primary measure of aggression. As predicted, men who interacted with the toy gun demonstrated an increase in testosterone and were more aggressive (i.e., these men put more hot sauce in the cup of water). Critically, the relationship between interacting with the toy gun and aggressive behavior was mediated by testosterone responses to the task. In other words, the relationship between interacting with a toy gun and aggressive behavior was no longer significant after controlling for variation in testosterone reactivity. This finding suggests that short-term fluctuations in testosterone are associated with eliciting aggressive behavior in the laboratory.

In our own research, we have used the PSAP to assess relationships between testosterone dynamics and aggressive behavior. In our first study, saliva samples were collected from men before and after the PSAP. After the PSAP, participants were asked whether they want to compete with the same person on a puzzle-solving task or help the investigator validate a computer program assessing puzzle-solving abilities (choices were counter-balanced across participants). Although baseline testosterone concentrations were unrelated to reactive aggression, we found that changes in testosterone during the PSAP were positively correlated with reactive aggression (Carré and McCormick, 2008). Moreover, we found that an increase in testosterone during the PSAP predicted subsequent willingness to choose the competitive versus non-competitive option (Carré and McCormick, 2008). Thus, similar to Mehta and Josephs (2006), our findings indicated that changes in testosterone within the context of a competitive interaction (i.e., during the PSAP) predicted subsequent behavior. In a second experiment, we found that competition outcome influenced the relationship between testosterone dynamics and reactive aggression (Carré et al., 2009). In this experiment, men and women competed in same-sex dyads on a 'rigged' competition wherein half were randomly assigned to a 'win' and half to a 'loss' condition. For men, changes in testosterone in response to a competitive loss were positively correlated with subsequent reactive aggression as assessed using the PSAP. Changes in testosterone in response to a competitive victory, however, were positively correlated with subsequent reactive aggression only among men with high trait dominance scores (Carré et al., 2009). In a more recent experiment, Geniole et al. (2010) reported that changes in testosterone in response to social inclusion (but not social exclusion) were positively correlated with subsequent reactive aggression among men tested on the PSAP. Finally, another recent study indicated that changes in testosterone concentrations during the Ultimatum Game were associated with increased rejections of unfair offers, but only among individuals who also demonstrated an increase in cortisol concentrations (Mehta et al., 2010).

In all of our experiments using the PSAP, men incurred a cost to extrinsic reward (i.e., earning money) when they punished others for slighting them during the task. This

Table 1 Relationship between acute fluctuations in testosterone and human social behavior.

Study	Sample	Outcome measures	Results
Mehta and Josephs (2006)	57 ♂	Competitive behavior	Rise in T predicted[a] willingness to compete[b]
Klinesmith et al. (2006)	30 ♂	Aggressive behavior	Rise in T predicted[a] enhanced aggression
Carré and McCormick (2008)	38 ♂	Competitive and aggressive behavior	Rise in T positively correlated[c] with aggression and predicted[a] willingness to compete
Carré et al. (2009)	27 ♂ 63 ♀	Aggressive behavior	Rise in T predicted[a] enhanced aggression in ♂[b]
Carré et al. (2010)	37 ♂	Aggressive behavior	Rise in T positively correlated[c] with aggression
Geniole et al. (2010)	63 ♂	Aggressive behavior	Rise in T predicted[a] enhanced aggression[d]
Mehta et al. (2010)	54 ♂ 61 ♀	Aggressive behavior	Rise in T positively correlated[b] with rejections of unfair offers[e]

[a] Predicted is used here to indicate that changes in testosterone occurred *prior* to the measurement of the main dependent variable.
[b] The effect was only observed among men who lost a previous competitive interaction.
[c] Correlated is used here to indicate that the direction of causality between change in testosterone and behavior is unknown.
[d] This effect was found among men who were socially included, but not excluded in a previous social interaction.
[e] This effect was only observed among participants who also showed a rise in cortisol concentrations (i.e., $\Delta T - x - \Delta C$ interaction).

finding suggests that there must be some intrinsic reward value to engaging in otherwise costly aggressive behavior. To evaluate this possibility, we assigned men to one of four experimental conditions of the PSAP in which they were provoked (points were stolen from them or not) and/or received reward for aggression (received points for aggression or not). Men who were provoked but did not receive reward for aggression (i.e., purely reactive aggression) enjoyed the task the most, demonstrated an increase in salivary testosterone and were more likely to choose a competitive versus non-competitive task than men in the other experimental conditions (Carré et al., 2010). Moreover, individual differences in reactive aggression among these men were positively correlated with the extent to which they enjoyed the task and with testosterone fluctuations during the task (Carré et al., 2010). Importantly, these effects were not observed among men who received reward for aggression and were not provoked (i.e., proactive aggression), suggesting that acute fluctuations in testosterone are specifically related to the reactive form of aggression. In addition to highlighting the importance of considering subtypes of aggression (e.g., reactive versus proactive), these results indicate that costly aggressive behavior is intrinsically rewarding and that testosterone dynamics during the PSAP may serve to strengthen the reward value of such behavior. Indeed, animal work indicates that testosterone has reward-

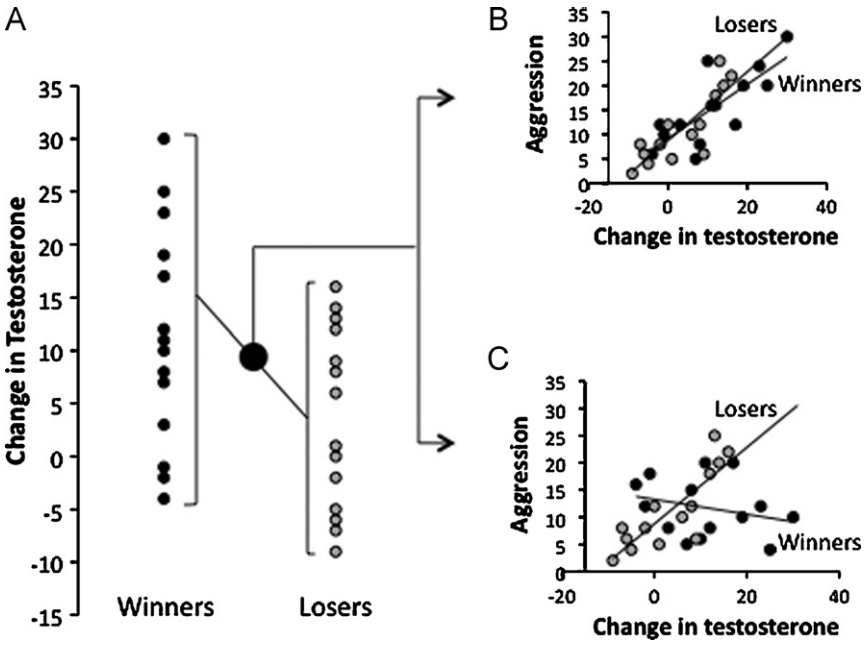

Figure 1 Hypothetical data of competition-induced testosterone fluctuations and aggressive behavior. (A) After competitive interactions, winners typically have elevated testosterone levels relative to losers. However, there is substantial individual variation in testosterone response patterns among winners and losers. (B) Variation in testosterone responses to competition (winners and losers) may predict subsequent aggressive behavior. (C) The association between competition-induced testosterone responses and subsequent aggressive behavior may depend on social context (e.g., won or lost previous competitive interaction). See Mehta and Josephs (2006) and Carré et al. (2009) for examples of the context dependent association between testosterone dynamics and human behavior.

ing properties through its effects on the mesolimbic dopamine system (see Wood, 2008 for review). A recent human neuroimaging study is consistent with this finding indicating that testosterone administration increased neural activity in mesolimbic processing circuits during reward anticipation (Hermans et al., 2010). The corpus of data reviewed above is consistent with the idea that acute fluctuations in testosterone within the context of human competition may have important effects on current and/or future social behavior (see Table 1 for a summary of these findings). The findings reviewed in this section indicate that although victory and defeat appear to produce divergent testosterone responses (see Archer, 2006 for meta-analysis), there is substantial individual variation in testosterone reactivity among winners and losers (see Fig. 1a). We argue that it is this individual variability that is most relevant to the prediction of ongoing and/or future social behavior (see Fig. 1b). Also, as demonstrated by recent studies (e.g., Mehta and Josephs, 2006; Carré et al., 2009), competition outcome moderates the association between individual differences in testosterone responses to competition and future social behavior (see Fig. 1c). Thus, future research that examines how variation in testosterone reactivity to competitive interactions maps onto social behavior should consider the role of competition outcome in moderating hormone—behavior relationships.

6. Animal models and the link between testosterone dynamics and aggression

Animal models are particularly useful for testing causal mechanisms shaping complex social behavior. In a recent experiment involving male California mice, Gleason et al. (2009) found that mice administered testosterone (without previous winning experience) were more aggressive, but not more likely to win future competitive interactions. In contrast, mice administered testosterone after winning a competitive interaction were more aggressive and more likely to win subsequent interactions. Another experiment by the same group found that castrated male California mice that received testosterone after a successful aggressive interaction were significantly more aggressive in subsequent aggressive interactions compared to mice that received a saline injection (Trainor et al., 2004). Similarly, Oliveira et al. (2009) examined the role of testosterone in mediating the 'winner' and 'loser' effects in male Mozambiquan tilapia. In control fish that did not receive any pharmacological challenge, winners of a first aggressive interaction were more likely to win a subsequent aggressive interaction (88% won second fight), whereas losers were more likely to lose subsequent interactions (87% lost second fight). Winners treated with an anti-androgen drug, which prevented the normal increase in testosterone in response to aggressive interactions, were less likely to win a subsequent aggressive interaction (relative to control males). In contrast, losers treated with an androgen (11-ketotestosterone) were not more likely to win a subsequent aggressive interaction. These findings indicate that the 'winner effect' (but not the 'loser effect') depends critically on acute fluctuations in testosterone. Going beyond the role of circulating testosterone concentrations, Fuxjager et al. (2010) reported that the 'winner effect' (i.e., the idea that winning an aggressive interaction increases one's probability of winning a subsequent interaction) was due to an up-regulation of androgen receptors in several key brain regions involved in reward and motivation (e.g., nucleus accumbens and ventral tegmental area) as well as social aggression (bed nucleus of the stria terminalis). Collectively, these experiments provide compelling support for the role of competition-induced testosterone dynamics in mediating ongoing and/or future social behavior. The next important step is to identify the neural mechanisms underlying the effect of testosterone dynamics on aggressive behavior.

7. Neural mechanisms of reactive aggression

Extensive work in animal models indicates that several interconnected cortical and subcortical structures within the so-called social behavior network (Newman, 1999) are involved in the modulation of reactive aggression (see Nelson and Trainor, 2007 for review). One specific model that has received support from lesion and electrical/chemical stimulation experiments (mainly in rodents and cats) indicates that a neural circuit comprising the medial amygdala, medial hypothalamus and periaqueductal grey (PAG) positively modulates reactive aggression (see Siegel et al., 2007 for review). Briefly, the medial amygdala provides excitatory input to glutamatergic neurons in the medial hypothalamus, which exert excitatory drive on PAG neurons, which ultimately mediate reactive aggressive responses (for review see Siegel et al., 2007). Aggression research in human studies has focused mainly on the role of the orbitofrontal cortex (OFC). Specifically, many studies have reported that patients with localized lesions to the OFC engaged in heightened reactive aggression (see Siever, 2008 for review). Given the extensive projections from the OFC to the hypothalamus and amygdala, it has been proposed that the propensity to engage in reactive aggression may emerge from impaired regulatory control of the OFC over these subcortical structures (see Nelson and Trainor, 2007; Davidson et al., 2000 for reviews).

One research approach aimed at elucidating the neurobiological mechanisms of human aggression examines behavioral and neural responses to angry facial expressions. Angry facial expressions represent honest signals of threat and, depending on the dominance relationship between sender and receiver, these threat stimuli may elicit fight or flight behavior from the receiver. Specifically, dominant individuals may perceive an angry facial expression as a challenge to their status, whereas submissive individuals may perceive the same angry facial expression as an enforcement of the prevailing relationship, thus promoting approach and avoidance behaviors, respectively (van Honk and Schutter, 2007). Behavioral and neuroimaging studies reported that individuals prone to anger and reactive aggression (e.g., intermittent explosive disorder, borderline personality disorder) displayed attentional biases, enhanced amygdala reactivity, and decreased OFC-amygdala coupling during processing of angry facial expressions, suggesting that such processes may represent a neurobiological marker for one's propensity to engage in reactive aggression (see Siever, 2008 for review). Indeed, studies in non-clinical samples reported that even normal variation in constructs linked to reactive aggression (e.g.,

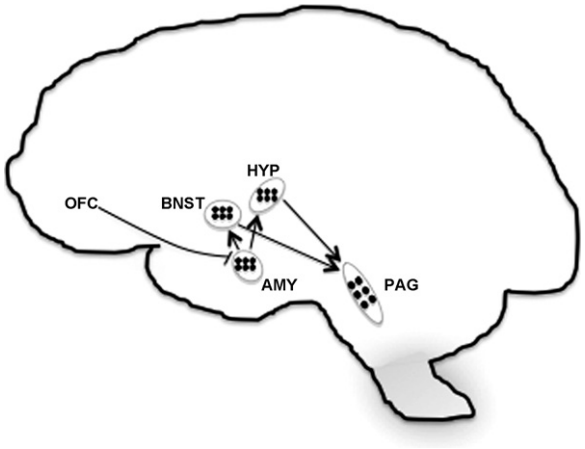

Figure 2 Threat signals are processed in the amygdala, which send projections to the bed nucleus of the stria terminalis (BNST) and hypothalamus (HYP), which activate the periaqueductal grey (PAG), ultimately mediating reactive aggression. In rodents and non-human primates, androgen and estrogen receptors (black dots) are found in each of these limbic structures. The orbitofrontal cortex (OFC) inhibits aggression by reducing responsiveness in the amygdala. This figure is re-drawn based on Nelson and Trainor (2007).

approach motivation, trait anger, trait anxiety) mapped onto variability in amygdala reactivity to angry facial expressions. For instance, Beaver et al. (2008) reported that individual differences in approach motivation, a measure of one's relative sensitivity to rewards and a construct linked to reactive aggression (Harmon-Jones, 2003), were positively correlated with amygdala reactivity to angry facial expressions. Also, given that trait anger and trait anxiety are positively correlated with each other (van Honk et al., 2001a) as well as with reactive aggression (Bettencourt et al., 2006; Marsee et al., 2008), we hypothesized that individuals high on both anxiety and anger would demonstrate amygdala hyper-reactivity to angry facial expressions. Consistent with this hypothesis, we found that individual differences in trait anger were positively correlated with amygdala reactivity to angry facial expressions, but only among men with relatively elevated trait anxiety scores (Carré et al., 2011). Other research has found that individual differences in approach motivation were associated with decreased ventral ACC-amygdala coupling during processing of angry facial expressions (Passamonti et al., 2008). Given the important role of highly interconnected prefrontal regions (e.g., ventral ACC, OFC) in mediating top-down regulation of amygdala driven emotional reactivity (see Davidson et al., 2000 for review), such decreased functional coupling may, in part, explain the positive link observed between approach motivation and aggressive behavior (Harmon-Jones, 2003). Collectively, clinical and pre-clinical data converge on a model in which relatively increased amygdala reactivity and/or decreased coupling of prefrontal regions (ventral ACC, OFC) with the amygdala during processing of threat-related stimuli may bias one's propensity to engage in reactive aggression.

Importantly, androgen and estrogen receptors are widely distributed in the neural circuitry underlying reactive aggression (see Newman, 1999 for review), suggesting that testosterone and/or its metabolites may directly modulate this circuitry by interacting with intra-cellular androgen or estrogen receptors, which affect gene transcription, protein expression and ultimately cell function. In addition to this slow genomic mode of action (i.e., it takes several minutes to hours for testosterone to influence gene transcription and subsequent protein formation), testosterone may also influence physiological processes within seconds through non-genomic mechanisms such as activation of G-protein coupled membrane-bound androgen/estrogen receptors and/or direct modulation of voltage- and ligand-gated ion channels

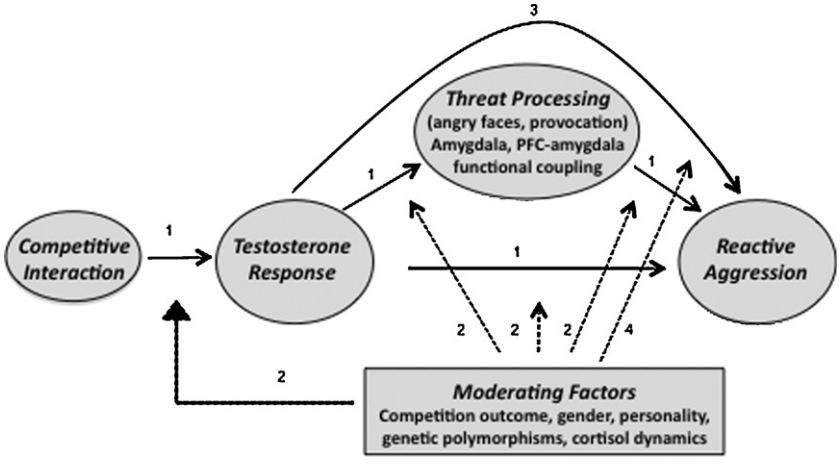

Figure 3 Relationship between testosterone dynamics and human reactive aggression. This model proposes that the effect of competition-induced testosterone dynamics on subsequent reactive aggression are mediated by heightened amygdala reactivity to social threat/provocation. A rise in testosterone in response to a competitive interaction would influence processing of threat stimuli (e.g., angry faces and/or provocation), as mediated through the amygdala, biasing one's propensity to engage in reactive aggression. This model also proposes that several factors may moderate relationships between testosterone dynamics, amygdala reactivity, and reactive aggression. Path labeled 1, direct effect; 2, moderation of direct effects; 3, indirect effect from testosterone dynamics to brain responses to behavior; and 4, moderation of this indirect effect.

(see Michels and Hoppe, 2008 for review). Given the high concentration of androgen and estrogen receptors in the amygdala and related structures within the social behavior network (Fig. 2), it is reasonable to predict that enhanced amygdala and behavioral reactivity to angry facial expressions may vary as a function of testosterone concentrations. Indeed, behavioral studies have reported that endogenous testosterone concentrations were positively correlated with attentional biases toward angry facial expressions (van Honk et al., 1999; Wirth and Schultheiss, 2007) and that exogenous testosterone administration increased cardiac responses to angry facial expressions (van Honk et al., 2001b). Moreover, functional neuroimaging studies reported that individual differences in baseline testosterone concentrations were positively correlated with amygdala reactivity to facial expressions of anger and fear (Derntl et al., 2009; Manuck et al., 2010) and negatively correlated with OFC responses to perceived provocation (Mehta and Beer, 2010). Moreover, exogenous administration of testosterone increased amygdala reactivity and decreased amygdala-OFC coupling during processing of angry facial expressions (Hermans et al., 2008; van Wingen et al., 2009, 2010). Thus, to the extent that enhanced behavioral and neural responses to social threat bias reactive aggression, the findings reviewed in this section converge on a model in which testosterone may modulate the expression of reactive aggression by enhancing amygdala reactivity and/or decreasing ventral ACC/OFC-amygdala coupling during processing of social threat (e.g., angry facial expression, social provocation; see Fig. 3).

8. Future directions

As described in this review, most research examining the relationship between testosterone dynamics and human aggression has been correlational. This is in stark contrast to the animal literature that is based on direct manipulation of testosterone concentrations to test for causality (e.g., Oliveira et al., 2009; Trainor et al., 2004; Gleason et al., 2009). We believe that human social neuroendocrinology research would benefit greatly by conducting similar testosterone manipulation studies to investigate the causal role of testosterone in mediating social behavior. van Honk et al. have used exogenous testosterone administration in their examination of testosterone's role in mediating behavioral and physiological processes relevant to human competition. Specifically, they have reported that testosterone administration increased amygdala reactivity and cardiac responses to angry facial expressions (Hermans et al., 2008; van Honk et al., 2001b). Although this body of work has made a major contribution to our understanding of the causal role of testosterone in shaping physiological and behavioral processes, it is limited by an exclusive focus on women. Thus, testosterone's role in mediating such processes in men remains unknown. Future work using this experimental design in men and women is needed to test the extent to which the effects of testosterone on behavior differ as a function of sex.

Future studies in human neuroendocrinology may also benefit by considering the role of functional genetic polymorphisms that moderate the effects of testosterone on both genomic and non-genomic signaling pathways. For example, recent research has established an important link between a functional polymorphism in the promoter region of the human androgen receptor (AR) gene and aggressive behavior (Rajender et al., 2008). The number of CAG repeats in this promoter polymorphism is associated with the transactivation potential of the AR *in vitro* (Chamberlain et al., 1994). Generally speaking, a greater number of CAG repeats confers less efficient AR transactivation. Thus, to the extent that testosterone acts via the AR to modulate aggressive behavior, one may predict that the effect would be more pronounced among men with fewer CAG repeats. Consistent with this prediction, variability in testosterone concentrations was positively correlated with aggressive behavior, but only among men with fewer CAG repeats (Vermeersch et al., 2010). A recent imaging genetics study has reported a positive correlation between baseline testosterone concentrations and amygdala reactivity to threatening faces, including angry facial expressions, but only among men with relatively fewer CAG repeats (Manuck et al., 2010). Roney et al. (2010) reported that variation in the number of AR CAG repeats was associated with men's testosterone reactivity to social interactions with potential mates. Men with fewer AR CAG repeats (i.e., more efficient AR) demonstrated a more robust surge in testosterone while interacting with an attractive woman relative to men with more AR CAG repeats.

Another important issue to consider is the role of individual variability in personality in modulating the effects of testosterone on aggressive behavior. Some studies indicate that personality may modulate testosterone responses to victory and/or defeat. For example, Schultheiss et al. (2005) reported that variation in the implicit power motive (a measure of one's need for social power and dominance) was associated with testosterone responses to competition. Specifically, power motivation was positively correlated with changes in testosterone for winners, and negatively correlated with changes in testosterone for losers. The above findings indicate that psychological and genetic factors may play an important role in modulating testosterone responses to social interactions and should be considered in studies attempting to identify neuroendocrine factors contributing to variability in human social behavior (see Fig. 3).

Further elucidating the neural mechanisms through which testosterone influences human aggression will be another major challenge for human social neuroendocrinology research. As reviewed in this paper, there is indirect support for the idea that heightened amygdala reactivity to angry facial expressions (i.e., social threat) may underlie the relationship between testosterone and human aggression. However, future experiments that directly assess aggressive behavior during neuroimaging will be required to make more firm conclusions concerning the neural mechanisms underlying the testosterone—aggression relationship. This approach was recently adopted in an experiment in which the association between testosterone concentrations and rejections of unfair offers in the ultimatum game (a putative measure of reactive aggression) was mediated by decreased bilateral OFC reactivity to unfair offers (Mehta and Beer, 2010). Although it is unclear what the role of the amygdala and/or ventral ACC/OFC-amygdala functional coupling may have played in mediating rejection of unfair offers, this experiment is the first to directly assess putative neural

mechanisms underlying the relationship between testosterone and human aggression.

9. Summary

In summary, the goal of this review paper was to highlight current research on the relationship between testosterone and aggressive behavior. Both animal and human studies provide compelling support for the idea that testosterone concentrations fluctuate rapidly in response to competitive/aggressive interactions. Importantly, experimental work in animal models and correlational studies in humans suggest that competition-induced testosterone dynamics may function to modulate ongoing and/or future aggressive behavior. Clearly, there are many questions that remain to be addressed and we believe that future research into the social neuroendocrinology of behavior will benefit by taking an integrative approach combining research techniques from social and personality psychology, neuroendocrinology, neuroimaging, pharmacology and molecular genetics (see Hariri, 2009 for review of this integrative approach).

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