Hormones and Behavior 122 (2020) 104754

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Review article

Testosterone administration in human social neuroendocrinology: Past, present, and future☆

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ARTICLE INFO

Keywords:
Testosterone
Pharmacological challenge
Human behaviour

ABSTRACT

Over the past 20 years, social neuroendocrinology researchers have developed pharmacological challenge paradigms to assess the extent to which testosterone plays a causal role in human psychological and behavioural processes. The current paper provides a brief summary of this research and offers recommendations for future research examining the neuroendocrine mechanisms underlying human behaviour.

1. Introduction

The role of testosterone in modulating physiological and behavioural processes can be traced back to the classic experiment of Arnold Berthold. In his experiment, Berthold castrated immature male chickens and observed that male-typical secondary sex characteristics and behaviours (e.g., aggression) did not develop. When Berthold transplanted a testis back into the chickens, they developed normally, leading him to conclude that the testes must release a substance into the bloodstream, which plays an essential role in modulating behaviour and physical development (Berthold, 1849). The discovery of that substance did not occur until later in the 20th century when David et al. (1935) extracted and isolated 10 mg of testosterone from over 200 pounds of bull testes. At around the same time, two other research groups simultaneously published the chemical synthesis of testosterone (Butenandt and Hanisch, 1935; Ruzicka and Wettstein, 1935), ultimately paving the way for modern-day clinical pharmacology and endocrinology (Nieschlag and Nieschlag, 2014). In this mini-review, we provide a summary of single-dose testosterone administration research, concluding with recommendations for future research in this area of work.

With the development of radioimmunoassay and enzyme immunoassay procedures (see Wudy et al., 2018 for review), researchers began to investigate the extent to which individual differences in testosterone concentrations were associated with a wide range of human behavioural and psychological processes (e.g., Persky et al., 1971; Kreuz and Rose, 1972; Monti et al., 1977). For instance, over the past 50 years, researchers have examined the extent to which individual differences in baseline testosterone concentrations map onto human aggression. Results of such work indicate a small correlation ($r = 0.07$) between baseline testosterone concentrations and aggressive behaviour. Notably, testosterone concentrations are not static, but fluctuate across the day, season, and in response to competition- and mating-related cues (see Geniole and Carré, 2018 for review). The Challenge Hypothesis (Wingfield et al., 1990) and other conceptually similar theoretical models (e.g., Biosocial Model of Status, see Mazur, 1985; Fitness Model of Testosterone Dynamics, see Geniole and Carré, 2018) posit that such acute changes in testosterone are functional in that they prepare the organism for competitive or aggressive interactions over resources important for survival and reproduction. Consistent with such predictions, a recent meta-analysis found a positive association ($r = 0.16$) between acute changes in testosterone (e.g., during competition and/or social provocation) and aggressive behaviour in men (see Geniole et al., in press). However, one significant limitation of this research (and other research examining associations between endogenous testosterone concentrations and behavioural outcomes) is that it is correlational, preventing researchers from making causal claims about the role of testosterone in modulating human psychology and behaviour.

Pharmacological challenge research examining the effects of testosterone on sexual function and anger/aggression began to emerge in the 1970s and 1980s (see Albert et al., 1993 for review). Most of this earlier work used chronic dosing of testosterone and was conducted with clinical samples of hypogonadal men. Results provided clear evidence that testosterone replacement therapy restored sexual function, and yielded mixed evidence for the role of testosterone in promoting human aggression (see Albert et al., 1993 for review). Single-dose

☆ This paper is part of the Virtual Special Issue, 50th Anniversary of Hormones and Behavior.

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https://doi.org/10.1016/j.yhbeh.2020.104754
Received 10 January 2020; Received in revised form 7 March 2020; Accepted 31 March 2020
Available online 08 May 2020
0018-506X/

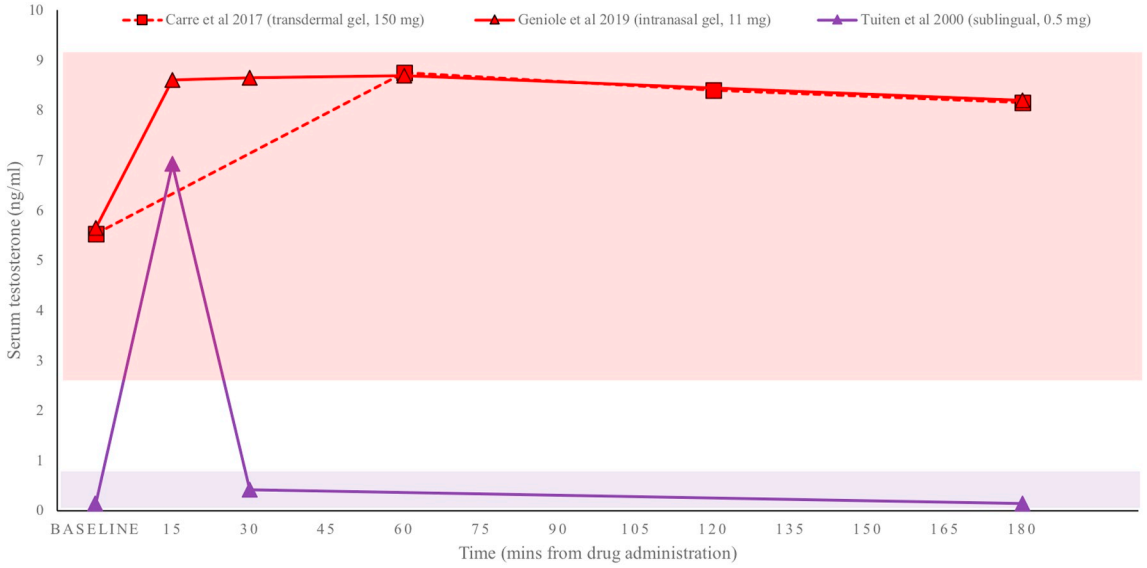

Fig. 1. Serum testosterone concentrations after sublingual, intranasal, and transdermal testosterone administration. Red shading = normal physiological range for men; Purple shading = normal physiological range for women. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
Based on Carré et al. (2017); Geniole et al. (2019a, 2019b); Tuiten et al. (2000)

pharmacological challenge paradigms were first developed and validated by Jack van Honk's group in the Netherlands. It is worth noting that in contrast to earlier work that used chronic dosing, this new paradigm involved the use a single, acute dose of testosterone, which more closely mimicked the time course of changes in testosterone that occur in the context of competitive interactions and/or social provocation. This program of research began with a study investigating the time course of the effects of a single sublingual dose of testosterone (0.5 mg) on women's subjective and physiological arousal. Tuiten et al. (2000) administered sublingual testosterone to a sample of healthy young women (n = 8, within-subject cross-over design) and assessed subjective and physiological (vaginal pulse amplitude) arousal in response to sexually explicit stimuli over 5 h. The authors reported that this sublingual dose produced a rapid, supraphysiological rise in serum testosterone concentrations (see Fig. 1), which returned to baseline within 90 min. Notably, no effects of testosterone were found on subjective or physiological indices of arousal at the time point corresponding to peak testosterone concentrations. Nevertheless, increases in subjective arousal and vaginal pulse amplitude were detected 3 to 4.5 h after peak testosterone concentrations were achieved. This landmark study motivated dozens of other experiments using the same time lag between drug administration and measurement of cognitive, neural, and behavioural processes (see sublingual studies in Table 1).

Research examining the effects of a single dose of testosterone on men's psychological and behavioural processes did not occur until about a decade later when Zak et al. (2009) utilized transdermal gel as a means to acutely elevate testosterone concentrations. The authors found that testosterone decreased men's generosity in an economic decision-making task (Zak et al., 2009). At the time, pharmacokinetic data with hypogonadal men indicated that serum testosterone concentrations peaked approximately 16 h after application of 100 mg of testosterone gel (Swerdloff et al., 2000), and thus, Zak et al. (2009) used a 16-hour time lag between administration of testosterone and measurement of behaviour. However, it is now clear from recent pharmacological challenge research in eugonadal men, using the same dosage of transdermal testosterone gel (100 mg), that testosterone concentrations reach peak levels within just 2 h post-application (Puiu et al., 2019). This evidence suggests that gonadal status (i.e., hypogonadal vs. eugonadal) is an important factor to consider when developing pharmacological challenge protocols.

One challenge in developing pharmacological paradigms in human research is that people vary substantially in 'baseline' testosterone concentrations (for women; 0.15 ng/mL to 0.82 ng/mL, Pesant et al., 2012; for men, 2.64 ng/mL to 9.16 ng/mL; Travison et al., 2017). A standard hormone manipulation experiment might modify hormone concentrations very differently for individuals with naturally low or high endogenous hormone levels (Williams, 2008), and thus, standardizing baseline neuroendocrine function may help to reduce such variability. Research in animal models effectively eliminates such differences in baseline neuroendocrine function through physical castration. For instance, in one experiment, male California mice were physically castrated and then replaced with a standard low dose of testosterone to maintain normal physiological function (Trainor et al., 2004). After an aggressive interaction (i.e., resident-intruder paradigm), mice were administered an acute dose of testosterone (mimicking a natural rise in testosterone that typically occurs after a victory) or placebo (mimicking no change in testosterone) and aggressive behaviour was assessed again 24 h later. Results indicated that mice administered testosterone after a victory were more aggressive in a subsequent interaction relative to mice that were administered placebo, providing the first evidence that a short-term rise in testosterone after an aggressive interaction positively modulates future aggressive behaviour (Trainor et al., 2004). Although this approach is highly effective in reducing variability in baseline neuroendocrine function, and in controlling for natural changes in testosterone that occur during aggressive interactions, it is not a feasible approach for research in humans. However, a gonadotropin releasing hormone (GnRH) antagonist can be used to substantially reduce variability in baseline testosterone concentrations in humans. This pharmacological agent acutely suppresses testosterone concentrations to the hypogonadal range, and at the same time, substantially reduces variability in testosterone concentrations. Using this approach, we have found that a single intramuscular injection of a GnRH antagonist (3 mg Cetrotide Acetate) rapidly suppresses, and substantially reduces variability in testosterone concentrations (see Fig. 2, Goetz et al., 2014). After standardizing testosterone concentrations using the GnRH antagonist, we then examined the extent to which a single dose of transdermal testosterone (100 mg) was sufficient to modulate threat-related neural function assessed using functional magnetic resonance imaging. Results indicated that testosterone rapidly (within 45 min) increased amygdala, hypothalamus, and

Table 1
Summary of single dose testosterone administration studies.

Authors	N	Sex	Drug route	Dose	Primary outcome
Dreher et al. (2016)	40	Male	IM Injection	250 mg	Ultimatum game
Bird et al. (2019)	400	Male	Intranasal	11 mg	Public goods game
Geniole et al. (2019a)	118	Male	Intranasal	11 mg	Ultimatum game
Geniole et al. (2019b)	308	Male	Intranasal	11 mg	Aggression
Van Wingen et al. (2008)	25	Female	Intranasal	0.9 mg	Memory for female and male faces
Van Wingen et al. (2010)	25	Female	Intranasal	0.9 mg	Neural functional connectivity
Van Wingen et al. (2009)	25	Female	Intranasal	0.9 mg	Threat-related amygdala function
Aarts and van Honk (2009)	24	Female	Sublingual	0.5 mg	Motivation
Aleman et al. (2004)	26	Female	Sublingual	0.5 mg	Visuospatial abilities
Boksem et al. (2013)	54	Female	Sublingual	0.5 mg	Trust game
Bos et al. (2010)	24	Female	Sublingual	0.5 mg	Social cognition
Bos et al. (2012)	16	Female	Sublingual	0.5 mg	Neural responses to faces
Bos et al. (2016)	16	Female	Sublingual	0.5 mg	Social cognition
Bos et al. (2013)	12	Female	Sublingual	0.5 mg	Threat-related neural function
Buskens et al. (2016)	82	Female	Sublingual	0.5 mg	Trust game
Chen et al. (2016)	20	Female	Sublingual	0.5 mg	Moral decision making
Eisenegger et al. (2010)	60	Female	Sublingual	0.5 mg	Ultimatum game
Enter et al. (2016)	19	Female	Sublingual	0.5 mg	Gaze avoidance
Enter et al. (2014)	24	Female	Sublingual	0.5 mg	Gaze avoidance
Heany et al. (2018)	30	Female	Sublingual	0.5 mg	Neural responses to threat and escape
Hermans et al. (2006a)	20	Female	Sublingual	0.5 mg	Fear-potentiated startle
Hermans et al. (2006b)	20	Female	Sublingual	0.5 mg	Facial mimicry
Hermans et al. (2007)	20	Female	Sublingual	0.5 mg	Autonomic reactivity
Hermans et al. (2008)	12	Female	Sublingual	0.5 mg	Threat-related neural function
Hermans et al. (2010)	12	Female	Sublingual	0.5 mg	Reward-related neural function
Mehta et al. (2015)	54	Female	Sublingual	0.5 mg	Competitive motivation
Montoya et al. (2013)	20	Female	Sublingual	0.5 mg	Moral decision-making
Postma et al. (2000)	15	Female	Sublingual	0.5 mg	Object location memory
Radke et al. (2015)	54	Female	Sublingual	0.5 mg	Approach and avoidance behaviour
Schutter et al. (2005)	14	Female	Sublingual	0.5 mg	Functional neural connectivity
Terburg et al. (2016)	15	Female	Sublingual	0.5 mg	Gaze avoidance
Terburg et al. (2012)	20	Female	Sublingual	0.5 mg	Gaze avoidance
Tuiten et al. (2000)	8	Female	Sublingual	0.5 mg	Vaginal pulse amplitude
Van Der Westhuizen et al. (2017)	26	Female	Sublingual	0.5 mg	Sense of urgency
Van Der Westhuizen et al. (2019)	49	Female	Sublingual	0.5 mg	Rubber hand illusion
Van Honk and JLG Schutter (2007)	16	Female	Sublingual	0.5 mg	Emotion recognition
Van Honk et al. (2004)	12	Female	Sublingual	0.5 mg	Sensitivity to reward and punishment
Van Honk et al. (2016)	20	Female	Sublingual	0.5 mg	Poker game
Van Honk et al. (2005)	16	Female	Sublingual	0.5 mg	Unconscious fear (Stroop Task)
Van Honk et al. (2001)	16	Female	Sublingual	0.5 mg	Cardiac responses to angry faces
Van Honk et al. (2012)	24	Female	Sublingual	0.5 mg	Public goods game
Van Honk et al. (2011)	16	Female	Sublingual	0.5 mg	Cognitive empathy
Wu et al. (2016)	26	Female	Sublingual	0.5 mg	Risk-taking
Arnocky et al. (2017)	30	Male	Transdermal	150 mg	Moral decision-making
Bird et al. (2016)	117	Male	Transdermal	150 mg	Preferences for facial femininity
Bird et al. (2017)	147	Male	Transdermal	150 mg	Social cognition
Carré et al. (2015)	30	Male	Transdermal	150 mg	Cognitive empathy
Carré et al. (2017)	121	Male	Transdermal	150 mg	Aggressive behaviour
Cueva et al. (2017)	38	Male	Transdermal	100 mg	Ultimatum game
Goetz et al. (2014)	16	Male	Transdermal	100 mg	Threat-related neural function
Hansen et al. (2017)	16	Male	Transdermal	150 mg	Inhibition of return
Henderson et al. (2018)	242	Male	Transdermal	100 mg	Lying behaviour
Knight et al. (2017)	120	Male	Transdermal	150 mg	Cortisol response to stress
Knight et al. (in press)	628	Male	Mixed[a]	Mixed[a]	Cognitive reflection
Kopsida et al. (2016)	68	Mixed	Transdermal	60 mg	Ultimatum game
Liao et al. (2018)	63	Male	Transdermal	150 mg	Decoy effect
Losecaat Vermeer et al. (2020)	173	Male	Transdermal	150 mg	Competitive motivation
Nadler et al. (2017)	140	Male	Transdermal	100 mg	Asset training
Nadler et al. (2019)	643	Male	Mixed[b]	Mixed[b]	Cognitive empathy
Nave et al. (2017)	243	Male	Transdermal	100 mg	Cognitive reflection
Nave et al. (2018)	243	Male	Transdermal	100 mg	Status brand preferences
Olsson et al. (2016)	33	Female	Transdermal	50 mg	Cognitive empathy
Panagiotidis et al. (2017)	90	Male	Transdermal	50 mg	Aggressive behaviour and anger
Wagels et al. (2017a)	103	Male	Transdermal	50 mg	Sequential decision-making
Wagels et al. (2017b)	82	Male	Transdermal	50 mg	Threat distance preference
Wagels et al. (2018)	103	Male	Transdermal	50 mg	Anger response to social provocation
Wagels et al. (2019)	93	Male	Transdermal	50 mg	Threat related neural responses
Welling et al. (2016)	30	Male	Transdermal	150 mg	Self-perceived masculinity
Wibral et al. (2012)	91	Male	Transdermal	50 mg	Lying behaviour
Wu et al. (2017)	64	Male	Transdermal	150 mg	Status

(*continued on next page*)

Table 1 (*continued*)

Authors	N	Sex	Drug route	Dose	Primary outcome
Wu et al. (2018)	64	Male	Transdermal	150 mg	Emotions and counterfactual choice
Wu et al. (2019)	174	Male	Transdermal	150 mg	Social discounting
Wu et al. (2020)	111	Male	Transdermal	150 mg	Intertemporal choice
Zak et al. (2009)	25	Male	Transdermal	100 mg	Economic decision-making

[a] Exp 1 and 3 used transdermal testosterone (150 mg) and Exp 2 used intranasal testosterone (11 mg).
[b] Exp 1 used transdermal testosterone (100 mg) and Exp 2 used intranasal testosterone (11 mg).

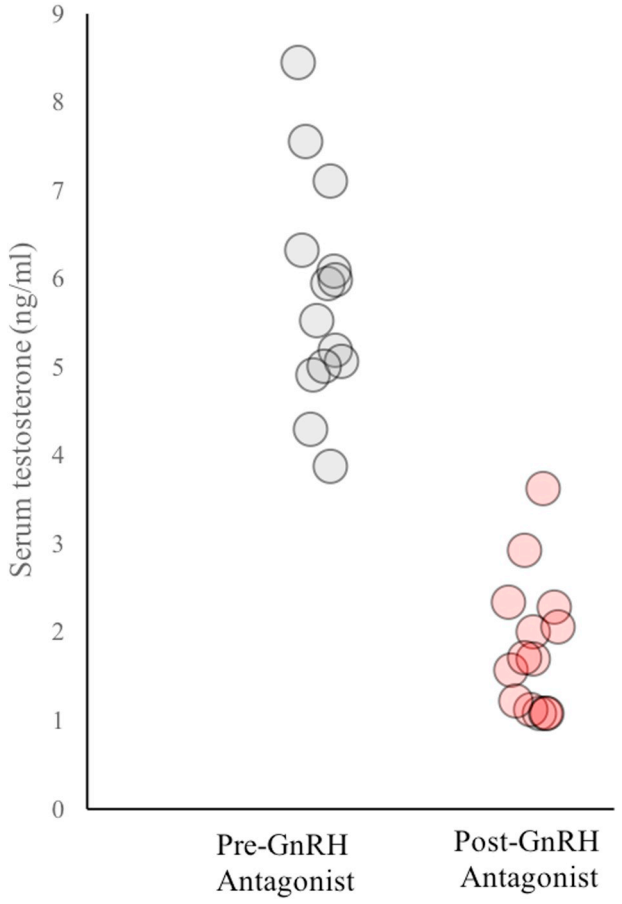

Fig. 2. Serum testosterone concentrations before- and after- receiving an intramuscular injection of a gonadotropin release hormone antagonist. Based on Goetz et al. (2014)

periaqueductal gray reactivity to threat-related facial cues (Goetz et al., 2014). These findings were noteworthy in light of evidence that heightened threat-related neural function may represent a neural marker for one's propensity to engage in reactive aggression (see Coccaro et al., 2011 for review).

Unfortunately, the high cost of the GnRH antagonist (> $400/injection) prohibited its widespread use in relatively large-scale studies examining the effects of testosterone on complex behavioural outcomes. Fortunately, several single-dose paradigms have been developed that acutely increase testosterone levels to the high-normal range at the cost of approximately $8 per research subject. In one paradigm, Eisenegger et al. (2013) examined the effects of a single dose of transdermal testosterone gel (150 mg) on serum testosterone concentrations in young men (n = 10). They reported that testosterone concentrations peaked approximately 3 h after drug application to levels slightly above the normal physiological range (11.45 ng/mL), decreasing over the next 3 h, but remaining slightly above baseline concentrations (Eisenegger et al., 2013). Other work with a larger sample of men (n = 120) found that serum testosterone concentrations reached the high-normal range (8.79 ng/mL) approximately 1 h after transdermal testosterone gel (150 mg) and remained elevated 3 h post-application (Carré et al., 2017). More recently, we have developed a pharmacological challenge protocol using a commercially-available intranasal testosterone gel. In a study of healthy young men (n = 13), we found that 11 mg of intranasal testosterone gel led to a rapid rise (within 15 min) in serum testosterone concentrations (Geniole et al., 2019a, 2019b). The rise in testosterone concentrations occurred much quicker with the intranasal gel compared to the transdermal gel, but otherwise, levels were similar to those observed using transdermal gel (see Fig. 1). The advantage of the intranasal gel is that the rapid rise in testosterone more closely mimics the natural increases in endogenous testosterone that are seen within the context of human social interactions (see Geniole et al., 2017; Roney, 2016), adding an element of ecological validity to the paradigm and enabling researchers to more effectively assess the extent to which acute fluctuations in testosterone play a functional role in preparing the organism for competitive or aggressive interactions over resources important for survival and reproduction.

2. Future directions

2.1. Development of pharmacological challenge paradigms for use in men and women

Neuroimaging work suggests that a single dose of testosterone increases threat-related amygdala and hypothalamic reactivity in women (Hermans et al., 2008) and men (Goetz et al., 2014). On the other hand, other work suggests that testosterone decreases empathic processes in women (van Honk et al., 2011; Hermans et al., 2006a, 2006b; Olsson et al., 2016), but not men (Carré et al., 2015; Nadler et al., 2019). One major limitation of this work is that none of these experiments included both men and women in the same paradigm. Further, data obtained from studies of men and women involved different modes of administration (e.g., sublingual vs. transdermal vs. intranasal), dosages used, and time lags between drug administration and assessment of outcome measures. These methodological differences make direct comparisons of the neuroendocrine mechanisms underlying behavioural processes in men and women challenging. Testosterone administration research in women typically involves the administration of a single sublingual dose that yields a very large (supraphysiological) increase in testosterone concentrations (Tuiten et al., 2000). Results from these paradigms are difficult to interpret because women cannot naturally produce this substantial of a testosterone response. Thus, a critical avenue for future work will be to develop a pharmacological challenge paradigm that increases testosterone concentrations to the high-normal range for women, producing a rise in testosterone that is proportionally similar to that observed in men using the same drug (e.g., 60% above baseline concentrations).

2.2. Time course of the effects of testosterone on psychological and behavioural processes

Single-dose testosterone administration studies have used various

time lags between drug administration and assessment of psychological and behavioural outcomes. The landmark study by Van Honk's group determined that 3 to 4.5 h was the optimal time lag to use between drug administration and assessment of self-reported sexual arousal and vaginal pulse amplitude (Tuiten et al., 2000). Since then, dozens of studies using this sublingual approach, and other studies using transdermal testosterone have utilized similar time-courses. However, we know from other studies in women (e.g., Van Wingen et al., 2009) and men (e.g., Carré et al., 2017; Geniole et al., 2019a, 2019b) that testosterone may have more rapid, and perhaps non-genomic effects (see Foradori et al., 2008) on physiological and behavioural processes. Thus, a significant challenge for single-dose research will be to map out the time-course for the effects of testosterone on psychological and behavioural processes. This type of time-course research has been conducted in other human neuroendocrinology research examining the effects of cortisol on cognitive, neural, and behavioural function. For instance, Henckens et al. (2011) found that a single dose of hydrocortisone (10 mg) leads to improvements in working memory performance if administered 240 min prior to testing, but not if administered 30 min before testing. In other work, preferences for small/immediate rewards versus large/delayed rewards (i.e., inter-temporal choice behaviour) were assessed after participants received either hydrocortisone (10 mg) or placebo. Results indicated that effects of hydrocortisone on inter-temporal choice were time-dependent: participants showed an increased preference for small/immediate rewards vs large/delayed rewards when tested 15 min after hydrocortisone administration, but not when tested 195 min after hydrocortisone administration (Riis-Vestergaard et al., 2018). These findings suggest that steroid hormones may exert rapid- and/or delayed- effects on psychological and behavioural processes.

2.3. Personality-based moderators of the relationship between testosterone and human behaviour

There is now a growing body of correlational and experimental evidence suggesting that testosterone's association with behavioural outcomes depends upon variability in personality traits (see Carré and Archer, 2018 for review). For instance, our work indicates that competition-induced changes in testosterone positively predicts subsequent aggressive behaviour in men scoring high in trait dominance (Carré et al., 2009) and independent self-construal (Welker et al., 2017). These findings were corroborated in pharmacological challenge studies whereby a single dose of testosterone potentiated aggressive behaviour among men scoring high in trait dominance, independent self-construal, and impulsivity (Carré et al., 2017; Geniole et al., 2019a, 2019b). Collectively, these findings suggest that individual differences in certain personality traits (e.g., dominance, impulsivity, independent self-construal) may serve as important risk-factors for testosterone-induced behavioural outcomes and should be considered in future research examining the causal role of testosterone in modulating human social behaviours.

2.4. Replicability of social neuroendocrinology findings

Although single-dose pharmacological challenge paradigms have afforded researchers the ability to make stronger causal claims concerning the role of hormones in modulating human behaviour, challenges related to the replicability of this research remain. In a landmark paper published in *Nature*, Kosfeld et al. (2005) reported that a single dose of intranasal oxytocin increased men's trust behaviour in an economic decision-making task. Despite strong enthusiasm in the academic community and popular press, these findings have generally failed to replicate (see Nave et al., 2015 for a review). Thus, it will be critical to replicate and extend the promising early findings from single-dose testosterone administration studies to determine the extent to which the effects are robust, and whether such effects are similar or different in men and women. Recent single-dose testosterone administration studies suggest that testosterone's effects on behavioural outcomes depend upon personality (Carré et al., 2017; Geniole et al., 2019a, 2019b) and/or social context (Mehta et al., 2015; Bird et al., 2019; Losecaat Vermeer et al., 2020), and thus, replication attempts will require relatively large sample sizes to provide sufficient statistical power to be able to detect complex hormone x personality and/or hormone x social context interactions.

3. Conclusions

Theoretical models have postulated that rapid fluctuations in testosterone during competition and/or mating-related cues may ultimately function to fine-tune the organism's ongoing and/or future fitness-related behaviours (see Wingfield et al., 1990; Mazur, 1985; Geniole and Carré, 2018). Correlational studies and more recent single-dose pharmacological challenge paradigms have provided support for some components of such models. As detailed in this mini-review, future research taking into account sex/gender, time lags, dosages, and personality traits will be required to further build upon and expand theoretical models on the role of testosterone in modulating human behaviour.

Acknowledgements

This work as supported by a Natural Sciences and Engineering Research Council of Canada Discovery Grant to JMC and Canada Graduate Scholarship to BAR.

References

Aarts, H., van Honk, J., 2009. Testosterone and unconscious positive priming increase human motivation separately. NeuroReport 20 (14), 1300–1303.
Albert, D.J., Walsh, M.L., Jonik, R.H., 1993. Aggression in humans: what is its biological foundation? Neurosci. Biobehav. Rev. 17, 405–425.
Aleman, A., Bronk, E., Kessels, R.P.C., Koppeschaar, H.P.P., van Honk, J., 2004. A single administration of testosterone improves visuospatial ability in young women. Psychoneuroendocrinology 29 (5), 612–617.
Arnocky, S., Taylor, S.M., Olmstead, N.A., Carré, J.M., 2017. The effects of exogenous testosterone on men's moral decision-making. Adapt. Hum. Behav. Physiol. 3 (1), 1–13.
Berthold, A.A., 1849. Transplantation of testes. Translated by D.P. Quiring. Bull. Hist. Med. 16 (1944), 399–401.
Bird, B.M., Welling, L.L.M., Ortiz, T.L., Moreau, B.J.P., Hansen, S., Emond, M., Goldfarb, B., Bonin, P.L., Carré, J.M., 2016. Effects of exogenous testosterone and mating context on men's preferences for female facial femininity. Horm. Behav. 85, 76–85.
Bird, B.M., Geniole, S.N., Little, A.C., Moreau, B.J., Ortiz, T.L., Goldfarb, B., ... Carré, J.M., 2017. Does exogenous testosterone modulate men's ratings of facial dominance or trustworthiness? Adapt. Hum. Behav. Physiol. 3 (4), 365–385.
Bird, B.M., Geniole, S.N., Procyshyn, T.L., Ortiz, T.L., Carré, J.M., Watson, N.V., 2019. Effect of exogenous testosterone on cooperation depends on personality and time pressure. Neuropsychopharmacology 44 (3), 538–545.
Boksem, M.A., Mehta, P.H., Van den Bergh, B., van Son, V., Trautmann, S.T., Roelofs, K., ... Sanfey, A.G., 2013. Testosterone inhibits trust but promotes reciprocity. Psychol. Sci. 24 (11), 2306–2314.
Bos, P.A., Terburg, D., Van Honk, J., 2010. Testosterone decreases trust in socially naive humans. Proc. Natl. Acad. Sci. 107 (22), 9991–9995.
Bos, P.A., Hermans, E.J., Ramsey, N.F., van Honk, J., 2012. The neural mechanisms by which testosterone acts on interpersonal trust. NeuroImage 61 (3), 730–737.
Bos, P.A., van Honk, J., Ramsey, N.F., Stein, D.J., Hermans, E.J., 2013. Testosterone administration in women increases amygdala responses to fearful and happy faces. Psychoneuroendocrinology 38 (6), 808–817.
Bos, P.A., Hofman, D., Hermans, E.J., Montoya, E.R., Baron-Cohen, S., van Honk, J., 2016. Testosterone reduces functional connectivity during the 'Reading the mind in the eyes' test. Psychoneuroendocrinology 68, 194–201.
Buskens, V., Raub, W., Van Miltenburg, N., Montoya, E.R., Van Honk, J., 2016. Testosterone administration moderates effect of social environment on trust in women depending on second-to-fourth digit ratio. Sci. Rep. 6, 27655.
Butenandt, A., Hanisch, G., 1935. Testosterone. The transformation of dehydroandrosterone into androstendiol and testosterone; a method for producing testosterone from cholesterin. Hoppe-Seyler's Z. Physiol. Chem. 237, 89–98.
Carré, J.M., Archer, J., 2018. Testosterone and human behavior: the role of individual and contextual variables. Curr. Opin. Psychol. 19, 149–153.
Carré, J.M., Putnam, S.K., McCormick, C.M., 2009. Testosterone responses to competition predict future aggressive behaviour at a cost to reward in men. Psychoneuroendocrinology 34, 561–570.

Carré, J.M., Ortiz, T.L., Labine, B., Moreau, B.J., Viding, E., Neumann, C.S., Goldfarb, B., 2015. Digit ratio (2D:4D) and psychopathic traits moderate the effect of exogenous testosterone on socio-cognitive processes in men. Psychoneuroendocrinology 62, 319–326.
Carré, J.M., Geniole, S.N., Ortiz, T.L., Bird, B.M., Videto, A., Bonin, P.L., 2017. Exogenous testosterone rapidly increases aggressive behavior in dominant and impulsive men. Biol. Psychiatry 82 (4), 249–256.
Chen, C., Decety, J., Huang, P.C., Chen, C.Y., Cheng, Y., 2016. Testosterone administration in females modulates moral judgment and patterns of brain activation and functional connectivity. Hum. Brain Mapp. 37, 3417–3430.
Coccaro, E.F., Sripada, C.S., Yanowitch, R.N., Phan, K.L., 2011. Corticolimbic function in impulsive aggressive behavior. Biol. Psychiatry 69, 1153–1159.
Cueva, C., Roberts, R.E., Spencer, T.J., Rani, N., Tempest, M., Tobler, P.N., ... Rustichini, A., 2017. Testosterone administration does not affect men's rejections of low ultimatum game offers or aggressive mood. Horm. Behav. 87, 1–7.
David, K., Dingemanse, E., Freud, J., Laquer, E., 1935. Crystalline male hormone from the testes (Testosterone) is more effective than androsterone derived from urine or cholesterin. Hoppe-Seyler's Z. Physiol. Chem. 233, 281–282.
Dreher, J., Dunne, S., Pazderska, A., Frodl, T., Nolan, J.J., O'Doherty, J.P., 2016. Testosterone causes both prosocial and antisocial status-enhancing behaviors in human males. Proc. Natl. Acad. Sci. 113 (41), 11633–11638.
Eisenegger, C., Naef, M., Snozzi, R., Heinrichs, M., Fehr, E., 2010. Prejudice and truth about the effect of testosterone on human bargaining behaviour. Nature 463 (7279), 356–359.
Eisenegger, C., von Eckardstein, A., Fehr, E., von Eckardstein, S., 2013. Pharmacokinetics of testosterone and estradiol gel preparations in healthy young men. Psychoneuroendocrinology 38, 171–178.
Enter, D., Spinhoven, P., Roelofs, K., 2014. Alleviating social avoidance: effects of single dose testosterone administration on approach–avoidance action. Horm. Behav. 65 (4), 351–354.
Enter, D., Terburg, D., Harrewijn, A., Spinhoven, P., Roelofs, K., 2016. Single dose testosterone administration alleviates gaze avoidance in women with social anxiety disorder. Psychoneuroendocrinology 63, 26–33.
Foradori, C.D., Weiser, M.J., Handa, R.J., 2008. Non-genomic actions of androgens. Front. Neuroendocrinol. 29, 169–181.
Geniole, S.N., Carré, J.M., 2018. Human social neuroendocrinology: review of the rapid effects of testosterone. Horm. Behav. 104, 192–205.
Geniole, S.N., Bird, B.M., Ruddick, E.L., Carré, J.M., 2017. Effects of competition outcome on testosterone concentrations in humans: an updated meta-analysis. Horm. Behav. 92, 37–50.
Geniole, S.N., Proietti, V., Bird, B.M., Ortiz, T.L., Bonin, P.L., Goldfarb, B., ... Carré, J.M., 2019a. Testosterone reduces the threat premium in competitive resource division. Proc. R. Soc. B Biol. Sci. 286 (1903), 1–8.
Geniole, S.N., Procyshyn, T.L., Marley, N., Ortiz, T.L., Bird, B.M., Marcellus, A.L., ... Carré, J.M., 2019b. Using a psychopharmacogenetic approach to identify the pathways through which—and the people for whom—testosterone promotes aggression. Psychol. Sci. 30 (4), 481–494.
Geniole, S.N., Bird, B.M., McVittie, J.S., Purcell, R.B., Archer, J., Carré, J.M., 2020. Is testosterone linked to human aggression? A meta-analytic examination of the relationship between baseline, dynamic, and manipulated testosterone on human aggression. Horm. Behav (in press).
Goetz, S.M., Tang, L., Thomason, M.E., Diamond, M.P., Hariri, A.R., Carré, J.M., 2014. Testosterone rapidly increases neural reactivity to threat in healthy men: a novel two-step pharmacological challenge paradigm. Biol. Psychiatry 76, 324–331.
Hansen, S., McAuliffe, J., Goldfarb, B., Carré, J.M., 2017. Testosterone influences volitional, but not reflexive orienting of attention in human males. Physiol. Behav. 175, 82–87.
Heany, S.J., Bethlehem, R.A., van Honk, J., Bos, P.A., Stein, D.J., Terburg, D., 2018. Effects of testosterone administration on threat and escape anticipation in the orbitofrontal cortex. Psychoneuroendocrinology 96, 42–51.
Henckens, M.J., van Wingen, G.A., Joels, M., Fermandez, G., 2011. Time-dependent corticosteroid modulation of prefrontal working memory processing. Proc. Natl. Acad. Sci. U. S. A. 108, 5801–5806.
Henderson, A., Thoelen, G., Nadler, A., Barraza, J., Nave, G., 2018. Testing the influence of testosterone administration on men's honesty in a large laboratory experiment. Sci. Rep. 8 (1), 11556.
Hermans, E.J., Putman, P., Baas, J.M., Koppeschaar, H.P., van Honk, J., 2006a. A single administration of testosterone reduces fear-potentiated startle in humans. Biol. Psychiatry 59 (9), 872–874.
Hermans, E.J., Putman, P., van Honk, J., 2006b. Testosterone administration reduces empathetic behavior: a facial mimicry study. Psychoneuroendocrinology 31 (7), 859–866.
Hermans, E.J., Putman, P., Baas, J.M., Gecks, N.M., Kenemans, J.L., van Honk, J., 2007. Exogenous testosterone attenuates the integrated central stress response in healthy young women. Psychoneuroendocrinology 32 (8–10), 1052–1061.
Hermans, E.J., Ramsey, N.F., van Honk, J., 2008. Exogenous testosterone enhances responsiveness to social threat in the neural circuitry of social aggression in humans. Biol. Psychiatry 63 (3), 263–270.
Hermans, E.J., Bos, P.A., Ossewaarde, L., Ramsey, N.F., Fernández, G., van Honk, J., 2010. Effects of exogenous testosterone on the ventral striatal BOLD response during reward anticipation in healthy women. NeuroImage 52 (1), 277–283.
Knight, E.L., Christian, C.B., Morales, P.J., Harbaugh, W.T., Mayr, U., Mehta, P.H., 2017. Exogenous testosterone enhances cortisol and affective responses to social-evaluative stress in dominant men. Psychoneuroendocrinology 85, 151–157.
Knight, E.K., McShane, B.B., Kutlikova, H.H., Morales, P.J., Christian, C.B., Harbaugh WT Mayr, U., Ortiz, T.L., Gilbert, K., Ma-Kellams, C., Riecansky, I., Watson, N.V., Eisenegger, C., Lamm, C., Mehta, P.H., Carré, J.M., 2020. Weak and variable effects of exogenous testosterone on cognitive reflection task performance in three experiments: commentary on Nave et al. (2017). Psychol. Sci (in press).
Kopsida, E., Berrebi, J., Petrovic, P., Ingvar, M., 2016. Testosterone administration related differences in brain activation during the ultimatum game. Front. Neurosci. 10, 66.
Kosfeld, M., Heinrichs, M., Zak, P.J., Fischbacher, U., Fehr, E., 2005. Oxytocin increases trust in humans. Nature 435, 673–676.
Kreuz, L.E., Rose, R.M., 1972. Assessment of aggressive behavior and plasma testosterone in a young criminal population. Psychosom. Med. 34, 321–332.
Liao, J., Zhang, Y., Li, Y., Li, H., Zilioli, S., Wu, Y., 2018. Exogenous testosterone increases decoy effect in healthy males. Front. Psychol. 9.
Losecaat Vermeer, A.B., Krol, I., Gausterer, C., Wagner, B., Eisenegger, C., Lamm, C., 2020. Exogenous testosterone increases status-seeking motivation in men with unstable low social status. Psychoneuroendocrinology 113.
Mazur, A., 1985. A biosocial model of status in face-to-face primate groups. Soc. Forces 64, 377–402.
Mehta, P.H., van Son, V., Welker, K.M., Prasad, S., Sanfey, A.G., Smidts, A., Roelofs, K., 2015. Exogenous testosterone in women enhances and inhibits competitive decision-making depending on victory–defeat experience and trait dominance. Psychoneuroendocrinology 60, 224–236.
Monti, P.M., Brown, W.A., Corriveau, D.P., 1977. Testosterone and components of aggressive and sexual behavior in man. Am. J. Psychiatry 134, 692–694.
Montoya, E.R., Terburg, D., Bos, P.A., Will, G., Buskens, V., Raub, W., van Honk, J., 2013. Testosterone administration modulates moral judgments depending on second-to-fourth digit ratio. Psychoneuroendocrinology 38 (8), 1362–1369.
Nadler, A., Jiao, P., Johnson, C.J., Alexander, V., Zak, P.J., 2017. The bull of wall street: experimental analysis of testosterone and asset trading. Manag. Sci. 64 (9), 4032–4051.
Nadler, A., Zava, D., Ortiz, T., Watson, N., Carre, J., Camerer, C., Nave, G., 2019. Does testosterone impair mens' cognitive empathy? Evidence from two large-scale randomized controlled trials. Proc. R. Soc. Biol. Sci. 286, 20191062.
Nave, G., Camerer, C., McCullough, M., 2015. Does oxytocin increase trust in humans? A critical review of research. Perspect. Psychol. Sci. 10, 772–789.
Nave, G., Nadler, A., Zava, D., Camerer, C., 2017. Single-dose testosterone administration impairs cognitive reflection in men. Psychol. Sci. 28 (10), 1398–1407.
Nave, G., Nadler, A., Dubois, D., Zava, D., Camerer, C., Plassmann, H., 2018. Single-dose testosterone administration increases men's preference for status goods. Nat. Commun. 9 (1), 2433.
Nieschlag, E., Nieschlag, S., 2014. Testosterone deficiency: a historical perspective. Asian J. Androl. 16, 161–168.
Olsson, A., Kopsida, E., Sorjonen, K., Savic, I., 2016. Testosterone and estrogen impact social evaluations and vicarious emotions: a double-blind placebo-controlled study. Emotion 16, 515–523.
Panagiotidis, D., Clemens, B., Habel, U., Schneider, F., Schneider, I., Wagels, L., Votinov, M., 2017. Exogenous testosterone in a non-social provocation paradigm potentiates anger but not behavioral aggression. Eur. Neuropsychopharmacol. 27 (11), 1172–1184.
Persky, H., Smith, K.D., Basu, G.K., 1971. Relation of psychologic measures of aggression and hostility to testosterone production in man. Psychosom. Med. 33, 265–277.
Pesant, M.H., Desmarais, G., Fink, G.D., Baillargeon, J.P., 2012. Reference ranges for total and calculate free and bioavailable testosterone in a young healthy women population with normal menstrual cycles or using oral contraception. Clin. Biochem. 45, 148–150.
Postma, A., Meyer, G., Tuiten, A., van Honk, J., Kessels, R.P., Thijssen, J., 2000. Effects of testosterone administration on selective aspects of object-location memory in healthy young women. Psychoneuroendocrinology 25 (6), 563–575.
Puiu, A.A., Radke, S., Votinov, M., Habel, U., Herpertz-Dahlmann, B., Turetskyu, B., Konrad, K., 2019. Serum testosterone and cortisol concentrations after a single-dose administration of 100-mg transdermal testosterone in healthy men. Front. Pharmacol. 10, 1397.
Radke, S., Volman, I., Mehta, P., van Son, V., Enter, D., Sanfey, A., ... Roelofs, K., 2015. Testosterone biases the amygdala toward social threat approach. Sci. Adv. 1 (5), e1400074.
Riis-Vestergaard, M.I., van Ast, V., Cornelisse, S., Joels, M., Haushofer, J., 2018. The effect of hydrocortisone administration on intertemporal choice. Psychoneuroendocrinology 88, 173–182.
Roney, J.R., 2016. Theoretical frameworks for human behavioral endocrinology. Horm. Behav. 84, 97–110.
Ruzicka, L., Wettstein, A., 1935. Synthesis of the testicular hormone (testosterone) (androstene 3-on-17-ol). Helv. Chim. Acta 18, 1264–1275.
Schutter, D.J., Peper, J.S., Koppeschaar, H.P., Kahn, R.S., van Honk, J., 2005. Administration of testosterone increases functional connectivity in a cortico-cortical depression circuit. J. Neuropsychiatr. Clin. Neurosci. 17 (3), 372–377.
Swerdloff, R.S., Wang, C., Cunningham, G., Dobs, A., Iranmanesh, A., Matsumoto, A.M., Synder, P.J., Weber, T., Longstreth, J., Berman, N., 2000. Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. J. Clin. Endocrinol. Metab. 85, 4500–4510.
Terburg, D., Aarts, H., van Honk, J., 2012. Testosterone affects gaze aversion from angry faces outside of conscious awareness. Psychol. Sci. 23 (5), 459–463.
Terburg, D., Syal, S., Rosenberger, L.A., Heany, S.J., Stein, D.J., van Honk, J., 2016. Testosterone abolishes implicit subordination in social anxiety. Psychoneuroendocrinology 72, 205–211.
Trainor, B.C., Bird, I.M., Marler, C.A., 2004. Opposing hormonal mechanisms of aggression revealed through short-lived testosterone manipulations and multiple winning experiences. Horm. Behav. 45, 115–121.
Travison, T.G., Vesper, H.W., Orwoll, E., Wu, F., Kaufman, J.M., Wang, Y., Lapauw, B.,

Fiers, T., Matsumoto, A.M., Bhasin, S., 2017. Harmonized reference ranges for circulating testosterone levels in men of four cohort studies in the United States and Europe. J. Clin. Endocrinol. Metab. 102, 1161–1173.
Tuiten, A., Van Honk, J., Koppeschaar, H., Bernaards, C., Thijssen, J., Verbaten, R., 2000. Time course of effects of testosterone administration on sexual arousal in women. Arch. Gen. Psychiatry 57 (2), 149–153.
Van Der Westhuizen, D., Moore, J., Solms, M., van Honk, J., 2017. Testosterone facilitates the sense of agency. Conscious. Cogn. 56, 58–67.
Van Der Westhuizen, D., Page, T., Solms, M., van Honk, J., 2019. The territory of my body: testosterone prevents limb cooling in the rubber hand illusion. Multisens. Res. 33, 161–187.
Van Honk, J., JLG Schutter, D., 2007. Testosterone reduces conscious detection of signals serving social correction: implications for antisocial behavior. Psychol. Sci. 18 (8), 663–667.
Van Honk, J., Tuiten, A., Hermans, E., Putnam, P., Koppeschaar, H., Thijssen, J., ... van Doornen, L., 2001. A single administration of testosterone induces cardiac accelerative responses to angry faces in healthy young women. Behav. Neurosci. 115 (1), 238.
Van Honk, J., Schutter, Dennis J.L.G., Hermans, E.J., Putman, P., Tuiten, A., Koppeschaar, H., 2004. Testosterone shifts the balance between sensitivity for punishment and reward in healthy young women. Psychoneuroendocrinology 29 (7), 937–943.
Van Honk, J., Peper, J.S., Schutter, D.J., 2005. Testosterone reduces unconscious fear but not consciously experienced anxiety: implications for the disorders of fear and anxiety. Biol. Psychiatry 58 (3), 218–225.
van Honk, J., Schutter, D.J., Bos, P.A., Kruijt, A.W., Lentjes, E.G., Baron-Cohen, S., 2011. Testosterone administration impairs cognitive empathy in women depending on second-to-fourth digit ratio. Proc. Natl. Acad. Sci. U. S. A. 108, 3448–3452.
Van Honk, J., Montoya, E.R., Bos, P.A., van Vugt, M., Terburg, D., 2012. New evide nce on testosterone and cooperation. Nature 485, E5–E6.
Van Honk, J., Will, G., Terburg, D., Raub, W., Eisenegger, C., Buskens, V., 2016. Effects of testosterone administration on strategic gambling in poker play. Sci. Rep. 6, 18096.
Van Wingen, G., Mattern, C., Verkes, R.J., Buitelaar, J., Fernández, G., 2008. Testosterone biases automatic memory processes in women towards potential mates. NeuroImage 43, 114–120.
Van Wingen, G.A., Zylicz, S.A., Pieters, S., Mattern, C., Jan Verkes, R., Buitelaar, J.K., Fernández, G., 2009. Testosterone increases amygdala reactivity in middle-aged women to a young adulthood level. Neuropsychopharmacology 34 (3), 539–547.
Van Wingen, G., Mattern, C., Verkes, R.J., Buitelaar, J., Fernández, G., 2010. Testosterone reduces amygdala–orbitofrontal cortex coupling. Psychoneuroendocrinology 35, 105–113.
Wagels, L., Votinov, M., Radke, S., Clemens, B., Montag, C., Jung, S., Habel, U., 2017a. Blunted insula activation reflects increased risk and reward seeking as an interaction of testosterone administration and the MAOA polymorphism. Hum. Brain Mapp. 38 (9), 4574–4593.
Wagels, L., Radke, S., Goerlich, K.S., Habel, U., Votinov, M., 2017b. Exogenous testosterone decreases men's personal distance in a social threat context. Horm. Behav. 90, 75–83.
Wagels, L., Votinov, M., Kellermann, T., Eisert, A., Beyer, C., Habel, U., 2018. Exogenous testosterone enhances the reactivity to social provocation in males. Front. Behav. Neurosci. 12.
Wagels, L., Votinov, M., Kellermann, T., Konzok, J., Jung, S., Montag, C., ... Habel, U., 2019. Exogenous testosterone and the monoamine-oxidase a polymorphism influence anger, aggression and neural responses to provocation in males. Neuropharmacology 156, 1–12.
Welker, K.M., Norman, R.E., Goetz, S., Moreau, B.J.P., Kitayama, S., Carré, J.M., 2017. Preliminary evidence that testosterone's association with aggression depends on self-construal. Horm. Behav. 92, 117–127.
Welling, L.L., Moreau, B.J., Bird, B.M., Hansen, S., Carré, J.M., 2016. Exogenous testosterone increases men's perceptions of their own physical dominance. Psychoneuroendocrinology 64, 136–142.
Wibral, M., Dohmen, T., Klingmüller, D., Weber, B., Falk, A., 2012. Testosterone administration reduces lying in men. PLoS One 7 (10), e46774.
Williams, T.D., 2008. Individual variation in endocrine systems: moving beyond the 'tyranny of the Golden Mean'. Philos. Trans. R. Soc. Lond. Biol. Sci. 363, 1687–1698.
Wingfield, J.C., Hegner, R.E., Dufty, A.M., Ball, G.F., 1990. The 'Challenge Hypothesis': Theoretical implications for patterns of testosterone secretion, mating systems, and breeding strategies. Am. Nat. 136, 829–846.
Wu, Y., Liu, J., Qu, L., Eisenegger, C., Clark, L., Zhou, X., 2016. Single dose testosterone administration reduces loss chasing in healthy females. Psychoneuroendocrinology 71, 54–57.
Wu, Y., Zilioli, S., Eisenegger, C., Clark, L., Li, H., 2017. The effect of testosterone administration and digit ratio (2D:4D) on implicit preference for status goods in healthy males. Front. Behav. Neurosci. 11, 193.
Wu, Y., Clark, L., Zilioli, S., Eisenegger, C., Gillan, C.M., Deng, H., Li, H., 2018. Single dose testosterone administration modulates emotional reactivity and counterfactual choice in healthy males. Psychoneuroendocrinology 90, 127–133.
Wu, Y., Liao, J., Zilioli, S., Wu, Y., Deng, H., Li, H., Tobler, P.N., 2019. Testosterone administration increases social discounting in healthy males. Psychoneuroendocrinology 108, 127–134.
Wu, Y., Shen, B., Liao, J., Li, Y., Zilioli, S., Li, H., 2020. Single dose testosterone administration increases impulsivity in the intertemporal choice task among healthy males. Horm. Behav. 118, 104634.
Wudy, S.A., Schuler, G., Sanchez-Guijo, A., Hartmann, M.F., 2018. The art of measuring steroids: principles and practice of current hormonal steroid analysis. J. Steroid Biochem. Mol. Biol. 179, 88–103.
Zak, P.J., Kurzban, R., Ahmadi, S., Swerdloff, R.S., Park, J., Efremidze, L., ... Matzner, W., 2009. Testosterone administration decreases generosity in the ultimatum game. PLoS One 4 (12), e8330.