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Single dose testosterone administration modulates emotional reactivity and counterfactual choice in healthy males☆

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ABSTRACT

Testosterone has been implicated in the regulation of emotional responses and risky decision-making. However, the causal effect of testosterone upon emotional decision-making, especially in non-social settings, is still unclear. The present study investigated the role of testosterone in counterfactual thinking: regret is an intense negative emotion that arises from comparison of an obtained outcome from a decision against a better, non-obtained (i.e. counterfactual) alternative. Healthy male participants (n = 64) received a single-dose of 150 mg testosterone Androgel in a double-blind, placebo-controlled, between-participants design. At 180 min post-administration, participants performed the counterfactual thinking task. We applied a computational model derived from behavioral economic principles to uncover latent decision-making mechanisms that may be invisible in simple choice analyses. Our data showed that testosterone increased the ability to use anticipated regret to guide choice behavior, while reducing choice based on expected value. On affective ratings, testosterone increased sensitivity to both obtained and counterfactual outcomes. These findings provide evidence that testosterone causally modulates emotional decision-making, and highlight the role of testosterone in affective sensitivity.

1. Introduction

Testosterone, a steroid hormone produced by the gonads, has substantial effects on body composition, skeletal muscles, and sexual function. There is increasing interest in the role of testosterone in human social cognition and decision-making. According to one theory, the status hypothesis, testosterone promotes behaviors that are conducive to increased social status, irrespective of the prosocial or antisocial nature of the behavior *per se* (Boksem et al., 2013; Eisenegger et al., 2010). Consistent with the status hypothesis, testosterone can promote aggressive behavior in response to status-threatening situations, such as provocations in the Ultimatum Game (Dreher et al., 2016), but may also promote prosocial behavior (e.g., generosity) in situations where reciprocity is likely to increase status (e.g., provocation-free trials in the Ultimatum Game, Dreher et al., 2016; or repaying trust in the Trust Game Boksem et al., 2013). Although the status hypothesis can be very helpful when predicting social decision-making, it has limited explanatory power in economic decision-making scenarios without social interaction.

The dual-process hypothesis is a broader framework in decision-making theory in which choice variables are processed using two competing systems, one characterized by rapid, automatic, emotion-based, intuitive processes (i.e., System 1), and the other characterized by slow, effortful, deliberate processes (i.e., System 2) (Evans, 2003). Recent studies suggest that testosterone skews decision-making towards System 1 processes (Nave et al., 2017). For example, using the

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Cognitive Reflection Test (CRT), Nave and colleagues found that testosterone administration increased participants' tendency to rely on intuitive judgments and reduced inhibition of incorrect responses (Nave et al., 2017). In line with the dual-process model, other cognitive effects of testosterone are thought to be mediated by changes in emotional reactivity (Eisenegger et al., 2011; van Wingen et al., 2011). For example, individuals with higher basal testosterone levels show enhanced vigilance to angry facial expressions, and testosterone administration increases heart rate responses to angry facial expressions (van Honk et al., 2001). Neuroimaging studies associate testosterone-induced emotional reactivity with increased neural activity in the amygdala, a key brain structure involved in emotion processing (Derntl et al., 2009; Goetz et al., 2014; Hermans et al., 2008; van Wingen et al., 2008). Taken together, these findings indicate that testosterone may shift the balance between System 1 and System 2, making individuals more reliant on automatic judgments and more likely to be biased by emotional factors.

The present study investigated this possibility by examining the causal effect of testosterone on decision-making using the paradigmatic example of regret. Regret is unpleasant emotion that arises from counterfactual thinking, when people realize that their current situation would have been better if they have chosen differently (Mellers et al., 1999). In a gambling task, negative affect is typically enhanced when the alternative (non-obtained) outcome is revealed to be better than the obtained choice outcome. Conversely, 'relief' is elicited when the non-obtained outcome is worse than the outcome obtained. These subjective responses are associated with heightened skin conductance, a physiological marker of emotional arousal (Camille et al., 2004; Wu et al., 2016b). In addition to its effect on affective states, regret modulates choice behavior in economic decision-making, as people tend to make choices that minimize the likelihood of experiencing regret (Coricelli et al., 2007). Neuropsychological and brain imaging studies have identified key structures in the brain, namely the orbitofrontal cortex and amygdala, that are associated with experiencing and anticipating regret (Camille et al., 2004; Coricelli et al., 2005; Steiner and Redish, 2014).

The present study examined whether and how testosterone affects decision-making and counterfactual thinking. On each trial, participants were presented with pairs of gambles involving different probabilities of monetary gain or loss. The expected values, and their potential to evoke regret/relief were manipulated across trials. Participants typically select gambles that minimize anticipated regret (Camille et al., 2004; Coricelli et al., 2005). Building upon the dual-system framework, we hypothesized that testosterone administration would enhance the affective sensitivity to regret and increase the effect of anticipatory regret on subsequent choices.

2. Methods

2.1. Participants

Sixty-four healthy males (mean age = 22.64 years, *SD* = 1.69; age range = 20–27) were recruited through university advertisement. One participant who started but did not finish the behavioral task was excluded, leaving 63 participants for final analysis. Participants were screened with a telephone interview and considered ineligible to participate if taking psychotropic medications or having any psychiatric/neurological disorders. We recruited males as the dosing and pharmacokinetics of single dose Androgel administration are only established for men (Eisenegger et al., 2013) (see Supplementary Material for additional data establishing the time course for Androgel in an independent sample). Participants were instructed to abstain from alcohol, caffeine intake, and smoking for 24 h before the testing session. Each participant received a single dose of Androgel or placebo gel in a double-blind, placebo-controlled, between-participants design. This study was conducted in accordance with Declaration of Helsinki and was approved by Shenzhen University Medical Research Ethics Committee. Written informed consent was obtained from all participants. Participants were paid 200 Chinese Yuan (~$30) as a participation fee. Participants were also endowed with 10 Yuan to play the gambling task. The points that were gained or lost during the task were added or subtracted from this initial endowment and added to the participation fee as a bonus payment.

2.2. Testosterone administration

All sessions started at 13:00 and lasted approximately 4.5 h. Participants in the testosterone group received a single dose of testosterone gel, containing 150 mg testosterone [Androgel®]. Participants in the placebo group received a colorless hydroalcoholic gel. In both treatment groups, the gel was applied to shoulders and upper arms by a male research assistant, who was blind to both the purpose of the study and the experimental condition (i.e. the Androgel and placebo were packed identically). The counterfactual thinking task commenced 3 h post-dosing in accordance with previous pharmacokinetic data (Carré et al., 2015; Eisenegger et al., 2013), corroborated by salivary data from an independent sample confirming that salivary testosterone levels peak 3 h after Androgel administration (see Supplementary Material). The participants also completed two additional tasks on social cognition that are not reported here. During the waiting period, participants rested in the testing rooms and were provided with newspapers and magazines that were not related to the study.

2.3. Counterfactual thinking task

Participants performed 80 trials of a counterfactual thinking task modified from Gillan et al. (2014), which involved real monetary wins and losses. The task was programmed using Presentation software (Neurobehavioral System Inc.). On each trial, participants chose between two wheels that displayed different potential gains and losses, and their respective probabilities. Each wheel offered two of the following possible outcomes: +70, +210, −70, −210, representing monetary values. Participants were informed that each point corresponded to 0.1 Chinese Yuan and that earnings would be paid as a bonus on the task. The outcome probabilities could be 0.25, 0.5, or 0.75, as indicated by the size of the segment in each wheel (see Fig. 1). As the participant selected a wheel, it was highlighted with a red surround. The outcome of the selected wheel (i.e., the obtained outcome) was presented for 2 s, with the non-selected wheel covered. Participants rated "How pleased were you with the outcome?" using an onscreen rating from 1 (*extremely unpleasant)* to 9 (*extremely pleasant)* (henceforth Rating 1). After a 1 s blank screen, the outcome on the non-selected wheel (i.e., the non-obtained outcome) was presented alongside the obtained outcome for 2 s. Participants again rated how pleased they were with the outcome (henceforth Rating 2). The inter-trial interval was 2 s. No time constraints were imposed on wheel selection or affect ratings. Outcomes were pre-specified to be in line with the displayed probabilities, ensuring that the task was fair (see Table S2 of Supplementary Material for the full task sequence).

2.4. Data analysis

2.4.1. Affective ratings

We used R and *lme4* (Bates et al., 2012) to perform a linear mixed effects analysis on the affect ratings. Treatment (testosterone, placebo) was entered as a fixed-effect factor, trial outcomes (see below) were continuous fixed-effect predictors, and subject was a random-effect factor.

We conducted analyses for ratings following the partial feedback (i.e. Rating 1) and for ratings following the complete feedback (i.e. Rating 2). For Rating 1, we modeled the influence of 1) the value of obtained outcome, and 2) the 'Chance Counterfactual', defined as the