Single dose testosterone administration increases impulsivity in the intertemporal choice task among healthy males

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ABSTRACT

Circulating levels of testosterone have been positively associated with impulsivity. The present study investigates the effect of testosterone administration on impulsivity in an intertemporal choice task, where participants are given a choice between smaller-sooner rewards and larger-later rewards. Healthy young male participants (n = 111) received a single-dose of 150 mg testosterone gel in a double-blind, placebo-controlled, between-subjects design. At 180 min post-administration, participants performed the decision-making task. Both model-free (i.e., higher indifference point) and model-based (i.e., steeper discounting rate) parameters revealed that testosterone administration increased impulsive choice. This finding supports the hypothesis that exogenous testosterone increases impulsivity among healthy young males in a laboratory task.

1. Introduction

A number of studies have tested the association between circulating testosterone and impulsivity, broadly defined as the tendency to behave with little forethought. Animal studies showed that neonatal testosterone exposure plays a role in mediating sex differences in impulsivity in prepubertal rats (Darling et al., 2019). However, the human literature on this topic remains elusive. A recent meta-analysis documented a significant, but small positive association between circulating testosterone and impulsivity (r = 0.06) (Kurath and Mata, 2018). Many of the existing studies measured impulsivity through self-report questionnaires (e.g., the Barratt Impulsivity Scale, BIS), and only few considered behavioral measures of impulsivity. This is a potential limitation of the current literature, particularly when considering reactivity problems associated with self-report measures (e.g., social desirability, self-promotion) and the low correlation between self-report and behavioral measures of impulsivity (r = 0.097) (Cyders and Coskunpinar, 2011). Studies using behavioral measures of impulsivity, albeit not without limitations, provide a snapshot of people’s actual behavior and thus might be better suited to reveal the strength of the association between impulsivity and testosterone.

An established way to assess impulsivity experimentally is by using the intertemporal choice task, which involves a series of decisions between smaller-sooner rewards and larger-later rewards available after a longer delay (Bickel and Marsch, 2001). In this task, individual differences in impulsivity correspond to discounting rate, which can be derived from choice behavior. More impulsive individuals have higher delay discounting rates, meaning they devalue future rewards more rapidly (Verdejo-García et al., 2008). The handful of studies that tested the association between circulating testosterone and individual differences in discounting rate have yielded inconsistent results. For example, Doi et al. (2015), found a positive correlation between salivary testosterone concentration and discounting rate in women. Circulating testosterone was negatively associated with discounting rate in men in Doi et al.’s study, indicating that high-testosterone men were less impulsive than low-testosterone men in the intertemporal choice task (Doi et al., 2015). Lastly, Takahashi et al. (2006) found an inverted-U relationship between salivary testosterone levels and discounting rate, suggesting that individuals with both the highest and the lowest levels of testosterone had the lowest discounting rates (Takahashi et al., 2006). One way to shed light on the inconsistencies found in the literature is to directly test the causal effect of
testosterone on intertemporal choice by pharmacologically manipulating testosterone. The first step in this direction was taken by Ortner et al. (2013), who found no effect of testosterone on intertemporal choice. In our current study, we investigate the effect of testosterone on impulsivity in the intertemporal choice task by using a well-established pharmacological challenge paradigm that has proved to be reliable for studying behavioral outcomes (Eisenegger et al., 2013). Moreover, we employed a self-adapted intertemporal choice task (Shen et al., 2016), which covers a wide range of individual differences and gives a fine-grained measurement of impulsivity.

2. Materials and methods

2.1. Participants

We recruited 121 male student volunteers (mean age = 21.7 years, SD = 2.0; age range = 18–27) from Shenzhen University to participate in this study. Participants were screened with a telephone interview and considered ineligible to participate if taking psychotropic medications or having any psychiatric/neurological disorders. We only recruited male participants since the dosing and pharmacokinetics of single dose testosterone administration used in this study have only been established for men (Eisenegger et al., 2013). Each participant received a single dose of Androgel or placebo gel in a placebo-controlled, double-blind, between-participant design. Before pharmacological manipulation, participants were asked to complete the Barratt Impulsiveness Scale version 11 (BIS-11), which is a trait measure of impulsivity (Patton et al., 1995). This study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Research Ethics Committee at Shenzhen University. All participants provided written informed consent. Participants were paid 200 Chinese Yuan as flat fee plus a bonus payment depending on their task performance (see details below).

2.2. Testosterone administration

All testing sessions were conducted in the afternoon, between 13:00 and 18:00. Participants in the testosterone condition received a single dose of testosterone gel, containing 150 mg testosterone [Androgel ®], while those in the placebo condition received a colorless hydroalcoholic gel. We administered the decision-making task 3 h post-dosing in accordance with previous pharmacokinetic data (Eisenegger et al., 2013; Wu et al., 2018).

2.3. Intertemporal choice (ITC) task

Participants completed 90 trials of ITC task adapted from Shen et al. (2016). During each trial, they were asked to choose between a smaller-sooner (SS) reward and a larger-later (LL) reward (see Fig. 1A). Participants were asked to make a choice within 5 s. The chosen option was highlighted with a red rectangle for 1 s after responding. If participants failed to respond within 5 s, a warning sign “Please respond faster” was presented before the task proceeded to the next trial (number of missing trials for each participant, \( M = 1.33, SD = 1.31, range = 0–6 \)).

For the ITC task, the SS delay was fixed at “today”. The difference in delays between LL and SS was selected from the time delay intervals (1, 3, 7, 14, 30, and 90 days), which were randomized across trials. The SS reward was fixed at 25 Chinese Yuan. To cover a wide range of baseline impulsivity levels across participants, the LL amounts were determined by a self-adaptive algorithm: the amount of the LL at each delay was independently adjusted to converge towards the same subjective value (SV) as the SS reward. Specifically, the initial LL rewards at each delay interval (D) were given randomly within the range of \[25(1 + .02D), 25(1 + .04D)]\] based on our previous work (Shen et al., 2016). Values under each D were controlled independently. On each trial, the LL reward was increased or decreased by a degree depending on whether participants chose SS or LL in the previous trial of the same D. The adapting degree started from .25D, shrank by 65/100 or expanded by 100/65 of the original value depending on whether participants reversed their preferences in the last two trials of the same D (e.g., changing preferences from SS to LL) or kept their choices the same in the last two trials of the same D. To prevent extreme values, we also set the lower and upper bounds for the LL amount to 25.1 and 200 across all D. The average percent of choices for the SS reward was 47.9% (SD = 11.3%, range = 27.8–87.6%). One trial payoff was randomly chosen from each participant's set of choices and delivered to them via “Alipay”, a popular mobile payment platform in China.

2.4. Statistical analysis

All the data and analysis scripts are available on the OSF page: https://osf.io/qyk9d/.

Data of eight participants were lost due to programme dysfunction, and two participants’ data could not be fit by the hyperbolic discounting function, leaving 111 participants (mean age = 21.7 years, SD = 1.9; age range = 18–27) for final analysis, 58 who received testosterone and 53 who received placebo.

Data were analyzed using the R statistical package (R Core Team, 2017). We used both model-free and model-based analysis. For the model-free analysis, we did not assume the discounting of LL reward across different delay intervals following a specific mathematical model. This liberal assumption allowed us to test if there was any interaction effect between the treatment and delay intervals. For the model-based analysis, we employed the standard hyperbolic model to derive each participant's temporal discounting rate (Mazur, 1987), which was used as an overall indicator of impulsivity.

In the model-free analysis, indifference points were estimated for each delay separately by fitting a logistic function to the proportion of choices of the LL option as a function of the LL amount

\[
\logit P(\text{choose LL}) = \beta_0 + \beta_1 \text{LL amount}
\]

At this indifference point, we hypothesized that participants would select the SS and LL option with the same probability. This assumption also implies that LL rewards at the indifference point had the same SV as the SS option:

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\[
\logit (0.5) = \beta_0 \text{indifference point} + \beta_1
\]

Thus, we calculated indifference point according to parameters \( \beta_0 \) and \( \beta_1 \) (representing slope and intercept fitted by the logistic function above) that were fitted by the logistic curve:

Indifference point = \(-\beta_0/\beta_1\)

Higher indifference points suggest greater impulsivity since they imply greater relative preference for SS reward overall (see Fig. 1B for an example from one of the study participants). To tolerate missing data points in estimation of indifference points and get a robust group-level fixed-effects, we used R and lme4 (Bates et al., 2012) to perform a linear mixed effects analysis on the indifference point. Values were derived using the Satterthwaite approach through lmerTest package (Kuznetsova et al., 2012). Treatment (as categorical variable) and delay intervals (as continuous variable) were entered as fixed-effect factor, and subject was a random-effect factor.

In the model-based analysis, the SV of the option with monetary amount A was assumed by the hyperbolic model \( SV_{LL} = A/(1 + \frac{k}{\text{Delay}}) \), where A is the amount of the delayed reward, and k is the parameter representing participant's discounting rate (i.e., a larger value of k indicates relatively greater impulsivity). Discounting rate k and choice stochasticity parameter \( \beta \) were optimized with maximum
likelihood by using logistic regressions, i.e., logit (choosing LL) = β (SV_{LL} − SS).

### 3. Results

The testosterone (M = 64.95, SD = 7.80) and placebo (M = 65.38, SD = 8.56) group did not differ on their trait impulsivity, as indexed by the BIS score (t_{111} = −0.28, p = .78). In Table 1, we reported the proportion of SS choices and mean LL amounts per treatment group across all delay levels and under each delay level. Group differences on proportion of SS choices disappeared in the last three blocks of the task (i.e., stage 4) for each delay level (i.e., Day 1, Day 3, Day 7, Day 14, Day 30) and across all delay levels (see Table 1), suggesting that the self-adaptive algorithm effectively worked for both groups when the task progressed. We assessed the effects of testosterone with indifferent points as the dependent variable. Model-free analysis revealed significant main effects of delay interval (b = 6.26, SE = 0.63, t = 9.92, p < .001). The main effect of treatment was not significant, b = 2.15, SE = 4.61, t = 0.47, p = .64. Note the interaction between treatment and delay interval was significant (b = 2.19, SE = 0.89, t = 2.47, p = .014, see Fig. 1B). Simple effect analysis showed that testosterone administration significantly increased indifference points (i.e., greater impulsivity) at the second (b = 3.65, SE = 1.57, t = 2.33, p = .022), third (b = 9.52, SE = 3.81, t = 2.50, p = .014), fourth (b = 15.66, SE = 5.26, t = 2.98, p = .0036), and fifth (b = 10.53, SE = 4.49, t = 2.34, p = .021) delay intervals. No group differences were found at the first and sixth delay intervals, b = 0.85, SE = 0.52, t = 1.62, p = .11, and b = 8.29, SE = 8.37, t = 0.99, p = .32, respectively.

We used the standard hyperbolic function to fit choice data (see Fig. 1C). Since k values were not normally distributed, we run the analyses after log-transforming them. Results revealed that participants

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**Fig. 1.** (A) Schematic illustration of the ITC choice. For each trial, participants were asked to choose between a sooner-smaller (SS) reward and later-larger (LL) reward within 5 s. (B) Example of LL amounts, choices, and modelling fitting from a study participant. The LL amount was determined based on self-adaptive algorithm. SS choices are shown as white triangles and LL as black triangles. The red stars represent indifference points. (C) The effect of testosterone administration on indifference points. (D) Subjective value as a proportion of delay intervals and fitted hyperbolic discount function. *p < .05, **p < .01, ***p < .001; error bars represent standard error of means. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
in the testosterone group (k value: $M = 0.10, SD = 0.21$) showed increased impulsivity (i.e., higher discounting rate) than those in the placebo group (k value: $M = 0.022, SD = 0.030$) (log k: $t_{109} = 2.39$, $p = .019$, Cohen’s d = 0.46).

### 4. Discussion

By combining testosterone administration with an intertemporal choice task, we demonstrated that testosterone administration increased impulsive choice in healthy young males. This result emerged when considering both model-free and model-based model parameters. This finding provides causal evidence that exogenous testosterone increases impulsivity in a laboratory task. Increased impulsivity has been proposed as a mechanism implicated in many psychiatric disorders, including substance-use disorder, gambling disorder, and criminal/violent behavior (Verdejo-García et al., 2008). Accordingly, investigating the role of testosterone in intertemporal choice behavior can provide important insights on the hormonal underpinning of these behavioral problems. Our findings are somewhat congruent with a recent study showing that more extended use of anabolic-androgenic steroids (AAS) predicted a higher level of impulsivity among young adults (Hildebrandt et al., 2014). Although randomized controlled trials are needed to unveil the short- and long-term effects of single and sustained testosterone administrations on impulsivity, users of AAS, Table 1

<table>
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<tr>
<th>Stage</th>
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<th>Difference</th>
<th>p</th>
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<td>0.44 ± 0.03</td>
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</tr>
<tr>
<td>5</td>
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<td>0.04 ± 0.02</td>
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</tr>
<tr>
<td>6</td>
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<td>0.09 ± 0.03</td>
<td>.36</td>
</tr>
<tr>
<td>7</td>
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<td>0.05 ± 0.03</td>
<td>.03</td>
</tr>
<tr>
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<td>0.04 ± 0.03</td>
<td>.04</td>
</tr>
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<tr>
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<tr>
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men undergoing testosterone replacement therapy, and physicians prescribing testosterone should be aware of this potential relationship. One possible neural mechanism by which testosterone increases impulsivity is through its effects on the dopaminergic system. Previous research showed that testosterone receptors are located on dopamine neurons projecting to the ventral striatum (Creutz and Kritzer, 2004), and testosterone administration increases brain activity in the ventral striatum during reward anticipation (Hermans et al., 2010). Pharmacologically enhancing dopamine activity through L-DOPA administration increases impulsivity in the intertemporal choice task (Pine et al., 2010). Future studies could fruitfully test the mediatory role of dopaminergic transmission on the effects of testosterone as well as the neural substrates by which these systems influence impulsivity.

A previous testosterone administration study showed null effect of testosterone administration in intertemporal choice using a similar protocol (Ortner et al., 2013). Some design differences warrant further discussion. First, Ortner and colleagues administered 50 mg testosterone gel (vs. 150 mg used in this study). Future research could fruitfully investigate whether the effect of testosterone on temporal discounting could be dose dependent. Second, Ortner et al. adopted a paper-and-pencil questionnaire version of intertemporal choice task (Kirby et al., 1999) that is more hypothetical than the one used here, which has the advantage to be more realistic and incentive compatible. Moreover, the self-adaptive algorithm employed in the current study was designed to capture impulsivity level in a more precise way (Shen et al., 2016). First, self-adapted range of choice options is able to cover a wide range of impulsivity level as to prevent ceiling or floor effect when applying to the participants at extreme impulsivity levels. Second, the algorithm concentrates the choice options around the indifference points of each participant, which increases estimation power in parameter estimation and allows to differentiate individual differences in impulsivity more accurately. However, in the self-adaptive algorithm used here, participants’ choices could influence their subsequent options. To avoid this potential confound, future studies using a fixed set of monetary pairs are needed to corroborate the current findings. Lastly, we only tested males in the present study. Future research needs to investigate if the exogenous testosterone effects found here could be generalized to females.

Declaration of competing interest
None of the authors have conflicts of interests to declare.

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References