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## Testosterone exposure, dopaminergic reward, and sensation-seeking in young men

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### ABSTRACT

To test the relationship between androgen exposure, dopaminergic reward and sensation-seeking, we compared variation in salivary testosterone (T), 2D:4D digit ratio, facial masculinity, Zuckerman's sensation-seeking scale (SSS) and the D4 dopamine receptor (*DRD4*) genes from 98 young men, between the ages of 18 and 23 years. In univariate analyses, both salivary T and facial masculinity were significantly correlated with the SSS boredom susceptibility subscale, while the presence of the 7-repeat allele (7R+) in the dopamine receptor D4 gene was associated with the SSS thrill and adventure-seeking and overall sensation-seeking. Neither left nor right 2D:4D digit ratio was associated with any sensation-seeking scale. In multivariate models, salivary T and facial masculinity were significant predictors of SSS boredom susceptibility, while 7R+ was a significant predictor of SSS thrill and adventure-seeking. For overall SSS, both 7R+ and salivary T were significant predictors. There was no significant interaction of 7R+ and androgen exposure for SSS or any of the SSS subscales. These results add to earlier reports of an association between T and sensation-seeking. In addition, our results also indicate that genetic variation in *DRD4* is independently associated with SSS sensation-seeking.

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### 1. Introduction

Testosterone (T), a male reproductive hormone produced in the testes, has been implicated in many "male-typical" behaviors, including impulsivity and sensation-seeking. Studies of prison inmates have reported a significant association of T with impulsivity [1], as well as aggression, violence, sexual curiosity, and social disinhibition [2–4]. Elevated T in cerebrospinal fluid has been associated with increased aggressiveness, monotony avoidance, and sensation-seeking among alcoholic men [5], as well as venturesomeness (a component of sensation-seeking) in men with personality disorders [6]. Finally, sensation-seeking was associated with free T among a sample of adolescents with Attention Deficit Hyperactivity Disorder (ADHD) [7].

Studies among samples drawn from the general population have provided more mixed results. Positive findings include a significant positive association between serum T and disinhibition in a sample of

40 male undergraduates [8], as well as a significant positive association between the free androgen index (a measure of bioavailable T) and Zuckerman's sensation-seeking scale (SSS) in a sample of 30 Spanish men [9]. However, another study [10] reported no association between salivary T (highly related to bioavailable T [11,12]) and SSS among 68 male college students. Others found no association between salivary T and SSS in a group of adolescent boys [13], or between sensation-seeking and serum T in a group of 47 college age males [13].

Inconclusive results regarding the association of T and sensation-seeking may reflect the impact of other potential androgenic influences on sensation-seeking. For instance, two separate studies ([14,15]) report a positive association between 2D:4D digit ratio, thought to reflect *in utero* androgen exposure ([16]; though see [17]), and SSS among college age men.

Furthermore, the positive associations of T and sensation-seeking come predominately from individuals with recognized behavioral problems, such as alcoholism or ADHD. Meanwhile, allelic variation in the *DRD4* dopamine gene, with a focus on the 48-bp variable number of tandem repeats (VNTR) polymorphism in exon III of chromosome 11, implicates the dopaminergic system in the expression of

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behavioral impulses. In particular, the presence of the 7-repeat (7R+) allele, which has been associated with novelty-seeking in both humans (see [18] for a recent meta-analysis) and other animals [19,20] as well as financial risk taking [21,22], has also been implicated in alcoholism [23], behavioral disinhibition [24], impulsivity [25], and ADHD [26,27].

In rodents, T has been shown to be self-reinforcing; individuals will work to self-administer exogenous T [28]. Furthermore, this effect can be blocked by dopamine receptor agonists [28], implicating the dopaminergic reward system. However, despite evidence that T can affect the release of dopamine from dopaminergic neurons *in vitro* [29], the neurological effects of T remain unclear. In particular, it is unclear if T plays a role in the expression of behavioral impulses as well as dopaminergic reward.

Thus, in the current study, we sought to further clarify the relationship between T, the dopaminergic system, and sensation-seeking in young men. This was done by examining androgen exposure, variation in the D4 dopamine gene, and Zuckerman's SSS in a sample of U.S. college undergraduates. Along with salivary T as a measure of current exposure, we included 2D:4D digit ratio as a proxy for *in utero* T exposure, and facial masculinity as a reflection of pubertal T exposure [30–32].

Based on previous results [9,10,14,15,18], we predict that in a sample of healthy young men, 2D:4D, along with DRD4 7R+, will show a significant relationship with the overall measure of sensation-seeking, while salivary T levels will not. We make no prediction for facial masculinity given the lack of previous findings.

## 2. Materials and methods

### 2.1. Sample

Participants were recruited by fliers distributed on the Harvard University campus, as well as via email solicitation to undergraduate residential houses. All 98 subjects were between the age of 18 and 23 years. Subjects were excluded if they were currently on psychotropic medication or reported having been diagnosed with bipolar depression, pathological gambling and/or attention deficient hyperactivity disorder (ADHD). The Harvard and Binghamton institutional review boards approved all aspects of the study. Written consent was obtained from all subjects before participating in the study.

### 2.2. Data collection

For data collection, subjects came to a central location. After an explanation of the study procedures, each subject provided an unstimulated saliva sample by spitting through a straw into a vial [33]. Participants then swished 10 ml of Scope™ in their mouths for 45 s to obtain buccal cells for DNA analyses. Next, participants filled out a questionnaire, including Zuckerman's sensation-seeking scale [34] and background information. After completion of the questionnaire, anthropometric measures and a frontal facial photograph were obtained. Finally, both right and left hands were scanned.

### 2.3. Measures

#### 2.3.1. Sensation-seeking

Sensation-seeking was measured using Zuckerman's sensation-seeking scale (SSS) [34]. In addition to a total sensation-seeking score, this scale yields four sub-scores: SSS disinhibition, SSS thrill and adventure-seeking, SSS boredom susceptibility and SSS experience-seeking.

#### 2.3.2. Facial masculinity

Full frontal facial photographs were taken of all participants with glasses and head wear removed. Sexual dimorphism measures were taken

from points marked on facial features used in previous studies (see [35] for a diagram of point placement). The identification of these features has been found to be reliable in previous studies [36,37]. In total, four sexual dimorphism measurements were taken. These were Cheekbone Prominence (ChP, Upper Face Width/Low Face Width, Jaw Height/Lower Face Height (JH/LFH, D9/D8), Lower Face Height/Face Height (LFH/FH), and Face Width/Lower Face Height (FW/LFH). Each of the four scores were converted into z-scores and combined  $[JH/LFH + LFH/FH] - [ChP + FW/LFH]$  to generate a single measure with higher scores indicating a greater degree of masculinity.

These measurements have been found to be sexually dimorphic in previous studies [38], although it is unclear how much of the variation is due to variation in pubertal testosterone levels. However, it is clear that testosterone during puberty facilitates the growth of bone and bone mass [39]. The mandibular ramus length, upper anterior face height and total cranial base length were significantly shorter in boys with delayed puberty compared to controls [40]. Furthermore, boys given low doses of testosterone showed significantly higher growth rates of the mandibular length, ramus length, and upper and total face height relative to untreated controls matched for height.

#### 2.3.3. 2D:4D

Participants were also asked to put both their hands on a Canon CanoScan LiDE 70 scanner, where all hands were scanned. The 2nd and 4th digits on both left and right hands were later measured from the center of the flexion crease proximal to the palm to the top of the digit, using the Adobe Photoshop tool. Measurements were in pixels to two decimals. All scans were rated by one observer (AD) and when creases could not be clearly visualized, results from that individual were not used to minimize possible errors.

#### 2.3.4. Genotyping

Buccal cell samples for DNA analysis [41] were obtained from 98% (96/98) of the recruited male subjects. All collected samples were shipped to the Laboratory of Evolutionary Anthropology and Health at Binghamton University, New York. DNA was extracted using an abbreviated version of the silica extraction protocol [42] previously described by [43].

#### 2.3.5. DRD4 VNTR

The human *DRD4* gene on chromosome 11 contains a 48 bp variable number tandem repeat (VNTR) polymorphism in exon 3. Sufficient DNA for *DRD4* PCR amplification was extracted from 99% (95/96) of the buccal cell samples.

Previous studies have highlighted problems associated with consistent genotyping of the *DRD4* VNTR region [44], suggesting multiple PCR and electrophoresis runs for each sample to control for allelic dropout. Thus, the PCR reaction was modified to reflect the high GC content (see below) and all samples that were initially scored as homozygotes were reanalyzed two additional times with different starting template concentrations to unambiguously confirm genotypes. The PCR reaction consisted of 1× Q-Solution (Qiagen), 1× Buffer (Qiagen), 1 μM Primer 1 (5' GCGACTACGTGGTCTACTCG 3'), 1 μM Primer 2 (5' AGGACCTCATGGCCTTG 3'), 200 μM dATP, 200 μM dTTP, 200 μM dCTP, 100 μM dITP, 100 μM dGTP, 0.3 units HotStar Taq (Qiagen), and 1 μl of DNA template, in a total volume of 10 μl. The PCR profile began with 15 min at 95 °C for enzyme activation and denaturing of template DNA followed by 40 cycles consisting of 1 min denaturation at 94 °C, 1 min annealing at 55 °C, 1.5 min extension at 72 °C, and finished with a 10 min extension at 72 °C. Amplicons were electrophoresed through 1.4–2.0% agarose gels containing ethidium bromide and genotypes were determined by comparison with a 100 bp ladder.

DRD4 alleles observed included 2R ( $n=24$ ), 3R ( $n=6$ ), 4R ( $n=128$ ), 6R ( $n=1$ ) and 7R ( $n=24$ ). Subjects were scored on the basis of alleles with 7 or more repeats; those with 2 were classed as 1/,

those with one as l/s, and those 0 = s/s. Only one individual was l/l, so for the purpose of statistical analysis the l/l and l/s groups were combined leaving 7R+ (at least one allele of 7 repeats) or 7R- (both alleles less than 7 repeats).

### 2.3.6. Salivary testosterone

Saliva samples were collected from each participant upon arrival. Participants were asked to rinse out their mouth and then spit through a straw into a small polystyrene tube. All samples were collected between 1:00 pm and 3:00 pm on days between April 9 and June 5, 2007. Neither time of waking or food intake was assessed. Saliva samples were frozen on the same day they were supplied. All samples were assayed for testosterone in the Human Behavioral Endocrinology Laboratory at the University of Nevada, Las Vegas. Testosterone assays relied on commercially available EIA kits (Salimetrics 1-2402). Sample and standard reactions were run in duplicate and the sample concentrations used in the analyses are the averages of the duplicates. Interassay coefficients of variation were 13.2% for low pools and 7.1% for high pools. The intrassay coefficient of variation was 6.8%. No significant differences in testosterone concentrations were found between subjects as a function of the hour in which the samples were collected.

### 2.3.7. Ethnicity

Individuals were asked to report the ethnicity of all four of their grandparents. From that report 65 individuals were classified as European, 9 as Asian, 4 as Hispanic, 4 as African-American and 14 as other.

### 2.4. Statistical methods

To determine if the DRD4 7R+ allele was associated with SSS, *t*-tests were performed comparing the total SSS score and SSS subscales for 7R+ and 7R-. Next, Pearson correlations between the other (continuous) variables were calculated, with particular attention paid to how the three measures of testosterone exposure and 7R+ were correlated with the sensation-seeking subscales. Next, to determine if the relationship of testosterone exposure to sensation-seeking is altered by differences in the DRD4 genotype, the presence/absence of the 7R allele was added as a predictor to the best "androgen exposure" model, using linear regressions (ordinary least squares). The hypothesized interaction between androgen exposure variables and the presence of a 7R allele was then tested by adding an interaction term as a predictor in all of the models.

We did not use corrections for multiple tests because such corrections may be too conservative for hypothesis driven analyses [45,46], such as those used here.

## 3. Results

Descriptive statistics for the variables used in subsequent analyses are given in Table 1. Sample sizes vary due to missing data. The sensation-seeking scale has similar values to those reported for a similarly aged student population [47]. The salivary testosterone results are also consistent with other results for young males using this same assay [33].

Comparison of SSS and SSS subscale values for DRD4 7R+ and 7R- genotypes is shown in Table 2. Overall SSS scores ( $t = 2.1$ ;  $p = 0.04$ ) as well as SSS adventure and thrill-seeking ( $t = 3.1$ ;  $p = 0.03$ ) are higher among 7R+ individuals. Sexual orientation also differed between the genotypes ( $t = 2.8$ ;  $p = 0.007$ ), while measures of androgen exposure show no significant differences.

For the continuous variables, first order correlations are given in Table 3. Among the outcome variables, the sensation-seeking subscales show moderate significant and positive associations ( $r = 0.21$  to  $0.41$ ;  $p = 0.03$  to  $<0.001$ ). Among the predictor variables,

**Table 1**  
Descriptive statistics.

Variable	Average $\pm$ S.D. (n)
Age (years)	20.1 $\pm$ 1.5 (98)
Sensation-seeking	21.8 $\pm$ 6.2 (93)
Disinhibition	4.9 $\pm$ 2.1 (97)
Thrill and adventure-seeking	7.0 $\pm$ 2.6 (96)
Boredom Susceptibility	3.9 $\pm$ 1.7 (96)
Experience-seeking	6.0 $\pm$ 2.3 (94)
Sexual orientation	85 heterosexual 7 homosexual (92)
Testosterone	101.8 $\pm$ 35.6 (98)
Facial masculinity	-0.008 $\pm$ 2.1 (96)
Left 2D:4D ratio	0.95 $\pm$ .03 (87)
Right 2D:4D ratio	0.95 $\pm$ .03 (91)
DRD4 7+	74.5% (94)

left and right 2D:4D ratios also show a strong correlation ( $r = 0.70$ ;  $p < 0.001$ ) while salivary T, facial masculinity and both left and right 2D:4D ratio do not show a significant relationship, consistent with some previous findings [48,49] but contrary to [50]. In terms of androgen exposure, both salivary T ( $r = 0.24$ ;  $p = 0.02$ ) and facial masculinity ( $r = 0.20$ ;  $p = 0.05$ ) are positively and significantly correlated with SSS boredom susceptibility, while neither left nor right 2D:4D ratio show a significant association with any of the sensation-seeking scales.

Table 4 shows the results of separate multivariate regression models for androgen exposure and 7R+ as predictors for SSS and each of the four SSS subscales. The overall models explain only a small part of the variance, ranging from 0.04 to 0.10. In terms of specific aspects of sensation-seeking variables, both DRD4 7R+ ( $\beta = 0.21$ ;  $p = 0.05$ ) and salivary T ( $\beta = 0.21$ ;  $p = 0.05$ ) are significant predictors of overall

**Table 2**  
Sensation-seeking and androgen exposure by DRD4 genotype.

Variable	DR4 7R- (n)	DRD4 7R+ (n)
Disinhibition	4.7 $\pm$ 2.2 (69)	5.3 $\pm$ 1.8 (24)
Thrill and adventure-seeking	6.5 $\pm$ 2.8 (68)	8.1 $\pm$ 1.9** (24)
Boredom susceptibility	3.9 $\pm$ 1.7 (69)	4.0 $\pm$ 1.8 (24)
Experience-seeking	5.9 $\pm$ 2.4 (67)	6.5 $\pm$ 2.1 (24)
Sensation	20.8 $\pm$ 6.5 (66)	23.8 $\pm$ 5.0* (24)
Sexual orientation	1.1 $\pm$ 0.30 (68)	1.0 $\pm$ 0.00** (24)
Testosterone	102.3 $\pm$ 35.4 (70)	100.7 $\pm$ 36.2 (24)
Facial masculinity	-0.14 $\pm$ 2.2 (69)	-0.25 $\pm$ 2.0 (24)
Left 2D:4D ratio	0.95 $\pm$ 0.03 (62)	0.95 $\pm$ 0.03 (23)
Right 2D:4D ratio	0.95 $\pm$ 0.03 (66)	0.96 $\pm$ 0.03 (22)

\*  $p < 0.05$ .

\*\*  $p < 0.01$ .

**Table 3**  
Correlation between variables. Pearson correlations (sample sizes).

Variable	DIS	AD	Bore	Exper	Sex orient	FM	L2:4	R2:4	T
SENS	0.68*** (93)	0.72*** (93)	0.59*** (93)	0.79*** (93)	−0.22* (91)	0.06 (91)	0.03 (83)	−0.04 (83)	0.17 (93)
DIS		0.27** (96)	0.22* (96)	0.41** (94)	−0.33** (94)	−0.07 (95)	0.02 (86)	−0.04 (90)	0.03 (97)
AD			0.21* (95)	0.37** (93)	−0.04 (93)	−0.09 (94)	−0.12 (85)	−0.06 (89)	0.05 (96)
Bore				0.41** (94)	−0.02 (93)	0.20* (94)	0.11 (86)	−0.06 (89)	0.24* (96)
Exper					−0.23* (92)	0.12 (92)	0.11 (84)	0.05 (87)	0.17+ (94)
Sex orient						(0.09) (94)	0.15 (85)	0.07 (89)	0.05 (95)
FM							0.04 (86)	−0.04 (90)	−0.01 (96)
L2:4								0.70*** (81)	0.14 (89)
R2:4									0.12 (91)

SENS = sensation-seeking total score; DIS = disinhibition; AD = adventure-seeking; Bore = boredom susceptibility; Exper = experience-seeking; Sex orient = sexual orientation; 0 = homosexual, 1 = heterosexual; FM = facial masculinity; L2:4 = left 2D:4D; R2:4 = right 2D:4D. DRD4 = presence of the 7R allele.

\* p<.05.  
\*\* p<.01.  
\*\*\* p<0.001.

SSS. In addition, DRD4 7R+ is a significant predictor of SSS adventure and thrill-seeking ( $\beta = 0.28$ ;  $p = 0.01$ ) while salivary T  $\beta = 0.26$ ;  $p = .001$  and facial masculinity  $\beta = 0.20$ ;  $p = 0.05$  remain significant predictors of SSS boredom susceptibility.

We tested for the significant interactions between all of the measures of androgen exposure, including salivary T, 2D:4D and facial masculinity and DRD4 7R+. None of the interaction terms was significant and the results are not shown here.

**4. Discussion**

Our results indicate a significant association between salivary T and both total SSS score and SSS boredom susceptibility when DRD4 7R+ taken into account. At the same time, DRD4 7R+ was a significant predictor of both overall SSS and SSS thrill and adventure-seeking, whether controlled for androgen exposure or not. Thus given both the relatively small number and type of individuals sampled in previous studies it is possible that differences in previous findings on androgen exposure and sensation-seeking may reflect differences in the frequency of 7R+ individuals across studies.

**4.1. Comparison with previous studies**

Our findings of a significant relationship between salivary T and overall SSS when controlled for DRD4 7R+, are potentially consistent with previous reports of both a positive relationship between free T in

serum from 30 males and the total sensation-seeking score [8], and the finding of no association between salivary T and overall sensation-seeking in a sample of college age males [9], neither of which controlled for DRD4 7R+. On the other hand, the lack of an association between either right or left 2D:4D digit ratios and any of the sensation-seeking scales, even without taking DRD4 7R+ into account differs from two previous reports of a significant relationship between 2D:4D and overall sensation-seeking, among 87 male undergraduates in Canada [15], as well as 278 English and German undergraduates [14].

Thus while our results on salivary T suggest that previous findings could reflect differences in the frequency of 7R+ alleles associated with sample size and/or cultural and ethnic diversity between the U.S. (current study, [10]), and Spain [9]), they do little to clarify results on 2D:4D and sensation-seeking. Our own sample was ethnically diverse, with individuals of European, Africa, Hispanic and Asian ancestry, though there was no difference in any of our predictors or outcome variables by ethnicity.

**4.2. Novel findings**

On the other hand, our results linking DRD4 7R+ to sensation-seeking in men, with or without our without controlling for androgen exposure, are novel, potentially instructive, and may help to illuminate previous results regarding T and sensation-seeking. While DRD4 7R+ has been linked to novelty-seeking [18], as far as

**Table 4**  
Androgen exposure, DRD4 genotype and sensation-seeking.

	Disinhibition	Thrill and adventure	Boredom susceptibility	Experience	Sensation-seeking
Model adj. $r^2$	0.08	0.04	0.07	0.08	0.10
N	89	88	89	88	89
Variable	$\beta$	$\beta$	$\beta$	$\beta$	$\beta$
Sex orient	−0.33**	0.01	−0.05	−0.24*	−0.21*
Salivary T	0.07	0.07	0.26*	0.20+	0.21*
Face M.	−0.01	−0.03	0.20*	0.17	0.13
DRD4 7R+	0.07	0.28*	0.05	0.11	0.21*

Sexual orientation. 0 = homosexual; 1 = heterosexual. Data entered in italics represents the sample size (N).

+ p<0.1.  
\* p<0.05.  
\*\* p<0.01.

we are aware this is the first report of a significant association between *DRD4* 7R+ and Zuckerman's sensation-seeking scale.

The fact that previous studies have not reported a significant relationship between allelic variation in *DRD4* and Zuckerman's sensation-seeking scale [25,51,52] may reflect little more than the vagaries of behavioral genetic findings. However, it might also reflect differences in sample composition. Not only does the frequency of the 7R allele vary widely across populations [53], but its relationship with behavior may be mediated by SES [54]. Thus, differences between this study and that of [25], for example, may reflect socio-economic status (SES) differences between a sample drawn from a state school and that from an elite private college.

Without placing too much reliance on the separate SSS subscales, the pattern of results with salivary T, facial masculinity and *DRD4* and the various SSS subscales as a whole are suggestive. Previous animal studies have suggested that testosterone has an effect on reward though its actions on the dopaminergic mesolimbic system, particularly the nucleus accumbens [28,55]. Thus the association of facial masculinity and salivary T, but not *DRD4*, with boredom susceptibility suggests that T exposure may be related to reward dependency associated with the striatum where there are few *DRD4* receptors relative to *DRD2* receptors [56,57].

On the other hand, given the greater density of *DRD4* receptors in the prefrontal cortex [56,57], the significant relationship between 7R+ and the disinhibition subscale in this study implicates prefrontal dopaminergic activity in sensation-seeking. The 7R allele is thought to reduce the efficiency of the D4 dopamine receptor, decreasing the signal to noise ratio in the prefrontal cortex [58], and thus decreasing prefrontal function. Congdon et al. [24] have shown an association between 7R+ and behavioral inhibition on a go/no go task in adults, suggesting that the role of 7R+ in sensation-seeking is related to decreased behavioral inhibition.

The significant association of facial masculinity with boredom susceptibility is also novel and may bear further interpretation, given earlier results from this sample linking facial masculinity to financial risk taking [21]. Facial masculinity is thought to reflect the impact of increases in testosterone at puberty [30,31]. At the same time, the development of judgment and executive control during adolescence is thought to reflect changes in the cortical-thalamic-striatal loop [59,60]. Thus pubertal increases in testosterone could interact with the development of dopaminergic neurons in the cortical-thalamic-striatal system, perhaps by altering the release of storage of dopamine at the synapse [29] and help shape the development of behavior, including sensation-seeking. Support for a link between facial masculinity and endocrine variability comes from a recent study that found that testosterone response to competition varied by facial masculinity [61].

Several caveats are important here. First, at the statistical level, our results explain at most 10% of the variation for SSS and SSS subscales. Thus, other factors play a much bigger role than testosterone and *DRD4*; the interesting point here is that these two factors explain any of the variation in sensation-seeking. Second, while our sample size is larger than some previous studies of testosterone and sensation-seeking and includes a mix of ethnicities, it is still relatively small and represents a highly selected group of college age males at the peak of their testosterone levels. Whether similar results would be obtained in older men for instance is worth investigation.

Finally, our interpretation of the association of testosterone and sensation-seeking is premised on the assumption that testosterone has an effect on the dopaminergic system. We can't, however, rule out the possibility that testosterone exposure is associated with sensation-seeking through its association with genetic quality, health and immune function (see [62]), and/or perceived dominance (see [32,63]). We do note however, that in this sample salivary T is not significantly associated with facial asymmetry, a measure of long-term developmental stability.

## 5. Summary

Our results suggest that testosterone exposure and allelic variation in the D4 dopamine receptor gene play independent roles in sensation-seeking among young males. This may reflect separate impacts of testosterone on the dopaminergic reward system [28,55], and the association of *DRD4* with prefrontal behavioral inhibition [24]. Furthermore, the positive association of facial masculinity with boredom susceptibility suggests that developmental effects of testosterone during puberty [59,60] may play a significant role in the development of individual variation in sensation-seeking in young adulthood. More research is called for that considers the interaction of testosterone and the dopaminergic reward system in the development of sensation-seeking. In particular, neuroimaging studies using fMRI or PET could be used to examine the potential impact of androgens on dopaminergic activity and sensation-seeking in adolescence and young adulthood.

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