Brief report:

Interaction of the (CAG)_n polymorphism in the androgen receptor gene and oral contraceptive use on moral judgement in women

Diana Armbruster¹, Klaus-Peter Lesch², Alexander Strobel³

¹ Personality Psychology and Assessment, Institute of Psychology, Chemnitz University of Technology, Chemnitz, Germany

² Division of Molecular Psychiatry, Center of Mental Health, University of Wuerzburg, Wuerzburg, Germany; Laboratory of Psychiatric Neurobiology, Institute of Molecular Medicine, Sechenov First Moscow State Medical University, Moscow, Russia; Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience (MHeNS), Maastricht University, Maastricht, The Netherlands

³ Personality and Individual Differences, Faculty of Psychology, Technische Universität Dresden, Dresden, Germany

Correspondence: Diana Armbruster

Personality Psychology and Assessment, Institute of Psychology, Chemnitz University of Technology, 09120 Chemnitz, Germany

Phone: +49 371 531 39090

Fax: +49 371 531 28459

E-mail: diana.armbruster@psychologie.tu-chemnitz.de

Abstract

Biological factors including genetic variation are contributors to differences in moral decisions. Recently, Gong et al. (2017) reported that female carriers of more shorter alleles of the functional (CAG)_n polymorphism in the androgen receptor (AR) gene showed enhanced endorsement of harmful actions. We aimed to replicate and extend these findings. $N = 155$ healthy young adults of Western European/German origin were genotyped for the AR (CAG)_n polymorphism and completed a set of moral dilemmas that are designed to allow an estimation of underlying utilitarian and deontological tendencies in addition to the traditional moral score. While AR (CAG)_n genotype did not affect moral judgement in men, there were (CAG)_n $\times$ endocrine status interactions in the female sample, particularly on deontology. Women using oral contraceptives who carried two short (CAG)_n alleles had reduced levels of deontology compared to carriers of long (CAG)_n alleles. Descriptively, the opposite pattern emerged for free cycling women. The findings underscore the importance of androgenic function for moral judgement and highlight the modulatory role of exogenous steroids.

Key words: moral judgement, deontology, utilitarianism, androgen receptor gene, CAG repeat polymorphism; combined oral contraceptives

1 Introduction

There is an ongoing research effort to investigate correlates and potential causes of differences in moral sentiments and judgements. One growing area of research focusses on biological factors (Reese et al., 2020) including genetic variation (Smith & Hatemi, 2020). Recently, Gong et al. (2017) reported in a sample of Han Chinese an effect of the trinucleotide (CAG) repeat polymorphism in exon 1 of the androgen receptor (AR) gene on the permissibility of harmful actions in women but not in men. Located on chromosome Xq11.2, AR expression is in part modulated by the (CAG)_n polymorphism (Takeyama et al., 2002). Less repeats, i.e., shorter (S) alleles, are associated with increased transcription and enhanced receptor sensitivity towards testosterone compared to longer (L) alleles (Irvine et al., 2000). Testosterone, in turn, is a modulator of moral decision-making and has additionally been linked to intermediate variables underlying moral judgements, e.g., empathy (e.g., Nitschke & Bartz, 2020), psychopathy (review: Yildirim & Derksen, 2012), and risk affinity (review: Kurath & Mata, 2018). Testosterone has been associated—although inconsistently—with enhanced endorsement of harmful actions serving the greater good (e.g., Carney & Mason, 2010). Correspondingly, Gong et al. (2017) reported increased permissibility ratings of harmful actions in women with more copies of AR (CAG)_n S alleles, i.e., genotypes which result in increased AR sensitivity.

Gong et al. (2017) pointed out that their results might be either due to an enhanced (utilitarian) bias towards overall beneficial outcomes, a reduced aversion to inflict harm (i.e., a disregard for deontological principles), or both. One way to solve this issue is the use of a process dissociation (PD) approach as has been suggested by Conway and Gawronski (2013). Briefly, the approach is based on parallel *congruent* and *incongruent* versions of moral dilemmas. *Incongruent* dilemmas pit deontological and utilitarian principles against each other by proposing harmful actions, which are offset by outcomes outweighing concurrent harm and maximize the

greater good. Contrariwise, in *congruent* dilemmas the harm inflicted is not outweighed by the outcome. Thus, the PD approach disentangles deontological and utilitarian inclinations underlying moral decisions (Conway & Gawronski, 2013) and can help to elucidate the reasons for an increased acceptance of harmful actions as observed in female carriers of *AR* (CAG)_n S alleles (Gong et al., 2017).

We used German versions of the dilemma set of Conway & Gawronski (2013) and aimed to (1) replicate the findings of Gong et al. (2017) in a European sample and to (2) extend them by investigating whether potential differences in moral judgements are due to variations in underlying utilitarianism, deontology, or both (cf. Conway & Gawronski, 2013). Since there is evidence that combined oral contraceptives (COC) modulate social cognition (Montoya & Bos, 2017), we included endocrine status (men vs. free cycling women vs. women using COC) in our analyses.

2 Materials and Methods

We report how we determined our sample size (see supplement), all data exclusions, all manipulations, and all measures in the study (Simmons et al., 2012). All materials, data, and analyses of this study are available online (<https://osf.io/yx3fa/>).

2.1 Participants

We recruited 158 participants at the Technische Universität Dresden. Due to technical problems, one session had to be aborted prematurely leaving 157 young adults of Western European/German origin (men: $n = 71$, 25.31 ± 4.30 years; women: $n = 86$, 23.31 ± 3.35 years). Free

cycling female participants took part during the early follicular or late luteal phase while COC users participated during active pill use (see supplement for further details).

2.2 Procedure

A detailed description of the study protocol can be found in the supplement. Briefly, after a 5-minutes resting period, during which electro-cardiographic and electro-dermal activity was assessed (data not reported here), participants completed a German version of the moral dilemma paradigm (cf. Conway & Gawronski, 2013) followed by personality questionnaires and the collection of saliva samples for later genotyping. The study was approved by the ethics committee of the Technische Universität Dresden (EK 225052019).

2.3 Genotyping

Genotyping for the *AR* (CAG)_n polymorphism followed the protocol used by Gong et al. (2017) as did S (≤ 22 repeats) and L (> 22 repeats) allele designations. In the female sample, genotype distribution was as follows: LL $n = 12$ (14%), SL $n = 46$ (53.5%), SS $n = 28$ (32.5%). In the male sample, $n = 26$ (37.7%) carried the L allele and $n = 43$ (62.3%) the S allele. Genotyping was unsuccessful in two men. Information on allele distributions are included in the supplement.

3.4 Statistical Analyses

We conducted an ANOVA with *AR* (CAG)_n genotype and endocrine status as between-subjects factors. Outcome variables were moral judgement parameters, i.e., (1) the proportion of decisions for outcome-based options in *incongruent* dilemmas (= traditional score), (2) estimated

utilitarianism, and (3) estimated deontology (cf. Conway & Gawronski, 2013). Ancillary analyses were performed to investigate potential effects of *AR* (CAG)_n genotype and endocrine status on response times and perceived difficulty in making moral decisions.

3 Results

Analysis in the total sample found no main effect of the *AR* (CAG)_n polymorphism on the traditional moral dilemma score ($F_{1,149} = 0.58$, $p = .449$, $\eta_p^2 = 0.004$), utilitarianism ($F_{1,149} = 0.18$, $p = .669$, $\eta_p^2 = 0.001$), or deontology ($F_{1,149} = 2.47$, $p = .118$, $\eta_p^2 = 0.016$). However, there was an interaction effect between endocrine status (men vs. free cycling women vs. COC users) and the *AR* (CAG)_n polymorphism on deontology ($F_{2,149} = 5.55$, $p = .005$, $\eta_p^2 = 0.069$; Figure 1) but not on the traditional score ($F_{2,149} = 2.33$, $p = .101$, $\eta_p^2 = 0.030$) or utilitarianism ($F_{2,149} = 0.19$, $p = .828$, $\eta_p^2 = 0.003$).

Figure 1: Mean deontology ($\pm$ SEM) as a function of *AR* (CAG)_n genotype and endocrine status.

Additional post hoc analyses in the female subsample (Supplemental Figure S1) confirmed the interaction effect between the *AR* (CAG)_n polymorphism and endocrine status on deontology ($F_{1,82} = 11.52, p = .001, \eta_p^2 = 0.123$). The interaction effect on the traditional score was also significant ($F_{1,82} = 4.82, p = .031, \eta_p^2 = 0.056$) while there was again no effect on utilitarianism ($p = .672$). In COC users, *AR* (CAG)_n SS homozygotes showed significantly reduced deontology ($F_{1,37} = 16.22, p \leq .001, \eta_p^2 = 0.305$) and had a higher proportion of outcome-based decisions (= traditional score; $F_{1,37} = 5.00, p = .031, \eta_p^2 = 0.119$) compared to L allele carriers. On a descriptive level, the opposite pattern emerged in free cycling women, although none of the effects reached significance (all $p \geq .299$). Furthermore, there was no effect of the *AR* (CAG)_n polymorphism in the male sample on any of the three moral judgement parameters (all $p \geq .913$).

Ancillary analyses of *response times* and *difficulty ratings* found no main effect of *AR* (CAG)_n ($p = .967$ and $p = .196$). There were also no interactions between genotype and endocrine status ($p = .334$ and $p = .119$) or between genotype and dilemma type (*congruent* vs. *incongruent*; $p = .584$ and $p = .234$). However, while the three-way interaction between (CAG)_n $\times$ endocrine status $\times$ dilemma type did not reach significance for *response times* ($p = .067$), it was significant for *difficulty ratings* ($F_{2,149} = 4.49, p = .013, \eta_p^2 = 0.057$). The effect was limited to *incongruent* dilemmas ($p = .007$; Supplemental Figure S2). In free cycling women, *AR* (CAG)_n SS genotypes rated moral decisions as more difficult compared to L allele carriers ($F_{1,45} = 7.16, p = .010, \eta_p^2 = 0.138$) while the opposite was found in women using contraceptives although the effect did not reach significance ($F_{1,37} = 2.91, p = .097, \eta_p^2 = 0.073$). In men, there were no differences between *AR* (CAG)_n genotypes ($p = .415$).

4 Discussion

Similar to Gong et al. (2017) we found no effect of the functional AR (CAG)_n polymorphism on moral judgement in men. However, in women there was an interaction effect between endocrine status and AR (CAG)_n on *deontology* and the traditional moral dilemma score, i.e., the proportion of outcome-based decisions that endorse harmful actions for the ‘greater good’. COC users with two (CAG)_n S alleles were more likely to opt for harmful choices that were nevertheless overall beneficial compared to L allele carriers. Analysis of underlying tendencies revealed that this was due to decreased *deontological* inclinations while there was no difference in utilitarianism between the genetic groups. On a descriptive level, the opposite was observed in free cycling women. In extension to Gong et al. (2017), our results indicate that while AR (CAG)_n genotype in interaction with endocrine status modulated the predisposition towards *deontological* rules (e.g., do no harm), consideration of the overall outcome and greater benefit (i.e., utilitarian tendencies) was unaffected. In addition, AR (CAG)_n genotype and endocrine status also affected difficulty ratings in *incongruent* dilemmas in women. In free cycling women, carriers of (CAG)_n L alleles reported *less* difficulty in making moral decisions compared to SS genotypes, while the opposite tendency was found in COC users. Thus, groups with reduced deontological inclinations also tended to report less difficulty in making moral decisions.

Although oral contraceptives are available in more than 40 different formulations (cf. Taylor et al., 2020), one general effect is the reduction of endogenous estrogens and progesterone while maintaining high levels of their synthetic counterparts (Burkman et al., 2011). So far, interaction effects of high exogenous and low endogenous steroid levels on downstream physiological and psychological processes are not exactly clear (Lewis et al., 2019). Furthermore, while endogenous androgen levels (e.g., testosterone) decrease in COC users as well, androgen receptor

signaling can be affected in various ways since synthetic progestogens also bind to the AR—with differing affinity (Burkman et al., 2011). Depending on progestin type, potential effects range from strongly androgenic to strongly anti-androgenic (Taylor et al., 2020). Thus, in addition to genetic variations, AR signaling in COC users also depends on COC formulation, which might partly explain the diverging findings in free cycling women vs. COC users.

There are several differences between our study and the study by Gong et al. (2017). We used a different dilemma set which allowed the investigation of underlying moral inclinations by using a PD approach (cf. Conway & Gawronski, 2013). Nevertheless, dilemma content features differed and might have contributed to the results. Furthermore, there are ethnic and cultural differences. While the sample of Gong et al. (2017) consisted of Han Chinese, our participants were of Western European/German origin. Our sample was also significantly older (24.2 ± 3.9 years vs. 20.4 ± 1.2 years, $t_{594} = 18.17$, $p \leq .001$, Hedges' $g = 1.69$). Limitations of our study include a rather small sample size and a predominantly student sample. Despite these differences and limitations, our findings provide further evidence that *AR* (CAG)_n genotype and oral contraceptive use are associated with differences in moral judgement in women.

Acknowledgments

We would like to thank Lara Schreiter for helping conducting the lab sessions and Nicole Schraud (University of Wuerzburg, Germany) for DNA sample processing and genotyping. We also thank Dr. Gawnhi Park (Hope College, MI, USA) and Dr. Paul Conway (Florida State University, FL, USA) for additional information on their original study designs, which we adapted, and for recommendations on analyzing the moral judgement data.

Conflict of interest

The authors declare no conflict of interest.

Funding

This work was partly funded by the Deutsche Forschungsgemeinschaft (DFG), grant number SFB 940/2.

References

- Burkman, R., Bell, C., & Serfaty, D. (2011). The evolution of combined oral contraception: improving the risk-to-benefit ratio. *Contraception*, 84(1), 19-34. <https://doi.org/10.1016/j.contraception.2010.11.004>
- Carney, D. R., & Mason, M. F. (2010). Decision making and testosterone: When the ends justify the means. *Journal of Experimental Social Psychology*, 46(4), 668-671. <https://doi.org/10.1016/j.jesp.2010.02.003>
- Conway, P., & Gawronski, B. (2013). Deontological and utilitarian inclinations in moral decision making: a process dissociation approach. *Journal of Personality and Social Psychology*, 104(2), 216-235. <https://doi.org/10.1037/a0031021>
- Gong, P., Fang, P., Yang, X., Ru, W., Wang, B., Gao, X., & Liu, J. (2017). The CAG polymorphism in androgen receptor (AR) gene impacts the moral permissibility of harmful behavior in females. *Psychoneuroendocrinology*, 80, 74-79. <https://doi.org/10.1016/j.psyneuen.2017.03.008>
- Irvine, R. A., Ma, H., Yu, M. C., Ross, R. K., Stallcup, M. R., & Coetzee, G. A. (2000). Inhibition of p160-mediated coactivation with increasing androgen receptor polyglutamine length. *Human Molecular Genetics*, 9(2), 267-274. <https://doi.org/10.1093/hmg/9.2.267>
- Kurath, J., & Mata, R. (2018). Individual differences in risk taking and endogenous levels of testosterone, estradiol, and cortisol: A systematic literature search and three independent meta-analyses. *Neuroscience & Biobehavioral Reviews*, 90, 428-446. <https://doi.org/10.1016/j.neubiorev.2018.05.003>
- Lewis, C. A., Kimmig, A. S., Zsido, R. G., Jank, A., Derntl, B., & Sacher, J. (2019). Effects of Hormonal Contraceptives on Mood: A Focus on Emotion Recognition and Reactivity, Reward Processing, and Stress Response. *Current Psychiatry Reports*, 21(11), 115. <https://doi.org/10.1007/s11920-019-1095-z>

- Montoya, E. R., & Bos, P. A. (2017). How Oral Contraceptives Impact Social-Emotional Behavior and Brain Function. *Trends in Cognitive Sciences*, 21(2), 125-136. <https://doi.org/10.1016/j.tics.2016.11.005>
- Nitschke, J. P., & Bartz, J. A. (2020). Lower digit ratio and higher endogenous testosterone are associated with lower empathic accuracy. *Hormones and Behavior*, 119, 104648. <https://doi.org/10.1016/j.yhbeh.2019.104648>
- Reese, M., Bryant, D., & Ethridge, L. (2020). Biomarkers for moral cognition: Current status and future prospects for neurotransmitters and neuropeptides. *Neuroscience & Biobehavioral Reviews*, 113, 88-97. <https://doi.org/10.1016/j.neubiorev.2020.03.009>
- Simmons, J., Nelson, L., & Simonssohn, U. (2012). A 21 Word Solution. Available at SSRN: <https://ssrn.com/abstract=2160588> or <http://dx.doi.org/10.2139/ssrn.2160588>.
- Smith, K., & Hatemi, P. K. (2020). Are Moral Intuitions Heritable? *Human Nature*, 31, 406–420. <https://doi.org/10.1007/s12110-020-09380-7>
- Takeyama, K., Ito, S., Yamamoto, A., Tanimoto, H., Furutani, T., Kanuka, H., Miura, M., Tabata, T., & Kato, S. (2002). Androgen-dependent neurodegeneration by polyglutamine-expanded human androgen receptor in *Drosophila*. *Neuron*, 35(5), 855-864. [https://doi.org/10.1016/s0896-6273\(02\)00875-9](https://doi.org/10.1016/s0896-6273(02)00875-9)
- Taylor, C. M., Pritschet, L., & Jacobs, E. G. (2020). The scientific body of knowledge - Whose body does it serve? A spotlight on oral contraceptives and women's health factors in neuroimaging. *Frontiers in Neuroendocrinology*, 60, 100874. <https://doi.org/10.1016/j.yfrne.2020.100874>
- Yildirim, B. O., & Derksen, J. J. (2012). A review on the relationship between testosterone and the interpersonal/affective facet of psychopathy. *Psychiatry Research*, 197(3), 181-198. <https://doi.org/10.1016/j.psychres.2011.08.016>