Genetic Placebo Effect on Psychological Resilience:

The Moderating Role of Self-compassion

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Abstract

The genetic placebo effect comprises the gene-related psychological, physiological and behavioral changes resulting from merely receiving genetic information. Although previous studies have found a genetic placebo effect resulting from fake genetic feedback, it is unclear whether the genetic placebo effect can occur independent of actual genetic dispositions and whether the genetic placebo effect varies across participants. Our research aimed to address this gap by testing the genetic placebo effect on psychological resilience when taking the impact of genes into consideration and investigating the moderating effect of self-compassion on the genetic placebo effect. Experiment 1 contained two groups of participants, a before-feedback group and an after-feedback group, whose psychological resilience was measured before (after) receiving genetic feedback about psychological resilience. We observed a weak genetic placebo effect independent of the impact of genes, indexed by the higher correlation between the genetic score and psychological resilience score in the after-feedback group. Moreover, self-compassion moderated the genetic placebo effect, and the participants with higher self-compassion were more sensitive to genetic feedback. These findings were replicated in experiment 2, in which we randomly gave genetic feedback to participants, reporting genetic predispositions of high or low psychological resilience. Our research enhanced the ecological validity of the genetic placebo effect and brought us insights into the use of genetic testing and feedback.

Keywords: genetic placebo effect, psychological resilience, self-compassion, genetic feedback

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Introduction

In recent years, genetic testing has become increasingly prevalent due to its decreased costs and broad application in precision medicine¹. On the one hand, genetic testing can help people learn their own risk of developing certain diseases, thereby motivating them to take effective measures to prevent these illnesses in advance². On the other hand, genetic feedback may alter individuals' mindsets and the mental frames that guide individuals' expectations and instruct individuals' responses to be consistent with these expectations^{3,4}, leading to some gene-related physiological, behavioral and psychological changes⁵⁻⁷. With this psychological impact of genetic feedback, which is referred to as the genetic placebo effect, genetic feedback indicating a high risk of certain features may increase individuals' risk of suffering from these features⁶.

Previous studies have mainly tested the genetic placebo effect by randomly providing fake genetic feedback to participants and reporting a genetic risk of certain diseases or no genetic risk⁵⁻⁷. Although this approach can effectively balance the impacts of genes across groups, it ignores the potential interaction between the impact of genes and the genetic placebo effect. To address this problem, we planned to test the genetic placebo effect by giving actual genetic feedback to participants in experiment 1.

We focused on the genetic placebo effect on psychological resilience because of its importance in individuals' well-being. Psychological resilience is "the process of, capacity for, or outcome of successful adaption despite challenging or threatening circumstances"⁸. As an important adaptive capacity, psychological resilience can enhance an individual's sense of well-being⁹, academic performance¹⁰ and working engagement¹¹ and is linked to a decreased risk of depression¹², posttraumatic stress disorder¹³ and obsessive-compulsive symptoms¹⁴. Additionally, the genetic placebo effect may vary across participants. Previous studies on the traditional placebo effect (an inert substance or treatment can lead to personal psychological or physiological changes and thereby improve symptoms^{15,16}) have found that individuals' sensitivities

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75 to the placebo effect are linked to certain personality traits^{17,18}. Researchers also found
76 that genetic explanations can alter self-concepts, such as by decreasing one's self-
77 efficacy¹⁹, which may thereby transform one's behavior²⁰. Therefore, one intuition was
78 to investigate whether individuals' attitudes toward themselves may influence their
79 sensitivities to the genetic placebo effect.

80 Self-compassion, a healthy attitude toward oneself, may be linked to individual
81 differences in the genetic placebo effect. Self-compassion consists of three basic
82 components²¹: self-kindness (versus self-judgment) involves treating oneself with
83 kindness and understanding instead of acute judgment and self-criticism; common
84 humanity (versus isolation) involves realizing that personal experiences are part of the
85 larger human experience; and mindfulness (versus overidentification) involves facing
86 personal painful thoughts and feelings with balanced awareness instead of
87 overidentification. People with high self-compassion can embrace all aspects of
88 personal experience, both success and failure, with open-hearted awareness²², therefore
89 leading to nonjudgmental acceptance of current experiences²³. Thus, people with high
90 self-compassion may be more likely to acknowledge their genetic susceptibility
91 information as part of themselves and adjust their own behavioral and psychological
92 performances to be consistent with the genetic feedback. Therefore, we hypothesized
93 that self-compassion may moderate individuals' sensitivities to the genetic placebo
94 effect and that people with higher self-compassion may show higher sensitivities to the
95 genetic placebo effect.

96 Thus, to investigate whether the genetic placebo effect occurs independently of
97 the impact of genes, we used a large sample to test the genetic placebo effect on
98 psychological resilience by providing genetic feedback to participants according their
99 actual genetic information in experiment 1. We also measured participants' self-
100 compassion to explore the moderating effect of self-compassion on the genetic placebo
101 effect. Moreover, to further exclude the confounding effect of irrelevant variables, we
102 designed a lab experiment to further test the moderating effect of self-compassion by

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randomly giving genetic feedback to participants in experiment 2, reporting genetic predispositions of high or low psychological resilience.

Results and Discussions

The Impact of Genes on Psychological Resilience

In the before-feedback group, the correlation between the polygenetic score and psychological resilience score was insignificant ($r(3303) < -.01, p = .942$). The correlation remained insignificant after including covariates ($r(3285) = .01, p = .446$), suggesting no significant association between polygenetic scores and the psychological resilience score.

The Genetic Placebo Effect of Psychological Resilience

In the after-feedback group, the correlation between the genetic score and psychological resilience score was insignificant ($r(856) = .06, p = .102$). However, after including covariates, the correlation became significant ($r(848) = .07, p = .049$), suggesting a weak genetic placebo effect.

The Moderating Effect of Self-compassion

We found a significant three-way interaction effect between the genetic score of psychological resilience, feedback group and self-compassion total score on the psychological resilience score ($B = 0.15, SE = 0.05, t = 3.05, p = .002, 95\% CI [0.05, 0.24]$). In the before-feedback group, the main effect of the genetic score was insignificant ($B = 0.01, SE = 0.01, t = 0.67, p = .505, 95\% CI [-0.01, 0.03]$), suggesting no significant direct genetic influence on the psychological resilience score. In the after-feedback group (see [Figure 2A](#)), people with high self-compassion total scores showed a positive correlation between the genetic score and the psychological resilience score ($B = 0.08, SE = 0.03, t = 2.51, p = .012, 95\% CI [0.02, 0.13]$), while this correlation was insignificant in those with low self-compassion total scores ($B < 0.01, SE = 0.03, t = 0.06, p = .956, 95\% CI [-0.06, 0.06]$). The included covariates did not change the direction or significance of our results (see Table S8 and Figure S2A).

In experiment 1, we found that the after-feedback group showed a weak genetic placebo effect and that self-compassion moderated individuals' sensitivities to genetic feedback. Specifically, we observed a stronger genetic placebo effect in individuals with higher self-compassion. However, in experiment 1, the participants subjectively chose whether to view their genetic report before they completed the questionnaires, which may have confounded the moderating effect of self-compassion. Therefore, in experiment 2, we designed a lab experiment to further test the genetic placebo effect and the moderating effect of self-compassion by randomly assigning genetic feedback to the participants.

Experiment 2

The Genetic Placebo Effect of Psychological Resilience

The independent-samples *t*-test revealed that the high-psychological-resilience feedback group had higher psychological resilience score than the low-psychological-resilience feedback group ($t(179) = 3.12$, $SE = 0.10$, $p = .002$, Cohen's $d = 0.46$). The difference remained significant after including covariates ($B = 0.24$, $SE = 0.09$, $t = 2.80$, $p = .006$, 95% *CI* [0.08, 0.40]), suggesting a medium genetic placebo effect.

The Moderating Effect of Self-compassion

We found a significant two-way interaction effect of group and self-compassion on the psychological resilience score ($B = 0.82$, $SE = 0.27$, $t = 3.06$, $p = .003$, 95% *CI* [0.29, 1.35]). Among those with high self-compassion total scores (see [Figure 2B](#)), the high-psychological-resilience feedback group had higher psychological resilience scores than the low-psychological-resilience feedback group ($B = 0.58$, $SE = 0.13$, $t = 4.40$, $p < .001$, 95% *CI* [0.32, 0.84]), while among those with low self-compassion total scores, the psychological resilience scores did not significantly differ between groups ($B = 0.03$, $SE = 0.13$, $t = 0.24$, $p = .812$, 95% *CI* [-0.23, 0.30]). The covariates did not change the direction or significance of our results (see Table S10 and Figure S4A). Thus, these results replicated the findings of a moderating role of self-compassion in experiment 1.

The Exploratory Mediation Analysis

We aimed to explore whether authenticity perception mediated the moderating effect of the self-compassion total score. The main effect of the self-compassion total score on authenticity perception was significant ($B = 0.64$, $SE = 0.19$, $t = 3.29$, $p = .001$, 95% CI [0.25, 1.02]). The two-way interaction effect of authenticity perception and group on the psychological resilience score was also significant ($B = 0.85$, $SE = 0.09$, $t = 9.73$, $p < .001$, 95% CI [0.67, 1.02]). The bootstrap CI of the conditional indirect effect excluded zero (95% CI [0.13, 0.97]), and the direct moderating effect of the self-compassion total score became insignificant ($B = 0.29$, $SE = 0.22$, $t = 1.33$, $p = .187$, 95% CI [-0.14, 0.73]), suggesting that authenticity perception fully mediated the moderating effect of the self-compassion total score on the genetic placebo effect. The conditional indirect effect of authenticity perception remained significant after including covariates in the model (see Figure S5).

In our research, we did not find a significant association between polygenetic scores and the psychological resilience score. However, we observed a weak genetic placebo effect independent of the impact of genes, indexed by the higher correlation between the genetic score and psychological resilience score in the after-feedback group. Moreover, we found that self-compassion moderated individuals' sensitivities to the genetic placebo effect, which was mediated by the authenticity perception toward genetic feedback, and those with higher self-compassion were more sensitive to the genetic placebo effect. This moderating effect was robust and further validated in experiment 2.

Our research did not detect a significant direct genetic impact on psychological resilience, indexed by the insignificant correlation between the genetic score and psychological resilience score in the before-feedback group. Previous studies have shown that the SNPs we used to calculate the genetic score, rs1033962 and rs1360780, are closely linked to psychological resilience. A genome-wide association study revealed the link between rs1033962 and PTSD²⁴, suggesting an impact of rs1033962

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on stress-related responses. The rs1360780 T-allele is associated with stress-related brain structures and neural activities because people carrying T alleles show smaller gray matter volume in the dACC²⁵ and higher activities of the amygdala when facing negative emotional stimuli²⁶. Although these two SNPs are closely linked to psychological resilience, we did not observe a significant correlation between the genetic score and psychological resilience score in the before-feedback group. One explanation was that the effect size of single genetic variants on psychological resilience was small, so our analysis did not have enough power to detect the relationship between these SNPs and the psychological resilience score³³. Future research should address this problem by calculating a polygenic score of psychological resilience for each participant and testing the impact of genes on psychological resilience by analyzing the correlation between the polygenic score and the psychological resilience score³³.

Consistent with previous findings, we observed the genetic placebo effect in both experiments 1 and 2. Previous studies have found that only the receipt of genetic information can result in gene-related transformations in physiological, psychological and behavioral performances⁵⁻⁷. Our research extended previous studies by considering the impact of genes and revealed that the genetic placebo effect can occur independently of the impact of genes. We also noticed that the genetic placebo effect in experiment 2 was much stronger, which can be explained by the differences in experimental designs. In experiment 2, the participants' psychological resilience was measured immediately after they received genetic feedback, while in experiment 1, some participants' psychological resilience was measured after a short time interval. Since the effect of test results can decrease over time³⁴, the genetic placebo effect in experiment 1 may have dissipated over the time interval, which weakened its impact on participants' psychological resilience scores.

We also found that the genetic placebo effect varied across participants and was moderated by self-compassion. This result was consistent with previous findings that

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individuals' personality traits were linked to their sensitivities to the traditional placebo effect^{17,18}. Consistent with our hypotheses, self-compassion moderated individuals' sensitivities to the genetic placebo effect, and those with higher self-compassion were more sensitive to the genetic placebo effect. High self-compassion may enable individuals to nonjudgmentally accept their genetic susceptibility information with open-hearted awareness^{22,23} and integrate these genetic messages into their self-concepts, resulting in higher authenticity perception toward genetic feedback. This high authenticity perception may lead to psychological changes consistent with this genetic susceptibility information, thereby promoting the genetic placebo effect.

We acknowledge that our research has some limitations. First, since people's beliefs about genetic explanations vary from trait to trait³⁵, whether our results can be generalized to the genetic placebo effect on other traits remains unclear. If people believe that genes account for a larger proportion of the phenotypic variance in a trait, the genetic placebo effect may be more prominent. Therefore, future research can explore the genetic placebo effect on other traits (e.g., loneliness and well-being) and retest the moderating effect of self-compassion on that genetic placebo effect. Second, regarding the moderating effect of self-compassion, we may ignore the potential impact of environmental variables. The interactionist perspective stresses that the moderating effect of personality traits on the placebo effect depends on contextual factors³⁶. In other words, under certain conditions, self-compassion may enhance individuals' sensitivities to the genetic placebo effect, while under other conditions, self-compassion may decrease or maintain individuals' sensitivities to the placebo effect. Therefore, future studies should discuss the impact of contextual factors (e.g., parenting rearing styles) on the moderating effect of self-compassion.

To conclude, our research complemented previous studies by revealing that the genetic placebo effect can occur independently of the impact of genes and thereby enhances the ecological validity of the genetic placebo effect because we provided actual genetic feedback to individuals rather than false genetic feedback. Moreover, our

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results extended previous studies by pointing out that the genetic placebo effect varied across participants, which was moderated by self-compassion, and those with higher self-compassion were more sensitive to the genetic placebo effect. This result calls for extra caution when providing genetic feedback to people with high self-compassion and help genetic testing serve us better.

Materials and Methods

Experiment 1

Participants

We recruited 4163 participants from the GeseDNA platform and provided 80 RMB yuan compensation. This whole sample contained two groups, with $n = 3305$ participants in the before-feedback group ($M_{\text{age}} = 26.75$, $SD = 6.36$, 1574 females) and $n = 858$ participants in the after-feedback group ($M_{\text{age}} = 28.36$, $SD = 6.96$, 379 females); the psychological resilience of the participants was measured before and after they received genetic feedback on psychological resilience. This research was approved by the local ethical committee, and all the participants provided informed consent before the experiment.

Measures

Genetic Score of Psychological Resilience. We collected the participants' saliva and conducted genetic testing on the GeseDNA platform (<https://www.gesedna.com/>). According to the protocol published by Illumina, genotyping of 700,079 SNPs was performed by using the Illumina® Global Screening Array (GSA) (Illumina, San Diego, California, USA). For quality controls, participants were removed if they had low genotyping call rates (lower than 97%), and SNPs with call rates lower than 95% were eliminated.

Previous studies suggested two candidate single nucleotide polymorphisms (SNPs) related to psychological resilience: rs1033962 located on chromosome 10-24927877 (GRCh38.p13) and in the PRTFDC1 gene and rs1360780 located on chromosome 6-35639794 (GRCh38.p13) and in the FKBP5 gene. We assessed Hardy–

Weinberg equilibrium (HWE) with the online calculator (<http://www.dr-petrek.eu/documents/HWE.xls>; accessed July 2021). We found no significant deviation in the genotype distribution of rs1033962 and rs1360780 from HWE in our sample (rs1033962:CC:50%; TC:41%; TT:8%; $p > .999$; rs1360780:CC:54%; TC:39%; TT:7%; $p > .999$). A genome-wide association study revealed that rs1033962 in the PRTFDC1 gene was associated with posttraumatic stress disorder (PTSD)²⁴, indicating its impacts on stress-related responses. The rs1360780 T-allele is linked to stress-related brain structures and neural activities because T carriers show a smaller gray matter volume in the dACC²⁵ and higher activities of the amygdala when facing negative emotional stimuli²⁶. For these SNPs, more T alleles pose a higher risk of low psychological resilience, so we calculated the total number of T alleles of these two SNPs as the genetic score of psychological resilience (1 = *the lowest psychological resilience*, 5 = *the highest psychological resilience*).

Psychological Resilience Score. Psychological resilience was measured with the Brief Resilience Scale²⁷, a 5-point Likert scale (1 = *totally disagree*, 5 = *totally agree*) with 6 items ($\alpha = .83$).

Self-compassion. Self-compassion was evaluated by the Chinese version of the Self-compassion Scale-Short Form (SCS-SF)^{28,29}, which includes 12 items scored on a 5-point Likert scale (1 = *totally not matched*, 5 = *totally matched*). The scale consists of six subscales: self-kindness ($\alpha = .81$), common humanity ($\alpha = .67$), mindfulness ($\alpha = .62$), self-judgment ($\alpha = .34$), isolation ($\alpha = .60$) and overidentification ($\alpha = .63$). We calculated the composite score of positive self-compassion by averaging the scores of self-kindness, common humanity and mindfulness. Similarly, we calculated the composite score of negative self-compassion by averaging the scores of self-judgment, isolation and overidentification. Additionally, we reversed the negative self-compassion score and calculated the mean of the positive self-compassion score and the reversed negative self-compassion score as the total score of self-compassion.

Covariates. We included age (continuous), sex (binary), annual household income

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(1. *Less than 10,000 yuan* to 8. *Larger than 1,000,000 yuan*, continuous) and type of birthplace (1. *Big city* to 6. *Village*, continuous) as covariates in our data analyses.

Procedure

In the first stage, the participants reported to the lab, and the experimenters collected their saliva to conduct genetic testing. Based on the genotypes of those two SNPs, we calculated the participants' genetic scores of psychological resilience and uploaded genetic feedback to the GeseDNA platform (1 = *the lowest psychological resilience*, 5 = *the highest psychological resilience*). After a few days, the participants obtained access to their genetic reports. The participants chose whether to view their genetic report about psychological resilience, and then they completed questionnaires that measured their psychological resilience and self-compassion. We separated the participants into two groups, a before-feedback group and an after-feedback group, after they finished the measurements.

Statistical Analyses

We examined the outliers, normality, linearity, and common method bias of the data using SPSS 22.0 (see *Supplemental Note 1*). To test the impact of genes on psychological resilience, we first checked the correlation between the genetic score of psychological resilience and the psychological resilience score in the before-feedback group. Then, we tested the genetic placebo effect by calculating the correlation between the genetic score and psychological resilience score in the after-feedback group. Since self-compassion is closely linked to psychological resilience^{30,31}, we replicated the above analyses while including positive and negative self-compassion as covariates. Finally, we examined the moderating effect of self-compassion on the genetic placebo effect (see [Figure 1](#)) using PROCESS Model 3³². Since the results of positive and negative self-compassion were similar to the self-compassion total score (see *Supplemental Note 2*), we focused on the self-compassion total score as our measure of self-compassion in the main text and figures.

Study 2

Participants

We recruited 181 participants from Sun Yat-sen University and provide 80 RMB yuan compensation. The sample was randomly separated into two groups, with $n = 88$ participants in the low-psychological-resilience feedback group ($M_{\text{age}} = 20.53$, $SD = 1.35$, 55 females) and $n = 93$ participants in the high-psychological-resilience feedback group ($M_{\text{age}} = 20.66$, $SD = 1.39$, 56 females), who received genetic feedback reporting genetic a predisposition of low or high psychological resilience. This research was approved by the local ethical committee, and all the participants provided informed consent before the experiment.

Procedure

The genotyping procedure and measures of the psychological resilience and self-compassion were the same as those in study 1.

Authenticity Perception. We measured the participants' authenticity perception toward the genetic feedback using two items: "*How much do you think the genetic feedback you received is consistent with your actual condition?*" and "*How much do you think the results of this genetic feedback reflect your actual condition?*" ($\alpha = .90$). We calculated the mean value of these two items as the index of authenticity perception.

In the first stage, the participants reported to the lab, and the experimenters collected their saliva to conduct genetic testing. After a few days, the participants returned to obtain their genetic reports. We randomly assigned the participants into one of two groups: the low-psychological-resilience group and the high-psychological-resilience group. After receiving genetic feedback and reading it carefully, all the participants were asked to finish the measurements of psychological resilience, self-compassion and authenticity perception. Finally, the participants were debriefed and received actual genetic feedback.

Statistical Analyses

We first examined the outliers, normality, linearity, and common method bias of the data using SPSS 22.0 (see *Supplemental Note 1*). To test the genetic placebo effect,

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an independent-samples *t*-test was conducted to detect the difference in the psychological resilience score between the low-psychological-resilience feedback group and the high-psychological-resilience feedback group. We observed a genetic placebo effect when the psychological resilience score in the high-feedback group was higher than that in the low-feedback group. Since psychological resilience is closely linked to self-compassion^{30,31} and authenticity perception toward genetic feedback, we replicated the above analysis while including positive and negative self-compassion and authenticity perception as covariates. Then, to explore the moderating effect of self-compassion, we tested a moderation model with group (low-psychological-resilience/high-psychological-resilience feedback) as the independent variable, self-compassion as the moderator and the psychological resilience score as the dependent variable using PROCESS Model 1³². Additionally, to investigate the potential mechanism of this moderating effect, we conducted an exploratory mediation analysis to test the mediative effect of authenticity perception (see [Figure 3](#) and *Supplemental Note 4*) using PROCESS Model 15³². As in experiment 1, we focused on the self-compassion total score as our measure of self-compassion in the main text and figures. *Supplemental Note 3* contains the results about the moderating effect of positive and negative self-compassion.

Declarations of Interest:

The Gese DNA Research Team are employees of Beijing Gese Technology Co., Ltd. The remaining authors declare that they have no conflict of interest.

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Ethical Approval

All experimental procedures conformed to the Declaration of Helsinki and were approved by the local Research Ethics Committee of the Department of Psychology, Sun Yat-sen University.

Informed Consent

Informed consents were obtained from participants prior to the study.

Author Contributions

THX and LSY designed the research; THX, LTW, HLQ, DQ, FLY, YMH, WJH, Gese DNA and LSY collected data, THX, LTW and LSY analyzed data; THX and LSY wrote the manuscript. All authors commented on the manuscript.

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Figure 1. Model about The Moderative Effect of Self-compassion on The Genetic Placebo Effect in Experiment 1. The Covariates (see *Materials and Methods*) are omitted for simplicity.

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Figure 2. Results about The Moderative Effect of Self-compassion Total Score on The Genetic Placebo Effect. *A)* The Moderative Effect of Self-compassion Total Score on The Genetic Placebo Effect (without Covariates) in the After-feedback Group in Experiment 1. *B)* The Moderative Effect of Self-compassion Total Score on The Genetic Placebo Effect (without Covariates) in Experiment 2. SC = self-compassion, PAS = psychological assessment score of psychological resilience, PR = psychological resilience. $*p < .05$, $**p \leq .01$, $***p \leq .001$.

Figure 3. Authenticity perception Mediated the Moderative Effect of Self-compassion Total Score (with Covariates) in Exp. 2. *Note.* The covariates (see *Materials and Methods*) are omitted for simplicity. SC = self-compassion, PR = psychological resilience, int. = interaction. * indicates $p < .05$. ** indicates $p \leq .01$. *** indicates $p \leq .001$.