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Variation in the μ-Opioid Receptor Gene (*OPRM1*) Does Not Moderate Social-Rejection Sensitivity in Humans

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Abstract

Given previous findings from animal studies and small-scale studies in humans, variation in the μ-opioid receptor gene (*OPRM1*) has been proposed as a strong biological candidate for moderating sensitivity to social rejection. Using a substantially larger sample (N = 490) than previous studies, a prospective genotyping strategy, and preregistered analysis plans, we tested the hypotheses that *OPRM1* variation measured by the functional A118G polymorphism (rs1799971) moderates (a) dispositional sensitivity to rejection and feelings of distress following social exclusion and (b) decision making involving social cognition. In three experimental tasks commonly used to assess altruism, reciprocity, and trust in humans, we found no evidence in favor of the hypotheses; nine main tests were preregistered, and all of them yielded small and statistically insignificant estimates. In secondary analyses, we used Bayesian inference and estimation to quantify support for our findings. Taken together, our results strongly suggest that the link between *OPRM1* A118G variation and social-rejection sensitivity is weaker than previously thought.

Keywords

exclusion, social pain, genetics, *OPRM1*, decision making, open data, open materials, preregistered

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Way, Taylor, and Eisenberger (2009) reported that variation in the μ-opioid receptor gene (*OPRM1*), measured by the functional A118G polymorphism, was associated with distress of social exclusion and with dispositional sensitivity to rejection. Their main finding was based on results from the Cyberball task, in which participants are excluded during an online ball-tossing game (Williams, Cheung, & Choi, 2000). This finding has also been supported by studies on rhesus monkeys, in which a functionally similar *OPRM1* polymorphism was associated with mothers' attachment behavior and infants' distress vocalization during maternal separation (Barr et al., 2008; Higham et al., 2011).

Way et al.'s (2009) intriguing findings are an important piece of evidence for the large and active literature investigating neurocognitive similarities between social pain and physical pain (Eisenberger, 2012; Eisenberger & Lieberman, 2004; Eisenberger, Lieberman, & Williams, 2003; Kross, Berman, Mischel, Smith, & Wager, 2011; Kross, Egner, Ochsner, Hirsch, & Downey, 2007; Lieberman & Eisenberger, 2015; Wager et al., 2016; Woo et al., 2014). The effects of *OPRM1* A118G variation on physical pain sensitivity, and in particular on analgesic efficacy of exogenously administered opioids, have been

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extensively studied, and a meta-analysis provided support for a significant effect, albeit of a modest size (Hwang et al., 2014). In contrast, the study by Way et al. and a small epidemiological study by Copeland et al. (2011) constitute the only evidence to date that *OPRM1* variation is directly linked to social pain in humans. These are two isolated discoveries based on small sample sizes and should therefore not be interpreted as conclusive until replicated (Button et al., 2013; Ioannidis, 2005).

Since the famous assertion that "most published research findings are false" (Ioannidis, 2005), replication has emerged as a cornerstone of scientific practice (Munafò et al., 2017; Open Science Collaboration, 2015). We conducted a conceptual replication and an extension of the work by Way et al. (2009) using a sample of 490 participants, which is more than 15 times larger than the sample used for the main experiment by Way et al. Study participants were prospectively genotyped and invited from a pool of 2,200 individuals who were matched on age, gender, education, and A118G genotype. In the replication, we assessed whether the A118G genotype was associated with self-reported feelings of social distress following exclusion in the Cyberball task and with dispositional sensitivity to social rejection using the Adult Rejection Sensitivity Questionnaire (A-RSQ; Berenson et al., 2009). In the Cyberball task, participants believe they are playing an online ball-tossing game with two other participants, who are in fact computer programmed (Williams et al., 2000). Participants played two versions of the Cyberball task: one in which they received one third of the throws (inclusion) and one in which the other two players excluded them after receiving only two throws (exclusion). After completing each version of the Cyberball task, participants completed a standard questionnaire of self-reported social distress, which was assessed on the basis of four fundamental psychological needs (Zadro, Williams, & Richardson, 2004). In the extension of Way et al.'s study, we assessed whether the A118G genotype was associated with social cognition and decision making in contexts in which participants' decisions have real monetary consequences for other people, conducting two versions of the dictator game, an ultimatum game, and finally, a trust game.

Method

Sample

We invited subjects registered in the LifeGene biobank (Almqvist et al., 2011) to participate in an online survey experiment. We genotyped everyone registered in this biobank for *OPRM1* A118G variation (rs1799971), which resulted in a sample of 4,375 individuals with genotype A/G or G/G and 14,588 individuals with genotype A/A. We decided that individuals who had used illegal drugs or had experienced detrimental social effects because of alcohol consumption were not eligible for participation. We invited 1,000 individuals with A/G and G/G genotype (G allele carriers) and 1,000 individuals with A/A genotype (A allele homozygotes) to participate. The sample of A allele homozygotes was matched on age, gender, and education to the sample of G allele carriers. The invitations were sent via e-mail.

We conducted a small pilot study prior to the main data collection, using the exact same survey, invitation protocol, and inclusion criteria. We invited 100 G allele carriers and 100 A allele homozygotes, and the purpose was to test the logistical procedures for data collection and administration. The pilot data collection was successful. No analysis took place before the main data collection was finished. The study and main analyses were preregistered at https://aspredicted.org/blind.php?x=6uq6sx (conceptual replication) and https://aspredicted.org/blind.php?x=89k5dj (decision-making experiments).

Our final sample consisted of all individuals (N = 490) who completed the Cyberball task (main data collection and the pilot study), which was the first part of the survey. In total, there were 230 G allele carriers (135 men, 95 women; age: M = 41.0 years, SD = 7.83, range = 27–58; 39 had G/G genotype, 191 had A/G genotype) and 260 A allele homozygotes (126 men, 134 women; age: M = 39.2 years, SD = 7.69, range = 27–57). With this sample size, we had 80% power to detect an effect (d) of 0.26 on the basis of quantitative trait (using the A-RSQ). For the disaggregated analyses, we had 80% power to detect an effect of 0.27 for genotype A/A versus genotype A/G and 0.49 for genotype A/A versus genotype G/G, which was around one half of the effect sizes reported in the original study by Way et al. (2009). The study was approved by the ethical review board for East Sweden (Reference No. 2014/251-31), and all individuals gave informed consent to participate.

Genotyping

Subjects were genotyped for *OPRM1* A118G variation (rs1799971) at the Mutation Analysis Facility of the Karolinska Institute, Stockholm, using standard Agena technology (http://agenabio.com/). Briefly, this single-nucleotide-polymorphism (SNP) genotyping method is based on matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) analysis and is performed on the MassARRAY platform from Agena. The system allows simultaneous genotyping of several SNPs. We used iPLEX Gold chemistry for the assay, which allows for analysis of up to 28 SNPs in a single reaction. The

assay was developed and validated at the Mutation Analysis Facility using reference DNAs from the HapMap Project, and 5% of samples were subsequently regenotyped for quality control. In addition to rs1799971, the assay included a set of 24 ancestry-informative markers (AIMs; see below), which have been validated for their ability to determine continental origin (Kosoy et al., 2009).

We conducted a principal factor analysis using our SNP panel (SNPs: rs10007810, rs1040045, rs12629908, rs1799971, rs1800497, rs2416791, rs260690, rs324420, rs4680, rs4918842, rs540825, rs6277, rs6422347, rs6451722, rs6548616, rs7554936, rs7657799, rs772262, rs7803075, rs7997709, rs870347, rs907094, rs9319336, rs9522149, rs9530435). We computed individual factor loadings for four principal components using EIGENSOFT's (Version 7.2.0; Patterson, Price, & Reich, 2006). smartPCA function. These four principal components (AIMs) were used as control regressors in the main analyses (see the Data Analyses section).

Cyberball task

Participants played the Cyberball social-exclusion task twice (Williams et al., 2000), on one occasion using an inclusion version of the game and on the other occasion using an exclusion version. Participants were informed that they would play a virtual ball-tossing game with two other individuals who took part in the same online survey experiment. In reality, the game was a preset program, and there were no other players. Participants saw cartoon images of three players including their own. One of the cartoon players started the game by tossing the ball to one of the other players. The participant could throw the ball by clicking the cartoon image of one of the players. The computer players waited for a randomly determined interval (500–3,000 ms) before tossing the ball. The task was programmed to have 30 throws per run. In the inclusion version of the task, the participant received the ball 33% of the time, but in the exclusion version, the participant received the ball twice during the first 8 throws and then was excluded (i.e., the computer players threw the ball to each other). The order of the two versions of the Cyberball task was counterbalanced among participants. After each version of the task, participants answered an identical questionnaire (for a transcript, see Section S4 in the Supplemental Material).

Our main dependent variable was self-reported social distress, which was assessed along four dimensions, namely, self-esteem (5 items), belonging (5 items), meaningfulness (5 items), and control (5 items). Each item was scored on a 5-point scale, from 1 (*not at all*) to 5 (*very much*), and reverse coded when necessary. For each individual, we computed the average score from these 20 items answered after the exclusion version of the Cyberball task and the average from the same 20 items answered after the inclusion version of the Cyberball task. The main dependent variable, social-distress difference, was the difference between these two averages. Our approach here was identical to that of Way et al. (2009) except that (a) participants completed the study online, (b) social distress was assessed using a standardized protocol based on self-reports rather than neuroimaging, (c) there were 30 rather than 60 throws during each task, and (d) we controlled for potential order effects by counterbalancing the order of the two versions of the Cyberball task among participants (Way et al. used a fixed order, in which the inclusion task was always conducted first).

Dispositional sensitivity to rejection

Participants responded to the A-RSQ to assess dispositional sensitivity to social rejection (Berenson et al., 2009). In the A-RSQ, participants read nine different scenarios; for each scenario, they indicated on a 5-point scale (a) how concerned or anxious they would be about rejection (1 = *very unconcerned*, 5 = *very concerned*) and (b) to what extent they expected not to be rejected (1 = *very unlikely*, 5 = *very likely*). Rejection expectancy was reverse coded. Then, for each of the nine scenarios, rejection expectancy was multiplied by rejection concern, and the average for the nine scenarios was taken as the dependent variable, rejection sensitivity. Our approach was identical to that of Way et al. (2009) except that we used the A-RSQ instead of the Mehrabian Sensitivity to Rejection Scale (Mehrabian, 1994).

Decision-making experiments

Having completed the two versions of the Cyberball task, participants played two versions of the dictator game (Forsythe, Horowitz, Savin, & Sefton, 1994): one in which they allocated 50 Swedish kronor (SEK; approximately US$6 at the time of the experiment) between themselves and another participant they had been randomly and anonymously paired with, and another version in which they instead allocated 50 SEK between themselves and a charitable cause (UNICEF). The order of the dictator games was randomly determined for each individual. We hypothesized that G allele carriers would be more generous than A homozygotes in both dictator games and that the difference would be larger in the version in which they allocated

money to the other participant because the psychological distance to this recipient was lower than in the dictator game with the charitable cause.

Then participants played the ultimatum game (Güth, Schmittberger, & Schwarze, 1982), which they completed twice, first in the role of responder and then in the role of first mover. In the game, the first mover proposed an allocation of 100 SEK (~US$12 at the time of the experiment) between themselves and another participant (the responder), who either accepted or rejected the proposal. If the proposal was accepted, both participants were paid according to the proposed division of money, but neither participant earned anything if the proposal was rejected. We hypothesized that G allele carriers would allocate more money to responders and that unfair proposals would evoke stronger negative feelings among them than among A homozygotes. We used the strategy method for responders' decisions, meaning that responders indicated whether they would reject or accept for each possible proposal (in 10-SEK increments) that could be made by the first mover. All decisions were incentive compatible because the actual proposal made by the first mover determined which of the responder's responses would ultimately be payoff relevant for each pair of participants.

All participants first made decisions in the role of responder, whereafter they indicated on a sliding scale from 0 (*not at all*) to 100 (*very much*) how they would feel if the first mover proposed (a) a 50-50 division of money (i.e., a fair allocation) and (b) a 90-10 division of money (i.e., an unfair allocation), separately for each of seven items. We calculated the average score for four of these feelings (nonexistent, meaningless existence, poorly accepted, and outsider) after the fair proposal and the average score for the same feelings after the unfair proposal. The dependent variable, social distress (ultimatum game), was the difference between these two averages, and in a similar way, we calculated the fair-unfair difference in stated anger, which was another of the seven items elicited on the scale from 0 to 100.

Finally, participants were rematched (randomly and anonymously) with another participant and made a decision in the role of first mover. After the survey, it was randomly determined for each participant whether his or her decision as first mover or responder would be payoff relevant, and this was clearly stated in the general instructions.

After the ultimatum game, participants played the trust game (Berg, Dickhaut, & McCabe, 1995), in which they were randomly and anonymously matched in new pairs and endowed with 50 SEK (~US$6 at the time of the experiment) each. First movers (trusters) decided how much of their 50 SEK to send to the other participant (the trustee), the amount sent was tripled, and then the trustee decided how much of the money to send back to the truster. We hypothesized that G allele carriers would be more concerned about betrayal on the part of the trustee and, therefore, would send less money to the trustee. We also hypothesized that betrayal would evoke stronger negative feelings among G allele carriers than among A homozygotes. All participants first made decisions in the role of truster, deciding how much to send to their paired trustee. Then they indicated on a sliding scale from 0 (*not at all*) to 100 (*very much*) how they felt when making their decision, separately for each of five items. Trusters who had sent more than 0 SEK also indicated on a sliding scale from 0 (*not at all*) to 100 (*very much*) how they would feel (a) if the trustee returned 50% of the maximal amount he or she could possibly return (i.e., a fair decision) and (b) if the trustee returned 0% (i.e., an unfair decision, a betrayal of trust), separately for each of seven items. The items were identical to those in the ultimatum game, and we used the exact same procedure to calculate the dependent variables, social distress and anger. Finally, participants were rematched (randomly and anonymously) with another participant (and endowed with another 50 SEK each) and made a decision in the role of trustee. This decision was based on the strategy method, that is, for each possible amount sent by the truster, trustees indicated how much of the tripled amount they would return, in 15-SEK increments. After the survey, it was randomly determined for each participant whether their decision as truster or trustee would be payoff relevant, and this was clearly stated in the general instructions.

Procedure

The data presented here were collected within a larger online survey. All participants who completed the entire survey earned a fee of 150 SEK (~US$18 at the time of the experiment) plus their realized payoffs from the decision-making experiments. After receiving the initial general instructions at the beginning of the survey, participants played the Cyberball task twice (i.e., inclusion and exclusion). We balanced the order by randomly assigning each participant to one of two versions of the survey: one in which Cyberball exclusion was followed by Cyberball inclusion, and another in which the order was reversed. In addition to having participants complete the social-distress questionnaires after each Cyberball task (described above), we included a standard manipulation check asking participants after each version of the Cyberball task to indicate the extent to which they felt excluded and ignored (on separate 5-point scales); they were also asked to estimate the proportion

of throws received during the game. The decision-making experiments described above were conducted after the Cyberball tasks, and then two additional experimental tasks were conducted that are not part of the current study. In the decision-making experiments, participants were always randomly and anonymously rematched with a new participant for each new payoff-relevant decision to be made, and this was clearly stated in the instructions (for a transcript of instructions and decision screens, see Section S4). Finally, participants answered a set of questions, including the A-RSQ.

Data analyses

Our main independent variable, carrier, was coded 0 for A allele homozygotes and 1 for G allele carriers. We tested our main hypotheses by regressing each dependent variable on carrier and AIMs. Nine tests were preregistered as main analyses: social-distress difference in the Cyberball task, rejection disposition in the A-RSQ, the difference in dictator giving between the two dictator games, proposals in the ultimatum game, social distress and anger for unfair proposals in the ultimatum game, amount sent to the trustee in the trust game, and finally, social distress and anger for betrayal in the trust game. To control for order effects in the Cyberball task, we carried out two regressions: one for exclusion first and another for inclusion first. Our approach was to combine the data from the two versions if the coefficient estimate for the carrier was of the same sign and significantly different from zero in both versions or if neither coefficient estimate was significantly different from zero.

In the secondary analyses, we used Bayesian inference and estimation to quantify support for our findings. For each of the nine main tests, we conducted Bayesian independent-samples *t* tests for A allele homozygotes versus G allele carriers as well as Bayesian regressions to compare a null model, in which the dependent variable was regressed on AIMs, with the alternative model that also included carrier as the regressor. We used the default priors in JASP (Version 0.9.1; JASP Team, 2018), a Cauchy prior located at zero with scale 0.707 for the *t* tests, and a Jeffrey-Zellner-Siow (JZS) prior with scale 0.354 for the regressions. We also explored dictator giving separately in each of the two dictator games as well as behavior by second movers in the ultimatum game and in the trust game. Because there was a gender imbalance in the final sample, we carried out a number of robustness checks in which we tested the effect of *OPRM1* A118G variation separately for men and women (for these and additional results, see Sections S1 and S2 in the Supplemental Material). Finally, we explored whether social-distress difference in the Cyberball task or rejection disposition in the A-RSQ could predict participants' responses in the decision-making experiments, disregarding genetic variation as a mediating factor.

Results

Conceptual replication of the Way et al. (2009) study

A manipulation check confirmed that participants in the Cyberball task felt ignored and excluded to a greater extent during exclusion than inclusion, mean difference = 2.3, $SE = 0.06$, $t(489) = 39.0$, $p < .001$, $d = 1.8$. They also reported stronger feelings of social distress, mean difference = 1.5, $SE = 0.04$, $t(489) = 37.9$, $p < .001$, $d = 1.7$, which was our main variable of interest. The difference in social distress is substantial and confirms the strong link between rejection and negative affect that has been found in previous studies (Eisenberger et al., 2003). However, we found no evidence that *OPRM1* A118G genotype moderates the strength of these feelings. The difference between A allele homozygotes and G allele carriers was small and statistically insignificant (Fig. 1, left panel), mean difference = –0.09, $t(488) = -1.2$, $p = .23$, $d = -0.11$, 95% confidence interval (CI) = [–0.29, 0.07]. This result was confirmed in a regression analysis in which AIMs calculated from our SNP panel were included as regressors ($\beta = 0.08$; $b = 0.13$, 95% CI = [–0.12, 0.38]). There were no additional effects when the G allele carrier group was disaggregated into A/G ($\beta = 0.06$; $b = 0.10$, 95% CI = [–0.17, 0.36]) and G/G ($\beta = -0.02$; $b = -0.05$, 95% CI = [–0.55, 0.46]) genotypes or when the four constituent subcategories of social-distress difference were analyzed separately for belonging ($\beta = 0.02$; $b = 0.03$, 95% CI = [–0.27, 0.34]), self-esteem ($\beta = 0.08$; $b = 0.16$, 95% CI = [–0.14, 0.46]), meaningfulness ($\beta = 0.07$; $b = 0.15$, 95% CI = [–0.19, 0.50]), and control ($\beta = 0.09$; $b = 0.17$, 95% CI = [–0.11, 0.46]). Similarly, the order in which participants completed the two different versions of the Cyberball task did not affect the main results; the difference between A allele homozygotes and G allele carriers was insignificant both in the inclusion-first group ($\beta = -0.01$; $b = -0.02$, 95% CI = [–0.36, 0.33]) and in the exclusion-first group ($\beta = 0.16$; $b = 0.27$, 95% CI = [–0.10, 0.64]). For a general summary of these results, see Tables S2 to S4 in the Supplemental Material; raw data are summarized in Figures S1 and S2 in the Supplemental Material.

Dispositional sensitivity to social rejection was measured using the A-RSQ (Berenson et al., 2009). We found no significant difference between A allele

homozygotes and G allele carriers (Fig. 1, right panel), mean difference = –0.12, $t(469) = -0.49$, $p = .62$, $d = -0.05$, 95% CI = [–0.23, 0.14], and this result was confirmed in a regression that controlled for ancestry ($\beta = 0.09$; $b = 0.46$, 95% CI = [–0.35, 1.27]). The result was similar when the G allele carrier group was disaggregated into A/G ($\beta = 0.10$; $b = 0.53$, 95% CI = [–0.32, 1.38]) and G/G ($\beta = 0.09$; $b = 0.85$, 95% CI = [–0.76, 2.47]) genotypes.

Extension to social decision making

We tested whether the *OPRM1* A118G genotype moderates social cognition and decision making in the dictator game, the ultimatum game, and the trust game. Figure 2 shows histograms of decisions made by first movers in these experiments. These results conform to standard results reported in the literature (Engel, 2011; Güth & Kocher, 2014; Johnson & Mislin, 2011). We found a clear preference for the equal split in the dictator game with another participant and a shift to full contribution in the dictator game with a charitable cause as recipient. Dictators on average allocated 26.5 percentage points more of their endowment to charity than to the other participant, $t(488) = 14.7$, $p < .001$, $d = 0.79$. However, there was no difference between A homozygotes' and G allele carriers' allocation decisions, $t(487) = -0.94$, $p = .35$, $d = -0.09$, 95% CI = [–0.26, 0.09], and this was confirmed in a regression that controlled for ancestry ($\beta = 0.07$; $b = 5.20$, 95% CI = [–6.69, 17.1]).

In the ultimatum game, there was also a clear preference for the equal split, but unlike in the dictator game, very few participants attempted to keep the whole endowment for themselves, presumably anticipating that low proposals would be rejected by responders. The estimated difference between A allele homozygotes and G allele carriers was again small and insignificant—only 3.16 SEK, or slightly more than 3% of the proposer's endowment, when we controlled for ancestry ($\beta = -0.08$; $b = -3.16$, 95% CI = [–9.06, 2.74]).

For the trust game, we could see a small tendency in the data to favor our hypothesis that G allele carriers would be more careful, sending smaller amounts to their paired trustees (Fig. 2). However, the estimated effect was small and insignificant ($\beta = -0.05$; $b = -3.02$, 95% CI = [–8.35, 2.31]), and when we controlled for ancestry, the direction of the effect was reversed (but

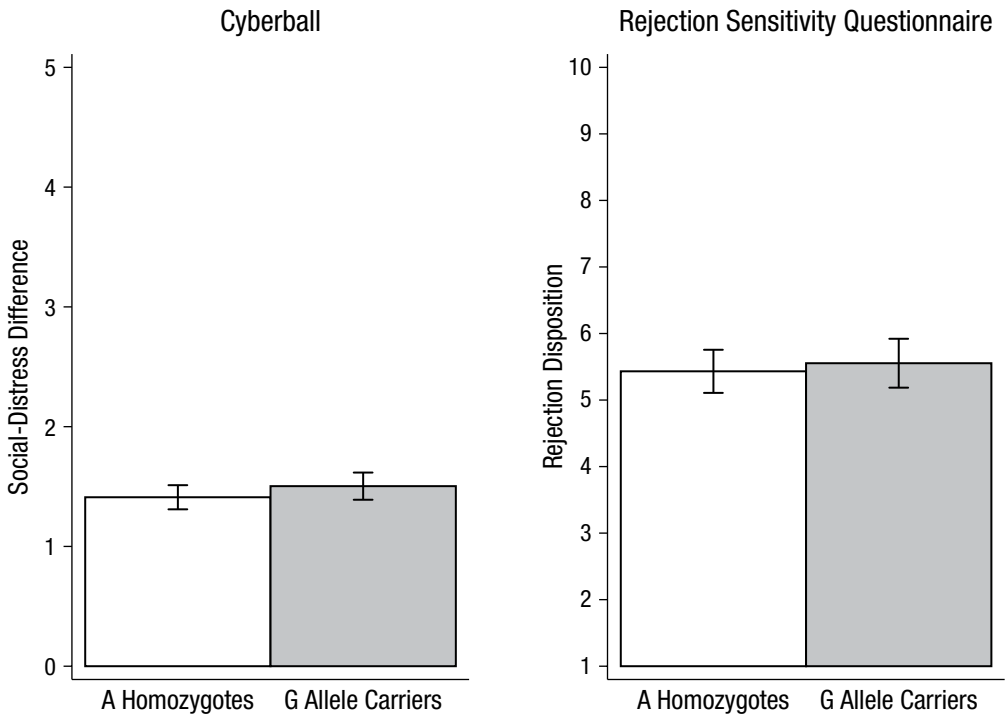

Fig. 1. Mean difference in social distress between exclusion and inclusion in the Cyberball task (left panel; $N = 490$; $n = 260$ A allele homozygotes, $n = 230$ G allele carriers) and mean dispositional sensitivity to social rejection as measured by the Adult Rejection Sensitivity Questionnaire (A-RSQ; right panel; $N = 471$; $n = 251$ A allele homozygotes, $n = 220$ G allele carriers). The scale for the A-RSQ is 1 to 25. Error bars represent 95% confidence intervals.

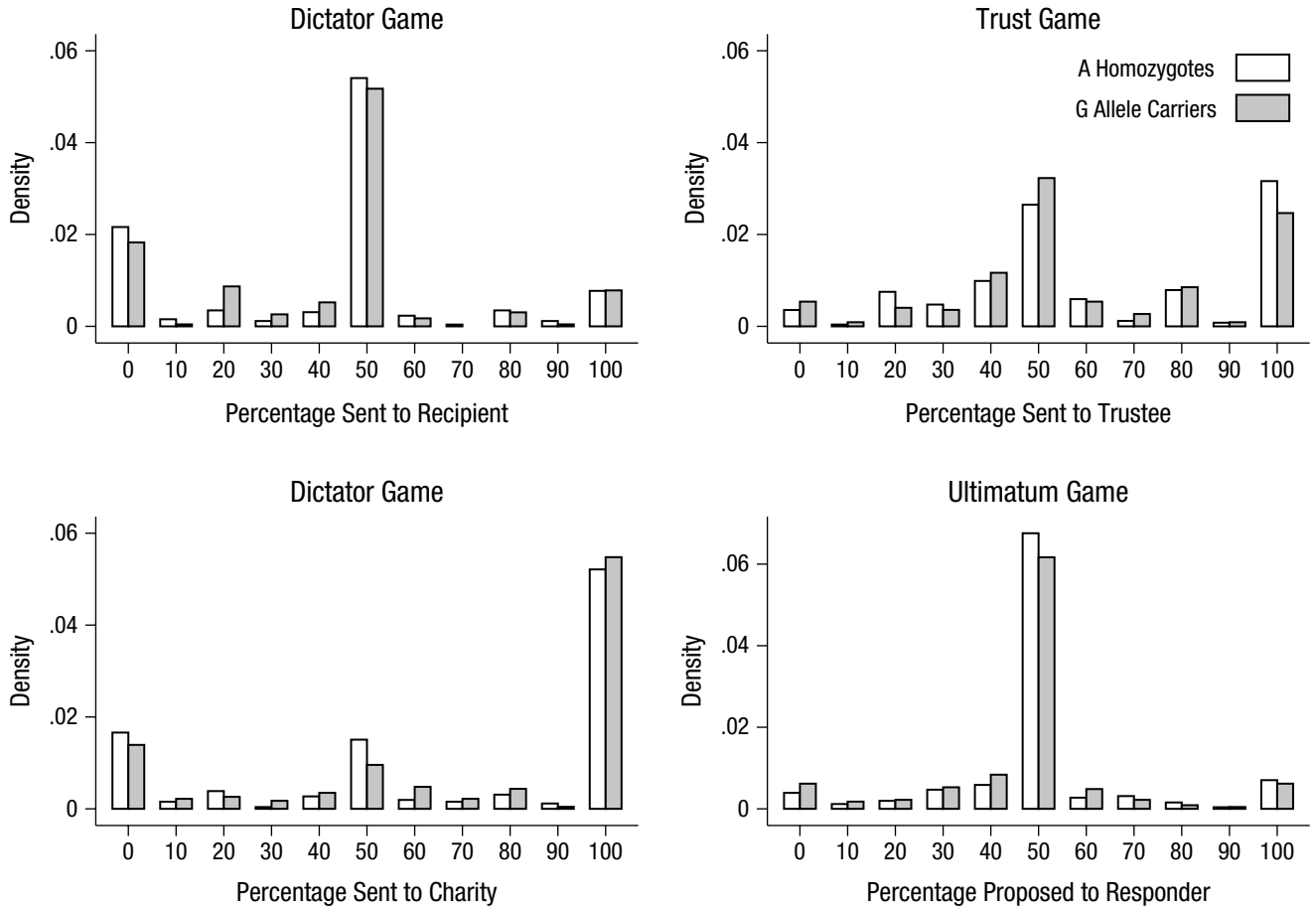

Fig. 2. Distribution of decisions made by first movers in the dictator games, the ultimatum game, and the trust game. Both dictator games were completed by 489 participants (n = 259 A allele homozygotes, n = 230 G allele carriers). Six participants dropped out during the ultimatum game (3 A allele homozygotes and 3 G allele carriers), and another 7 participants dropped out during the trust game (3 A allele homozygotes and 4 G allele carriers).

still insignificant); G allele carriers, on average, sent slightly more than 3 percentage points more of their endowment to the trustee (β = 0.05; b = 3.17, 95% CI = [–5.75, 12.1]).

Next, we tested whether *OPRM1* A118G variation was associated with negative affect following unfairness and betrayal in the ultimatum game and the trust game (Table 1). Participants reported that an unfair proposal in the ultimatum game would evoke substantially stronger negative feelings compared with a fair proposal—social distress: mean difference = 10.2, SE = 0.92, $t(482)$ = 11.1, $p < .001$; anger: mean difference = 16.3, SE = 1.45, $t(482) = 11.2$, $p < .001$. An even stronger effect was found for betrayal vis-à-vis fairness in the trust game—social distress: mean difference = 14.5, SE = 1.12, $t(454) = 13.0$, $p < .001$; anger: mean difference = 27.8, SE = 1.62, $t(454) = 17.2$, $p < .001$. However, the estimated differences between G allele carriers and A allele homozygotes were small and insignificant (Table 1). This was confirmed in regressions that controlled for ancestry, social distress (β = 0.10; b = 4.03, 95% CI = [–1.96, 10.0]), and anger (β = 0.05; b = 2.99, 95% CI = [–6.57, 12.5]) in the ultimatum game and for social distress (β = –0.06; b = –2.67, 95% CI = [–9.96, 4.61]) and anger (β = –0.001; b = –0.022, 95% CI = [–10.7, 10.6]) in the trust game.

We explored whether *OPRM1* A118G variation was associated with second movers' decision making in the ultimatum game and in the trust game. Because these two experiments were conducted using the strategy method, second movers' decisions were made conditional on decisions made by the first movers (for details, see the Method section). Figure 3 shows the proportion of responders who accepted the proposal in the ultimatum game, separately for each possible proposal that could be made by the first mover. As the figure shows, the proportion of responders who accepted the proposal was greatest for the equal split; from there, it declined in both directions, with the sharpest fall

Table 1. Anticipated Reactions to Unfairness and Betrayal

	Ultimatum game		Trust game	
Genotype	Social distress	Anger	Social distress	Anger
A homozygotes	10.2 (20.4)	15.6 (32.1)	15.8 (25.5)	27.6 (34.1)
G allele carriers	10.1 (20.0)	17.1 (31.6)	13.1 (21.7)	28.0 (35.2)
p	.98	.61	.22	.91

Note: The top two rows show the mean difference in anticipated feelings following a fair versus unfair proposal by the first mover in the ultimatum game (50% vs. 10% of endowment, respectively) and following a fair versus unfair response by the second mover in the trust game (50% vs. 0% returned, respectively). Standard deviations are given in parentheses. Anger was elicited on a scale from 0 to 100. Social distress was the mean score from four items for which responders stated the extent to which they would feel "nonexistent," "meaningless," "rejected," and "as an outsider"; each item was scored on a scale from 0 to 100. The ultimatum game was completed by 483 participants (n = 256 A allele homozygotes, n = 227 G allele carriers). The sample size was smaller in the trust game (N = 455; n = 244 A allele homozygotes, n = 211 G allele carriers) because first movers (trusters) who sent nothing to their paired second mover (trustee) did not answer questions concerning possible back transfers. Significance (p) values were derived from t tests. For further details, see the Method section.

observed as proposals decreased. This is a common pattern for responder behavior found in studies using the ultimatum game (Güth & Kocher, 2014).

It is clear in Figure 3 that G allele carriers and A allele homozygotes made very similar decisions, and this was confirmed in a regression that controlled for ancestry (β = 0.01; b = 0.005, 95% CI = [–0.080, 0.090]). A similar conclusion can be made for trustees' decisions in the trust game. Figure 4 shows the average amount returned by trustees for each possible amount they could receive from the truster. Trustees' strategies were virtually identical across G allele carriers and A allele homozygotes, which was confirmed in a regression that controlled for ancestry (β = 0.10; b = 0.038, 95% CI = [–0.019, 0.094]).

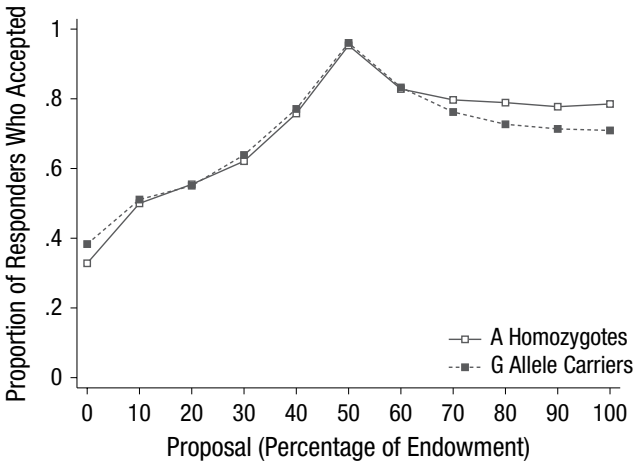

Fig. 3. Responders' strategy in the ultimatum game (N = 483; n = 256 A allele homozygotes, n = 227 G allele carriers): proportion of responders who accepted the first movers' proposal as a function of the percentage of the first movers' endowment.

We also explored whether rejection sensitivity in the Cyberball task and dispositional sensitivity to rejection elicited in the A-RSQ could predict participants' responses in the decision-making experiments, disregarding genetic variation as a mediating factor (this analysis was not part of our preregistered analysis plan). We found a significant and positive correlation between Cyberball rejection sensitivity and anticipated reactions to unfairness and betrayal in the ultimatum game and the trust game. Greater Cyberball rejection sensitivity implied increased anger (β = 0.17; b = 6.77, 95% CI = [3.04, 10.5]) and social distress (β = 0.21; b = 5.78, 95% CI = [3.23, 8.33]) following betrayal in the trust game and increased anger (β = 0.12; b = 4.53, 95% CI = [1.19, 7.88]) and social distress (β = 0.12; b = 2.89, 95% CI = [0.77, 5.0]) following unfairness in the ultimatum game. A similar relationship was found between dispositional sensitivity to rejection and anger following unfairness in the ultimatum game (β = 0.14; b = 1.69, 95% CI = [0.62, 2.76]). Cyberball rejection sensitivity was not correlated with decisions made in the dictator game (β = 0.04; b = 1.71, 95% CI = [–2.48, 5.89]), the ultimatum game (β = 0.03; b = 0.67, 95% CI = [–1.42, 2.76]), or the trust game (β = –0.06; b = –2.10, 95% CI = [–5.25, 1.04]). Dispositional sensitivity to social rejection was correlated in the expected direction with giving in the dictator game (β = –0.09; b = –1.40, 95% CI = [–2.75, –0.05]) and weakly with decisions made in the ultimatum game (β = 0.08; b = 0.61, 95% CI = [–0.06, 1.28]), but not with decisions in the trust game (β = 0.04; b = 0.44, 95% CI = [–0.56, 1.44]). For a general

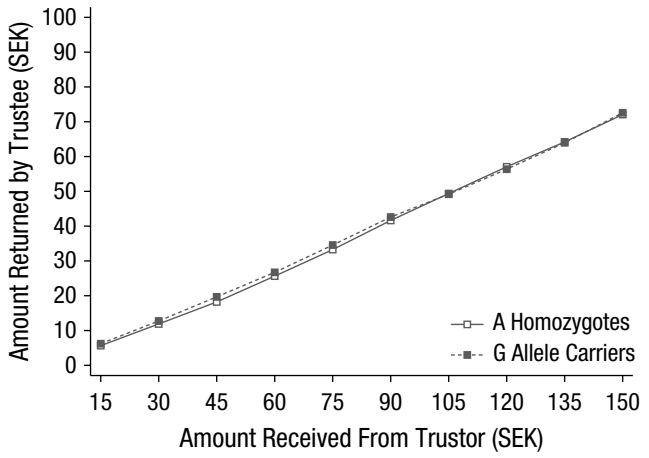

Fig. 4. Trustees' strategy in the trust game ($N = 476$; $n = 253$ A allele homozygotes, $n = 223$ G allele carriers): average amount returned by trustees as a function of the amount that they could receive from the truster. In the trust game, the truster's transfer was tripled and then given to the trustee (*x*-axis), who then decided how much, if anything, to return to the truster (*y*-axis). For details, see the Method section. SEK = Swedish kronor.

summary of these analyses, see Tables S8 to S11 in the Supplemental Material.

Bayesian analyses

We conducted Bayesian analyses to quantify support for our findings. We computed a Bayes factor (BF_{01}) to capture the extent to which the observed data would shift our belief about the effect of interest by comparing the relative predictive performance of the null hypothesis (H0) and the alternative hypothesis (H1; *OPRM1* A118G variation moderates social-rejection sensitivity) when a prior distribution captures uncertainty about the true effect specified under H1. For example, a Bayes factor (BF_{01}) of 5 can be interpreted as the observed data being 5 times more likely to occur under H0 than under H1. A common rule of thumb is to interpret a BF_{01} ranging from 1 to 3 as anecdotal evidence for H0, a BF_{01} between 3 and 10 as moderate evidence for H0, and a BF_{01} between 10 and 30 as strong evidence for H0 (Lee & Wagenmakers, 2013). We used the default priors in JASP (Version 0.9.1), a Cauchy prior located at zero with scale 0.707 for the *t* tests, and a JZS prior with scale 0.354 for the regressions. Our results indicated substantial support against *OPRM1* A118G variation as a moderating factor of social-distress difference and dispositional sensitivity to social rejection. BF_{01}s from independent-samples *t* tests amounted to 4.89 for social-distress difference and 8.68 for rejection disposition. The effect was weaker but still in favor of the null hypothesis in regressions that controlled for ancestry (social-distress difference: $BF_{01} = 2.47$; rejection disposition: $BF_{01} = 2.23$). Posterior distributions of true effect sizes (Figs. 5 and 6), provided they exist, cover a wide range including zero and have less than 5% of their mass on (absolute) values greater than the effect sizes observed by Way et al. (2009; $d > 0.4$, for rejection disposition using the Mehrabian scale).

Analysis of social decision making yielded BF_{01}s between 4.17 and 6.47 with independent-samples *t* tests and between 2.41 and 3.20 in regressions controlling for ancestry. Estimated parameters were 4.78 (95% credible interval, or CrI = [–2.94, 11.95]) for the dictator game, –2.91 (95% CrI = [–7.23, 0.69]) for the ultimatum game, and 2.92 (95% CrI = [–2.46, 8.24]) for the trust game. For example, provided an effect exists in the trust game, we can be 95% confident that G allele carriers send at most 8.24 percentage points (upper bound of the 95% credible interval) more of their endowment compared with A allele homozygotes to the trustee. Similarly, a true difference between A allele homozygotes and G allele carriers in the ultimatum game will with 95% confidence not exceed 0.69 percentage points in the expected direction. The analysis of anticipated reactions to unfairness and betrayal in the ultimatum game and in the trust game yielded similar results. BF_{01}s ranged between 4.69 and 9.87 using independent-samples *t* tests and between 1.83 and 3.97 in regressions that controlled for ancestry. Point estimates of the difference between A allele homozygotes and G allele carriers were small, and posterior distributions carried substantial mass around zero, for social distress ($b = 3.73$, 95% CrI = [–0.62, 8.01]) and anger ($b = 2.74$, 95% CrI = [–3.22, 8.44]) in the ultimatum game, and for social

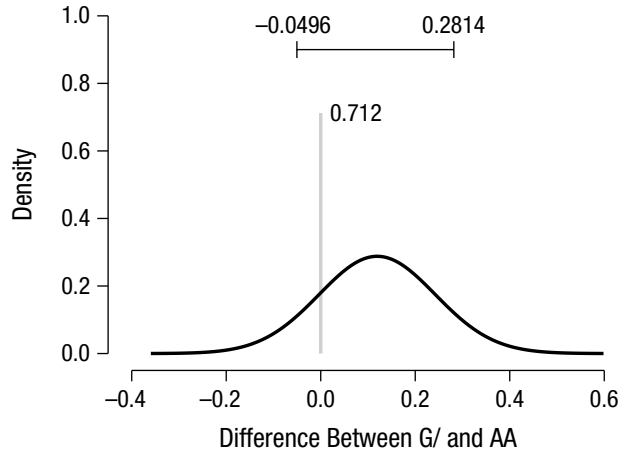

Fig. 5. Posterior distribution for social-distress difference: estimated difference between G allele homozygotes (G/; $n = 230$) and A allele carriers (AA; $n = 260$). The probability of the null model (in which the dependent variable is regressed on ancestry-informative markers) given the data is 0.712. Values on the *x*-axis should be scaled with the sample standard deviation (0.85) for a measure of effect size.

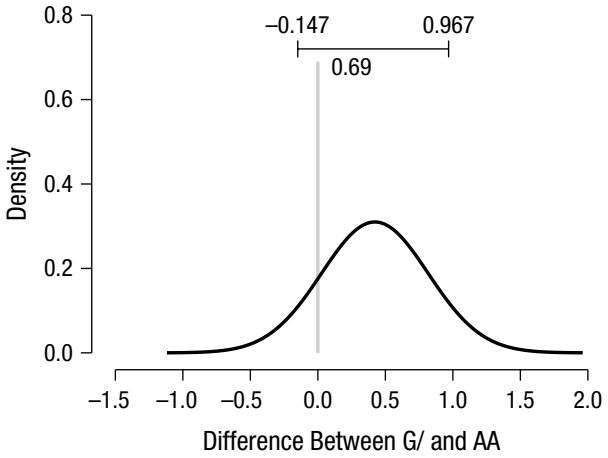

Fig. 6. Posterior distribution for rejection disposition: estimated difference between G allele homozygotes (G/; n = 220) and A allele carriers (AA; n = 251). The probability of the null model (in which the dependent variable is regressed on ancestry-informative markers) given the data is 0.69. Values on the x-axis should be scaled with the sample standard deviation (2.68) for a measure of effect size.

distress (b = –2.47, 95% CrI = [–6.52, 2.15]) and anger (b = –0.02, 95% CrI = [–6.13, 5.62]) in the trust game.

Discussion

We conducted a conceptual replication of the study by Way et al. (2009) and used a substantially larger sample to assess whether allelic variation at the *OPRM1* locus would influence social-rejection sensitivity. We further reasoned that altered rejection sensitivity could be expected to influence social cognition and decision making, a hypothesis that has not been tested to date. To evaluate these additional hypotheses, we carried out experiments using three tasks commonly used to assess altruism, reciprocity, and trust. Our design benefited from a large, population-based sample of Swedish volunteers with banked DNA, the LifeGene cohort (Almqvist et al., 2011); we sampled from this population using a prospective genotyping strategy to generate balanced genotype groups. To control for the possible confound of population admixture, we used an established panel of AIMs. Data collected in the course of our experiments were analyzed according to a preregistered plan. Using this stringent approach, we consistently found support against *OPRM1* A118G variation as a moderator of (a) social-distress feelings after rejection in the Cyberball task, (b) dispositional sensitivity to rejection in the A-RSQ, and (c) social cognition and decision making in the dictator game, the ultimatum game, and the trust game. It should be emphasized that we replicated known reliable patterns of results with all of our behavioral tasks, most notably, the Cyberball task and the economic games, suggesting that our findings are unlikely a result of experimenter incompetence. Our exploratory analyses revealed a significant relationship between rejection sensitivity and affective responses to unfairness and betrayal in the trust game and the ultimatum game. This is a new and interesting finding that we hope will be formally assessed in future replications using confirmatory analyses.

The hypothesis that *OPRM1* A118G variation moderates social-rejection sensitivity has a plausible basis. First, there is conclusive evidence that allelic variation at this locus is functional. At the most fundamental level, it alters the physical composition of the receptor by encoding an amino-acid substitution in the N-terminal extracellular loop of the receptor protein (Bond et al., 1998). It also robustly alters several biological responses to receptor activation when the respective isoform of the receptor is inserted into mice with otherwise identical genomes (Bilbao et al., 2015; Ramchandani et al., 2010; Robinson et al., 2015; Zhang, Wang, Johnson, Papp, & Sadée, 2005). Second, *OPRM1* A118G variation influences sensitivity to physical pain and, in particular, to analgesic effects of exogenous opioids (Hwang et al., 2014). Third, similarities have been proposed in brain processing between physical pain and social pain (Eisenberger, 2012; Eisenberger & Lieberman, 2004; Eisenberger et al., 2003; Kross et al., 2011; Perini et al., 2018; cf. Woo et al., 2014). The negative emotional state triggered by social rejection is in part thought to be represented in the anterior insula and anterior cingulate cortex (Eisenberger et al., 2003; Kross et al., 2007; cf. Perini et al., 2018), brain structures that also encode aversive interoceptive states, such as those associated with nausea or pain (Craig, 2002). Fourth, the experience of physical pain and the feeling of distress following social rejection share correlates at the neurochemical level. Studies in animals have suggested that endogenous opioids mediate the reward from social attachment and buffer the stress of rejection (Machin & Dunbar, 2011), and these findings translate to humans (Hsu et al., 2013; Zubieta et al., 2003). Because endogenous opioid activity is moderated by genetic factors, such as functional variation at the *OPRM1* locus, *OPRM1* variation has been proposed as a strong biological candidate for moderating sensitivity to social rejection. Despite this indirect support for its potential role, our findings substantially weaken the claim for a direct link between *OPRM1* variation and sensitivity to social rejection. More research is needed to characterize the specific neurocognitive correlates of social pain and to determine the role of endogenous opioid activity as a moderating factor.

A limitation of our study is that we relied on self-reported distress following exclusion in the Cyberball task, as opposed to Way et al. (2009), who used brain

imaging. It is possible that this prevented us from detecting small but still relevant effects of *OPRM1* A118G variation on rejection sensitivity. Still, we used a standardized protocol for self-reports that is widely employed by studies using the Cyberball paradigm. Moreover, in the original neuroimaging Cyberball study by Eisenberger et al. (2003), self-reported distress predicted both increased neural activity in the anterior cingulate cortex during exclusion and decreased activation in the right ventral prefrontal cortex, the latter finding suggesting that the right ventral prefrontal cortex was recruited to mitigate the distressing effects of social exclusion. Thus, it may be argued that self-reports on their own can capture feelings of social exclusion induced by the Cyberball paradigm. This is also in line with recent research by Torre and Lieberman (2018), who showed that self-reports consistently detect emotion-regulation attempts, despite that participants predict an effect in the opposite direction. In fact, self-reports are crucial for interpretation of brain-imaging data. Without a concurrent self-report of a feeling of exclusion, activation in a certain part of the region is difficult to interpret (Clark-Polner, Wager, Satpute, & Barrett, 2016). Together, this alleviates the potential concern that demand effects due to using self-reports might have obfuscated a small but still relevant link between *OPRM1* A118G variation and rejection sensitivity. This is also counteracted by our study design, in which we fully accounted for potential order effects by counterbalancing the order of inclusion and exclusion during the Cyberball task. Another potential weakness is the within-subjects design, in which both parts of the Cyberball task were conducted during the same session, which could increase demand and make the research hypotheses more transparent. It is, however, unlikely that this alone could explain our findings, because Way et al. used a similar protocol for the Cyberball task, having participants complete both tasks during a single session.

Reproducibility of research has become a key issue across the major disciplines of science. In a survey of 1,576 scientists conducted by *Nature*, a clear majority of respondents thought that there was a reproducibility crisis (Baker, 2016). In light of the worrisome development echoed by these respondents, replication has emerged as a vital tool for advancing scientific knowledge. The goal of replication is not to discredit single previous studies but rather to build a solid foundation for establishing empirical regularities. A parallel development has been the push for transparency of research and, in particular, the greater emphasis being put on preregistration of analysis plans, which enables structured collection of data for credible testing of prespecified hypotheses (Munafò et al., 2017). Our study has several strengths, including a sample size that is unusually large for controlled psychological experiments, a prospective genotyping strategy that enriches the low-frequency *OPRM1* A118G allele, and an extensive investigation following a prespecified analysis plan, combining a conceptual replication protocol with a plausible extension to the domain of actual decision making involving social cognition. For the replication, we had 80% power to detect an effect on the basis of quantitative trait (using the A-RSQ) that was around one half of the effect sizes reported in the original study by Way et al. (2009). In our study, point estimates were insignificant and close to zero, and Bayesian estimation revealed posterior distributions of true effect sizes, provided they exist, with substantial mass around zero and less than 5% on values previously observed in the literature.

Social rejection represents a major threat to an individual's physical and mental well-being. It is therefore important to understand the underpinnings and consequences of social rejection and of social pain more broadly. Our findings contribute to this issue by weakening the claim for a specific genetic factor as a major moderator of social-rejection sensitivity. However, they do not address the broader question of whether there is a significant biologically heritable contribution to this important psychological trait, an important question that remains to be addressed. On a general level, our findings also contribute to the ongoing debate about the functional architecture of brain structures known to process both physical and social pain (Lieberman & Eisenberger, 2015; Wager et al., 2016; Woo et al., 2014) and to our understanding of the overlap between social and physical pain more broadly. An interesting ancillary finding of our study was that rejection sensitivity elicited in the Cyberball task predicted social cognition in the context of trust and reciprocity. This broadens the scope for future research and underscores that the need to belong is a strong human motivation. Sensitivity to rejection plausibly affects both cognition and behavior in social environments, but a significant link to functional variation at the *OPRM1* locus seems unlikely at present.

Action Editor

Michael Inzlicht served as action editor for this article.

Author Contributions

G. Tinghög, M. Heilig, E. Persson, E. Asutay, and D. Västfjäll designed the study. E. Persson and E. Asutay analyzed the data. E. Persson, G. Tinghög, and E. Asutay drafted the manuscript. All the authors revised the manuscript and approved the final manuscript for submission.

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Declaration of Conflicting Interests

The author(s) declared that there were no conflicts of interest with respect to the authorship or the publication of this article.

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Supplemental Material

Additional supporting information can be found at http://journals.sagepub.com/doi/suppl/10.1177/0956797619849894

Open Practices

All data and materials have been made publicly available via the Open Science Framework and can be accessed at osf.io/nqas7. The design and analysis plans for the study were preregistered at https://aspredicted.org/blind.php?x=6uq6sx (conceptual replication) and https://aspredicted.org/blind.php?x=89k5dj (decision-making experiments). The complete Open Practices Disclosure for this article can be found at http://journals.sagepub.com/doi/suppl/10.1177/0956797619849894. This article has received the badges for Open Data, Open Materials, and Preregistration. More information about the Open Practices badges can be found at http://www.psychologicalscience.org/publications/badges.

References

Almqvist, C., Adami, H.-O., Franks, P. W., Groop, L., Ingelsson, E., Kere, J., . . . Pedersen, N. L. (2011). LifeGene—A large prospective population-based study of global relevance. *European Journal of Epidemiology*, *26*, 67–77. doi:10.1007/s10654-010-9521-x

Baker, M. (2016). Is there a reproducibility crisis? *Nature*, *533*, 452–454.

Barr, C. S., Schwandt, M. L., Lindell, S. G., Higley, J. D., Maestripieri, D., Goldman, D., . . . Heilig, M. (2008). Variation at the mu-opioid receptor gene (*OPRM1*) influences attachment behavior in infant primates. *Proceedings of the National Academy of Sciences, USA*, *105*, 5277–5281.

Berenson, K. R., Gyurak, A., Ayduk, Ö., Downey, G., Garner, M. J., Mogg, K., . . . Pine, D. S. (2009). Rejection sensitivity and disruption of attention by social threat cues. *Journal of Research in Personality*, *43*, 1064–1072. doi:10.1016/j.jrp.2009.07.007

Berg, J., Dickhaut, J., & McCabe, K. (1995). Trust, reciprocity, and social history. *Games and Economic Behavior*, *10*, 122–142. doi:10.1006/game.1995.1027

Bilbao, A., Robinson, J. E., Heilig, M., Malanga, C. J., Spanagel, R., Sommer, W. H., & Thorsell, A. (2015). A pharmacogenetic determinant of mu-opioid receptor antagonist effects on alcohol reward and consumption: Evidence from humanized mice. *Biological Psychiatry*, *77*, 850–858. doi:10.1016/j.biopsych.2014.08.021

Bond, C., LaForge, K. S., Tian, M., Melia, D., Zhang, S., Borg, L., . . . Yu, L. (1998). Single-nucleotide polymorphism in the human mu opioid receptor gene alters β-endorphin binding and activity: Possible implications for opiate addiction. *Proceedings of the National Academy of Sciences, USA*, *95*, 9608–9613. doi:10.1073/pnas.95.16.9608

Button, K. S., Ioannidis, J. P. A., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S. J., & Munafò, M. R. (2013). Power failure: Why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience*, *14*, 365–376. doi:10.1038/nrn3475

Clark-Polner, E., Wager, T. D., Satpute, A. B., & Barrett, L. F. (2016). Neural fingerprinting: Meta-analysis, variation, and the search for brain-based essences in the science of emotion. In L. F. Barrett, M. Lewis, & J. M. Haviland-Jones (Eds.), *Handbook of emotions* (4th ed., pp. 146–165). New York, NY: Guilford.

Copeland, W. E., Sun, H., Costello, E. J., Angold, A., Heilig, M. A., & Barr, C. S. (2011). Child μ-opioid receptor gene variant influences parent–child relations. *Neuropsychopharmacology*, *36*, 1165–1170. doi:10.1038/npp.2010.251

Craig, A. D. (2002). How do you feel? Interoception: The sense of the physiological condition of the body. *Nature Reviews Neuroscience*, *3*, 655–666. doi:10.1038/nrn894

Eisenberger, N. I. (2012). The pain of social disconnection: Examining the shared neural underpinnings of physical and social pain. *Nature Reviews Neuroscience*, *13*, 421–434. doi:10.1038/nrn3231

Eisenberger, N. I., & Lieberman, M. D. (2004). Why rejection hurts: A common neural alarm system for physical and social pain. *Trends in Cognitive Sciences*, *8*, 294–300. doi:10.1016/j.tics.2004.05.010

Eisenberger, N. I., Lieberman, M. D., & Williams, K. D. (2003). Does rejection hurt? An fMRI study of social exclusion. *Science*, *302*, 290–292.

Engel, C. (2011). Dictator games: A meta study. *Experimental Economics*, *14*, 583–610. doi:10.1007/s10683-011-9283-7

Forsythe, R., Horowitz, J. L., Savin, N. E., & Sefton, M. (1994). Fairness in simple bargaining experiments. *Games and Economic Behavior*, *6*, 347–369. doi:10.1006/game.1994.1021

Güth, W., & Kocher, M. G. (2014). More than thirty years of ultimatum bargaining experiments: Motives, variations, and a survey of the recent literature. *Journal of Economic Behavior & Organization*, *108*, 396–409. doi:10.1016/j.jebo.2014.06.006

Güth, W., Schmittberger, R., & Schwarze, B. (1982). An experimental analysis of ultimatum bargaining. *Journal of Economic Behavior & Organization*, *3*, 367–388. doi:10.1016/0167-2681(82)90011-7

Higham, J. P., Barr, C. S., Hoffman, C. L., Mandalaywala, T. M., Parker, K. J., & Maestripieri, D. (2011). Mu-opioid receptor (OPRM1) variation, oxytocin levels and maternal attachment in free-ranging rhesus macaques *Macaca mulatta*. *Behavioral Neuroscience*, *125*, 131–136. doi:10.1037/a0022695

Hsu, D. T., Sanford, B. J., Meyers, K. K., Love, T. M., Hazlett, K. E., Wang, H., . . . Zubieta, J. K. (2013). Response of the μ-opioid system to social rejection and acceptance. *Molecular Psychiatry*, *18*, 1211–1217. doi:10.1038/mp.2013.96

Hwang, I. C., Park, J.-Y., Myung, S.-K., Ahn, H. Y., Fukuda, K.-i., & Liao, Q. (2014). OPRM1 A118G gene variant and postoperative opioid requirement: A systematic review and meta-analysis. *Anesthesiology*, *121*, 825–834. doi:10.1097/ALN.0000000000000405

Ioannidis, J. P. A. (2005). Why most published research findings are false. *PLOS Medicine*, *2*(8), Article e124. doi:10.1371/journal.pmed.0020124

JASP Team. (2018). JASP (Version 0.9.1) [Computer software]. Retrieved from https://jasp-stats.org/

Johnson, N. D., & Mislin, A. A. (2011). Trust games: A meta-analysis. *Journal of Economic Psychology*, *32*, 865–889. doi:10.1016/j.joep.2011.05.007

Kosoy, R., Nassir, R., Tian, C., White, P. A., Butler, L. M., Silva, G., . . . Seldin, M. F. (2009). Ancestry informative marker sets for determining continental origin and admixture proportions in common populations in America. *Human Mutation*, *30*, 69–78. doi:10.1002/humu.20822

Kross, E., Berman, M. G., Mischel, W., Smith, E. E., & Wager, T. D. (2011). Social rejection shares somatosensory representations with physical pain. *Proceedings of the National Academy of Sciences, USA*, *108*, 6270–6275.

Kross, E., Egner, T., Ochsner, K., Hirsch, J., & Downey, G. (2007). Neural dynamics of rejection sensitivity. *Journal of Cognitive Neuroscience*, *19*, 945–956. doi:10.1162/jocn.2007.19.6.945

Lee, M. D., & Wagenmakers, E. J. (2013). *Bayesian cognitive modeling: A practical course*. Cambridge, England: Cambridge University Press.

Lieberman, M. D., & Eisenberger, N. I. (2015). The dorsal anterior cingulate cortex is selective for pain: Results from large-scale reverse inference. *Proceedings of the National Academy of Sciences, USA*, *112*, 15250–15255.

Machin, A. J., & Dunbar, R. (2011). The brain opioid theory of social attachment: A review of the evidence. *Behaviour*, *148*, 985–1025. doi:10.1163/000579511X596624

Mehrabian, A. (1994). Evidence bearing on the Affiliative Tendency (MAFF) and Sensitivity to Rejection (MSR) scales. *Current Psychology*, *13*, 97–116. doi:10.1007/BF02686794

Munafò, M. R., Nosek, B. A., Bishop, D. V. M., Button, K. S., Chambers, C. D., Percie du Sert, N., . . . Ioannidis, J. P. A. (2017). A manifesto for reproducible science. *Nature Human Behaviour*, *1*, Article 0021. doi:10.1038/s41562-016-0021

Open Science Collaboration. (2015). Estimating the reproducibility of psychological science. *Science*, *349*, Article aac4716. doi:10.1126/science.aac4716

Patterson, N., Price, A. L., & Reich, D. (2006). Population structure and eigenanalysis. *PLOS Genetics*, *2*(12), Article e190. doi: 10.1371/journal.pgen.0020190

Perini, I., Gustafsson, P. A., Hamilton, J. P., Kämpe, R., Zetterqvist, M., & Heilig, M. (2018). The salience of self, not social pain, is encoded by dorsal anterior cingulate and insula. *Scientific Reports*, *8*(1), Article 6165. doi:10.1038/s41598-018-24658-8

Ramchandani, V. A., Umhau, J., Pavon, F. J., Ruiz-Velasco, V., Margas, W., Sun, H., . . . Heilig, M. (2010). A genetic determinant of the striatal dopamine response to alcohol in men. *Molecular Psychiatry*, *16*, 809–817. doi:10.1038/mp.2010.56

Robinson, J. E., Vardy, E., DiBerto, J. F., Chefer, V. I., White, K. L., Fish, E. W., . . . Malanga, C. J. (2015). Receptor reserve moderates mesolimbic responses to opioids in a humanized mouse model of the *OPRM1* A118G polymorphism. *Neuropsychopharmacology*, *40*, 2614–2622. doi:10.1038/npp.2015.109

Torre, J. B., & Lieberman, M. D. (2018). Putting feelings into words: Affect labeling as implicit emotion regulation. *Emotion Review*, *10*, 116–124. doi:10.1177/1754073917742706

Wager, T. D., Atlas, L. Y., Botvinick, M. M., Chang, L. J., Coghill, R. C., Davis, K. D., . . . Yarkoni, T. (2016). Pain in the ACC? *Proceedings of the National Academy of Sciences, USA*, *113*, E2474–E2475.

Way, B. M., Taylor, S. E., & Eisenberger, N. I. (2009). Variation in the μ-opioid receptor gene (*OPRM1*) is associated with dispositional and neural sensitivity to social rejection. *Proceedings of the National Academy of Sciences, USA*, *106*, 15079–15084. doi:10.1073/pnas.0812612106

Williams, K. D., Cheung, C. K. T., & Choi, W. (2000). Cyberostracism: Effects of being ignored over the Internet. *Journal of Personality and Social Psychology*, *79*, 748–762. doi:10.1037/0022-3514.79.5.748

Woo, C.-W., Koban, L., Kross, E., Lindquist, M. A., Banich, M. T., Ruzic, L., . . . Wager, T. D. (2014). Separate neural representations for physical pain and social rejection. *Nature Communications*, *5*, Article 5380. doi:10.1038/ncomms6380

Zadro, L., Williams, K. D., & Richardson, R. (2004). How low can you go? Ostracism by a computer is sufficient to lower self-reported levels of belonging, control, self-esteem, and meaningful existence. *Journal of Experimental Social Psychology*, *40*, 560–567. doi:10.1016/j.jesp.2003.11.006

Zhang, Y., Wang, D., Johnson, A. D., Papp, A. C., & Sadée, W. (2005). Allelic expression imbalance of human mu opioid receptor (*OPRM1*) caused by variant A118G. *Journal of Biological Chemistry*, *280*, 32618–32624. doi:10.1074/jbc.M504942200

Zubieta, J., Ketter, T. A., Bueller, J. A., Xu, Y., Kilbourn, M. R., Young, E. A., & Koeppe, R. A. (2003). Regulation of human affective responses by anterior cingulate and limbic μ-opioid neurotransmission. *Archives of General Psychiatry*, *60*, 1145–1153. doi:10.1001/archpsyc.60.11.1145