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THE EFFECT OF THE A118G SINGLE NUCLEOTIDE POLYMORPHISM OF THE MU-OPIOID RECEPTOR GENE (OPRM1) ON LONELINESS, SOCIAL SUPPORT, RUMINATION AND MOOD

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ABSTRACT

The A118G single nucleotide polymorphism (SNP) for the mu-opioid receptor gene (OPRM1) influences how both physical and social pain are experienced in primates and in humans. The G118 allele has been associated with decreased production of the associated mRNA and protein, increased pain after surgery and higher doses of morphine post-surgery, relative to the A118 allele. It has also been associated with increased sensitivity to social rejection. Based on these data, we hypothesized that the G118 allele would be associated with higher levels of loneliness (UCLA Loneliness Scale), lower levels of social support (Interpersonal Support Evaluation List, ISEL), higher levels of rumination (brooding; Ruminative Response Scale, RRS), lower levels of positive affect and higher levels of negative affect (modified version of the Positive and Negative Affect Schedule, PANAS) as well as greater changes in mood, in comparison to the A118 allele. These measures were administered to 107 undergraduate students at a large Eastern university (mean (*M*)=19.06 years, SD=1.19). Participants were randomly assigned to a recall task condition (either neutral recall, loneliness recall or academic failure recall). As part of a larger study, the participants were monitored for the duration of the study. Mood was assessed at the end of the initial baseline period, at the end of the recall task, and at the end of the recovery period. Buccal swabs were then used to collect DNA samples to determine the participant's genotype for the A118G SNP. Those with the G118 allele (referred to as the G118 Group) showed a trend of having a higher mean loneliness score, a lower mean social support score, a higher mean rumination score, a lower mean baseline positive affect score and a higher mean baseline negative affect score than those without the G118 allele (referred to as the A118 Group); however, due possibly to inadequate power, these relationships were found to not be significant (ps>.05). Significant findings include that the positive affect of the G118 Group decreased to a greater degree than did that of the A118 Group in response to the academic failure recall task (p<.05), and that the positive affect of the G118 Group increased to a greater degree than did that of the A118 Group in response to the neutral recall task (p<.05). The trends suggest a possible association between the A118G SNP and social pain. Studies with larger sample sizes are required to further evaluate the relationship between the G118 SNP for the OPRM1 and social pain.

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Introduction

The mu-opioid receptor has been associated with the experience of differential degrees of both physical and social pain (Carden, Barr, & Hofer, 1991; Sia, et al., 2008; Way, Taylor, & Eisenberger, 2009); and is the target of both morphine and heroin (Basbaum & Fields, 1984; Kreek, 1996; Pasternak, 1993). Studies that focused on the commonly occurring A118G functional single nucleotide polymorphism (SNP) have found associations between the G118 allele and decreased production of the associated mRNA and protein (Zhang, Wang, Johnson, Papp, & Sadee, 2005), increased pain after surgery and self-administering higher doses of morphine post-surgery (Sia, et al., 2008), and an increased sensitivity to social rejection (Way, Taylor, & Eisenberger, 2009), relative to the A118 allele. The purpose of the present study was to investigate the possible relationship between the A118G SNP of the OPRM1 and constructs that relate to social pain, including loneliness, social support, rumination and mood.

Loneliness

Loneliness has been defined as the deficit between an individual's desired and actual social relations (Peplau & Perlman, 1982). Social isolation does not necessarily mean that an individual is lonely; one can be alone and not be lonely, and, conversely, one can be at a social event in a room full of people that he or she knows, and yet, can still be lonely (Peplau & Caldwell, 1978). The literature discusses two types of loneliness, state and trait. State loneliness refers to the degree to which an individual feels lonely during a given moment or during a specific situation, while trait loneliness refers to the degree to which an individual feels lonely over the long term (Perlman & Peplau, 1998). Trait loneliness is relatively consistent over an individual's lifetime and state loneliness is situation-specific (Perlman & Peplau, 1998). The present study focused on trait loneliness because of its stability across the life span.

Social Support

An individual's perception of loneliness is influenced by his or her perceived social support. Social support includes instrumental support (tangible assistance), informational support and emotional support that leads an individual to believe that he or she is cared for, loved, esteemed and valued, and that he or she belongs to a network of communication and mutual obligation (Cobb, 1976; Taylor, 2006). Research has shown that, when predicting health outcomes, an individual's perceived social support may be more important than the social support that he or she actually receives (Helgeson, 1993; Stroebe, Stroebe, Abakoumkin, & Schut, 1996). Stroebe and colleagues found that those who perceived more

social support reported fewer depressive symptoms than those who perceived less social support, and Helgeson found that the individuals who perceived more social support were more likely to better adjust after experiencing a cardiac event than the individuals who perceived less social support receives (Helgeson, 1993; Stroebe, Stroebe, Abakoumkin, & Schut, 1996). The present research assessed perceived social support because of its strong predictive value regarding health outcomes and wellbeing.

Rumination

According to the response styles theory explained by Nolen-Hoeksema (1991), rumination is a response to distress that involves repetitively rethinking previous events (Nolen-Hoeksema & Morrow, 1991). This response style involves self-focus, enhances the effects of negative mood, and involves passively reanalyzing the prior events without taking action to solve any of the problems that may have occurred (Nolen-Hoeksema, 1990; Nolen-Hoeksema, 1991). Individuals with depressive symptoms who tend to ruminate about the causes and implications of their depressive symptoms are more likely to experience longer periods of depression than individuals who distract themselves from reanalyzing the causes and implications of their depression (Nolen-Hoeksema, 1987; Nolen-Hoeksema, 1990; Nolen-Hoeksema & Morrow, 1991). Research suggests that perceived social support mediates the extent to which trait ruminators ruminate on a daily basis; Puterman and colleagues found that higher levels of perceived social support protected trait ruminators from ruminating on a daily basis (Puterman, Delongis, & Pomaki, 2010).

The Mu-Opioid Receptor Gene (OPRM1)

The A118G SNP of the OPRM1 is thought to be involved in the experience of physical and social pain (Carden, Barr, & Hofer, 1991; Sia, et al., 2008; Way, Taylor, & Eisenberger, 2009). The mu-opioid receptor is a G protein-coupled receptor located in the brain and is the primary target of the endogenous opioid peptide beta-endorphin in addition to the opiates morphine and heroin (Basbaum & Fields, 1984; Kreek, 1996; Pasternak, 1993; Selley & Bidlack, 1992). The A118G SNP affects the functioning of the receptor because the change in the nucleotides causes adenine to be replaced with guanine, which leads to the incorporation of aspartic acid instead of asparagine into the 40^{th} amino acid in the nascent protein (Asn40Asp) (Mahmoud, et al., 2011). While this change has been associated with reduced levels of both mu-opioid receptor mRNA and protein when compared to the A118 allele, the SNP is not lethal (Zhang, Wang, Johnson, Papp, & Sadee, 2005). The A118G functional polymorphism occurs at the beginning of exon 1 in humans, and the G118 allele is present in approximately 15-30% of people of European ancestry, 40-50% of people of Asian

ancestry and approximately 1-3% of people of African American and Hispanic ancestry (Mague & Blendy, 2010).

Additional studies have investigated the effects of morphine on the mu-opioid receptor with respect to social pain, and a study conducted with rats demonstrated that the administration of low doses of morphine to rat pups reduces isolation calls when the pups are separated from their mother (Carden, Barr, & Hofer, 1991). Through a social rejection simulation with humans and the analysis of fMRI brain scans, researchers found that humans with at least one copy of the G118 allele (either homozygous or heterozygous for the G118 allele) were more likely to be more sensitive to social rejection than humans without the G118 allele (Way, Taylor, & Eisenberger, 2009). The above findings, combined with the fact that the G118 allele has been associated with the experience of more physical pain post-surgery and an increased self-administration of post-surgical morphine usage relative to individuals without the G118 allele, suggest that the OPRM1 may be associated with the moderation of both physical and social pain (Sia, et al., 2008).

If the OPRM1 affects both physical and social pain, the genotype at the A118G SNP may predict an individual's level of trait loneliness, perceived social support, trait rumination, baseline positive and negative affect and mood fluctuation. The purpose of the present study was to ascertain if the A118G SNP predicts trait loneliness, perceived social support, rumination, positive and negative affect, and mood fluctuation. It was hypothesized that individuals with the G118 allele of the mu-opioid receptor (genotype A/G or G/G) would (H1) be more likely to score higher on the trait loneliness scale and therefore be more lonely than those without the G118 allele (A/A genotype), (H2) be more likely to report lower levels of perceived social support, and (H3) be more likely to score higher on the trait rumination scale than individuals without the G118 allele. We also predicted that individuals with the G118 allele would (H4) be more likely to report lower baseline positive affect and higher baseline negative affect than individuals without the G118 allele, and that (H5) their mood would be more likely to be affected to a greater degree by the recall task than the mood of the individuals without the G118 allele. These hypotheses were based on the association found by Way and colleagues between individuals who have the G118 allele and high sensitivity to social rejection (Way, Taylor, & Eisenberger, 2009). If the G118 allele is a genetic predisposition for high sensitivity to social rejection, it may indicate that these individuals are also more likely to be both acutely and chronically stressed by social situations, which may cause them to experience more social pain than those without the G118 allele.

Methods

Participants

A total of 110 participants completed the study. Three participants were excluded from the analysis because the genotype determination revealed that only one of the participants was homozygous for the G118 allele (G/G) and genotype determination in two of the participants was inconclusive. Of the 107 participants included in the analysis, 85 were women and 22 were men, the mean (*M*) age was 19.06 years (SD=1.19), and 74.8% were Caucasian, 10.3% African American, 5.6% Asian, 4.7% Hispanic and 4.7% identified as "Other". Demographic information is shown in Table 1. The participants were recruited from introductory Psychology Department courses, and received credit in exchange for their participation in the study. All participants gave their informed consent, consistent with the requirements and approval of the Penn State Institutional Review Board.

Table 1
Demographic Information

	n	**Mean**	**SD**
Age (years)	107	19.06	1.188
	n	**%**	
Sex			
Male	22	20.6	
Female	85	79.4	
A118G Genotype			
A/A	82	76.6	
A/G	25	23.4	
Race			
Caucasian	80	74.8	
African American	11	10.3	
Asian	6	5.6	
Hispanic	5	4.7	
Other	5	4.7	

Materials

DNA Collection and Genotyping

Cotton wool buccal swabs were used to collect epithelial cells from the participants. DNA from the swabs was extracted by the Genomics Core Facility of Huck Institutes for Life Sciences at Pennsylvania State University. Genotypes were determined using a TaqMan assay (LifeTech/Applied Biosystems Assay ID: C__8950074_1, rs1799971) following the manufacturer's protocol on an Applied Biosystems Genetic Analyzer.

Variables

Independent Variable

The independent variable was the participant's genotype for the A118G SNP of the OPRM1, either homozygous for the A118 allele (A/A) or heterozygous (A/G).

Dependent Variables

There were two types of dependent variables, the trait variables that included the UCLA loneliness score, the ISEL perceived social support score, the RRS rumination score, and the state variable which was PANAS mood score.

Loneliness

The UCLA Loneliness Scale (ULS; 20 items; Russell, 1996) was used to assess trait loneliness, the degree to which the participants were lonely in their daily lives ($\alpha = .92$ in the present sample). Participants responded to the questions using a 1 (Never) to 4 (Always) Likert-type scale. Each participant's score was calculated by averaging the items of the scale after reverse coding when appropriate. Higher scores indicate a greater level of loneliness.

Social Support

The Interpersonal Support Evaluation List (ISEL; 48-items; Cohen, Mermelstein, Kamarack, & Hoberman, 1985) was used to measure the amount of social support the participants felt that they had ($\alpha = .85$ in the present sample). Participants responded to items using a 1 = True and 2 = False scale and the scores were averaged together such that higher scores indicate more social support.

Rumination

The Ruminative Response Scale (RRS; 22 items; Nolen-Hoeksema & Morrow 1991), a subscale of the Response Styles Questionnaire, was used to evaluate trait rumination, the degree to which the participant used rumination to cope with negative feelings ($\alpha = .93$ in the present sample). Each participant's score was calculated by averaging the items of the scale after reverse coding when appropriate. Higher scores indicate a greater level of rumination.

Mood

A modified version of the Positive and Negative Affect Schedule (PANAS; 14 items; Watson, Clark, & Tellegen, 1988) was used to assess the degree to which the participants were experiencing a positive or negative affect. The scale was adapted to reduce the number of items, and during the analyses, the positive affect items were separated from the negative affect items to create two subscales. The positive affect items assessed the degree to which the participant was feeling calm, certain, happy, pleasant, confident and positive. The negative affect items assessed the degree to which the participant was feeling unpleasant, sad,

angry, negative, uncertain, doubtful and anxious. The last item, loneliness, assessed state loneliness and was not included in the affect analysis. Participants responded to items using a 1 (Not at All) to 7 (Very Much) Likert-type scale. Across the three time points, the reliabilities for the positive (αs = .90 - .93) and negative (αs = .87 - .90) affect scales were high. For each time point, items were combined such that higher scores indicate more positive and more negative affect.

Procedure

As part of a larger study, the participants first completed the UCLA Loneliness Scale, the Interpersonal Support Evaluation List and the Ruminative Response Scale. Mood was assessed after an initial ten minute baseline period. The participant was then asked to complete the neutral, loneliness or academic failure recall task, depending on the condition that the participant was randomly assigned to. During this task (stressor) the participant was asked to spend eight minutes writing about a time in their life that related to their assigned condition (neutral condition= a time when the participant felt relaxed, loneliness condition= a time when the participant felt lonely, academic failure recall= a time when the participant failed an academic task). Mood was assessed a second time after the recall task was completed. After the participant remained seated for a ten minute recovery period mood was assessed a third time.

Epithelial cells were then collected from each participant using cotton wool buccal swabs. Each participant was instructed to gently, yet firmly, rub the swab along the inside of their mouth for 20 seconds, taking care to collect cheek cells and not rub against the gum. This was repeated for a total of ten swabs for each participant. The participants were asked to target a different area of their cheek with each swab to try to avoid excessive overlap in an effort to collect an adequate amount of cells. After the buccal swabs were collected, they were sent to the Genomic Core Facility at Pennsylvania State University to be extracted and processed using a TaqMan SNP Assay for the mu-opioid receptor gene that was purchased from Applied Biosystems (Assay ID: C__8950074_1, rs1799971). After the study was completed the participants were debriefed.

SPSS software was used to organize and analyze the collected data. The statistical analysis was conducted through independent t-tests, three-way repeated measure analyses of variance (ANOVAs) and pairwise comparisons.

Results

Of the 107 participants, 82 were homozygous for the A118 allele (A/A) (Caucasian n=62, African American n=11, Asian n=4, Hispanic n=4, Other n=1) and 25 were heterozygous (A/G) (Caucasian n=18, African American n=0, Asian n=2, Hispanic n=1, Other n=4). We will refer to the participants who were homozygous for the A118 allele (A/A) as the **A118 Group**, and those who were heterozygous (A/G) as the **G118 Group**. In the present study, the frequency of the A118 allele was 87.5% and the frequency of the G118 allele was 12.5% (Caucasian 88.75% A118, 11.25% G118; African American 100% A118, 0% G118; Asian 83.3% A118, 16.7% G118; Hispanic 90% A118, 10% G118; Other 60% A118, 40% G118).

Between-Subjects Analyses

Independent sample t-tests were performed to analyze the effect of the specific allele on each of the outcome measures (loneliness, social support, rumination and mood). The significance level for all tests was set at $p<.05$. The results of these between-subject analyses, including the mean loneliness, social support, rumination and mood scores, are shown in Table 2. The mean loneliness score of the G118 Group was 0.04 higher than that of the A118 Group, the mean social support score of the G118 Group was 0.01 lower than the A118 Group, and the mean rumination score of the G118 Group was 0.11 higher than that of the A118 Group, however these findings were not significant (all *p*s>.05). At baseline, the mean positive affect score of the G118 Group was 0.32 lower than that of the A118 Group, and the mean negative affect score was 0.15 higher than that of the A118 Group; after the stressor the mean positive affect score of the G118 Group was 0.01 higher than that of the A118 Group, and the mean negative affect score of the G118 Group was 0.08 lower than that of the A118 Group; at the end of the recovery period the mean positive affect score of the G118 Group was 0.09 lower than that of the A118 Group, and the mean negative affect score of the G118 Group was 0.08 higher than that of the A118 Group, however these findings were not significant (all *p*s>.05). Although these findings were not found to be significant, as the table shows, there was a trend for the analyses to be in the hypothesized direction: the G118 Group had a higher mean loneliness score, a lower mean social support score, a higher mean rumination score, a lower mean baseline positive affect score and a higher mean baseline negative affect score than did the A118 Group.

Table 2
T-Test Results Comparing Loneliness, Rumination and Social Support by A118G SNP Genotype

	T score	**DF**	**P value**	**A/A (*M*)**	**A/G (*M*)**
UCLA Loneliness Score	-.500	60.643	.619	1.78	1.82
ISEL Score	.450	105	.654	1.19	1.18
RRS Score	-1.067	105	.288	1.75	1.86
Positive Affect					
Baseline	1.316	105	.191	5.09	4.77
Stressor	-.054	105	.957	4.76	4.77
Recovery	.321	105	.749	4.90	4.81
Negative Affect					
Baseline	-.686	105	.494	2.09	2.24
Stressor	.323	105	.747	2.53	2.45
Recovery	-.319	105	.750	2.21	2.29

Note: Affect was assessed at the end of the baseline period, immediately after the stressor (recall task) was completed and at the end of the recovery period.

Within-Subjects Analyses

Comparisons of the mean positive and negative affect scores recorded during each of the three phases – baseline, stressor (recall task) and recovery, between the A118 Group and the G118 Group were made using a repeated measures analysis of variance (ANOVA). Preliminary analyses revealed that eight participants with the G118 allele completed the neutral recall task, 13 completed in the failure recall task, but that only four completed the loneliness recall task. As a result, the loneliness recall task was excluded from further analyses. A three-way repeated measures analysis ANOVA was used to assess the impact of the A118G SNP genotype (A/A or A/G) and the recall task condition (neutral recall or academic failure recall) on mood at Time 1 (immediately after the baseline period), Time 2 (immediately following the stressor), and Time 3 (at the end of the recovery period). Participants were divided into groups according to their A118G genotype (Group 1: G118 allele absent, Group 2: G118 allele present). The repeated measures ANOVA for positive affect revealed a significant within-subjects effect ($p<.05$) as shown in Table 3, and the mean positive affect scores at Time 1, Time 2 and Time 3 by A118G SNP genotype and recall task condition are shown in Table 4. The three-way repeated measures ANOVA for negative affect revealed no significant relationship between the A118G SNP genotype, the recall task condition and mood ($p>.05$) as shown in Table 3.

Table 3
Three-Way ANOVA Results Comparing A118G SNP Genotype on Mood During Randomly Assigned Recall Task

	F score	DF	P value
Between-Subjects Effects			
Positive Affect	.016	1	.901
Negative Affect	.089	1	.767
Within-Subjects Effects			
Positive Affect	3.796	2	.025
Negative Affect	2.429	2	.092

Table 4
Mean Positive Affect by A118G SNP Genotype and Recall Task Condition

	Mean	Standard Error	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Academic Failure Recall Condition				
A/A				
Baseline	4.95	.237	4.48	5.42
Stressor	4.53	.260	4.01	5.05
Recovery	4.76	.259	4.239	5.28
A/G				
Baseline	4.89	.294	4.30	5.47
Stressor	4.24	.323	3.60	4.89
Recovery	4.64	.322	4.00	5.29
Neutral Recall Condition				
A/A				
Baseline	5.12	.216	4.69	5.55
Stressor	5.51	.238	5.03	5.98
Recovery	5.24	.237	4.77	5.72
A/G				
Baseline	4.52	.374	3.77	5.27
Stressor	5.65	.411	4.82	6.47
Recovery	5.02	.410	4.20	5.84

Note: Affect was assessed at the end of the baseline period, immediately after the stressor (recall task) was completed and at the end of the recovery period.

Pairwise comparisons were conducted to further assess the significance of the interaction between the A118G SNP genotype, the randomly assigned recall condition, and positive affect; the results are shown in Table 5, and also in Figures 1 and 2. The comparisons showed that the mean positive affect of the G118 Group decreased to a greater degree than did that of the A118 Group in response to the academic failure recall task ($M_{difference}$ = -0.64, p<.05; $M_{difference}$ = -0.43, p<.05, respectively), and that recovery of positive affect following the academic failure recall task tended to be approximately the same for both the G118 and

the A118 Group ($M_{difference}$= -0.24, p>.05; $M_{difference}$ = -0.19, p>.05). The pairwise comparisons also showed that the mean positive affect of the G118 Group increased to a greater degree than did that of the A118 Group in response to the neutral recall task ($M_{difference}$= +1.13 , p<.05; $M_{difference}$= +0.39, p<.05, respectively).

Table 5
Pairwise Comparisons of the A118G SNP Genotype by Randomly Assigned Task Condition on Positive Affect

	Difference in Means	Standard Error	P value
Academic Failure Recall Condition			
A/A			
Baseline-Stressor	-0.43*	.149	.006
Stressor-Recovery	+0.23	.139	.099
Baseline-Recovery	-0.19	.139	.174
A/G			
Baseline-Stressor	-0.64*	.185	.001
Stressor-Recovery	+0.40*	.173	.025
Baseline-Recovery	-0.24	.173	.164
Neutral Recall Condition			
A/A			
Baseline-Stressor	+0.39*	.136	.006
Stressor-Recovery	-0.26*	.127	.042
Baseline-Recovery	+0.16	.127	.330
A/G			
Baseline-Stressor	+1.13*	.236	.000
Stressor-Recovery	-0.63*	.220	.006
Baseline-Recovery	+0.50*	.221	.027

Note: Positive affect was assessed at the end of the baseline period, immediately after the stressor (recall task) was completed and at the end of the recovery period. The difference in the means was calculated by subtracting the mean positive affect score of the latter assessment point from the mean positive affect score of the former assessment point. * p<0.05.

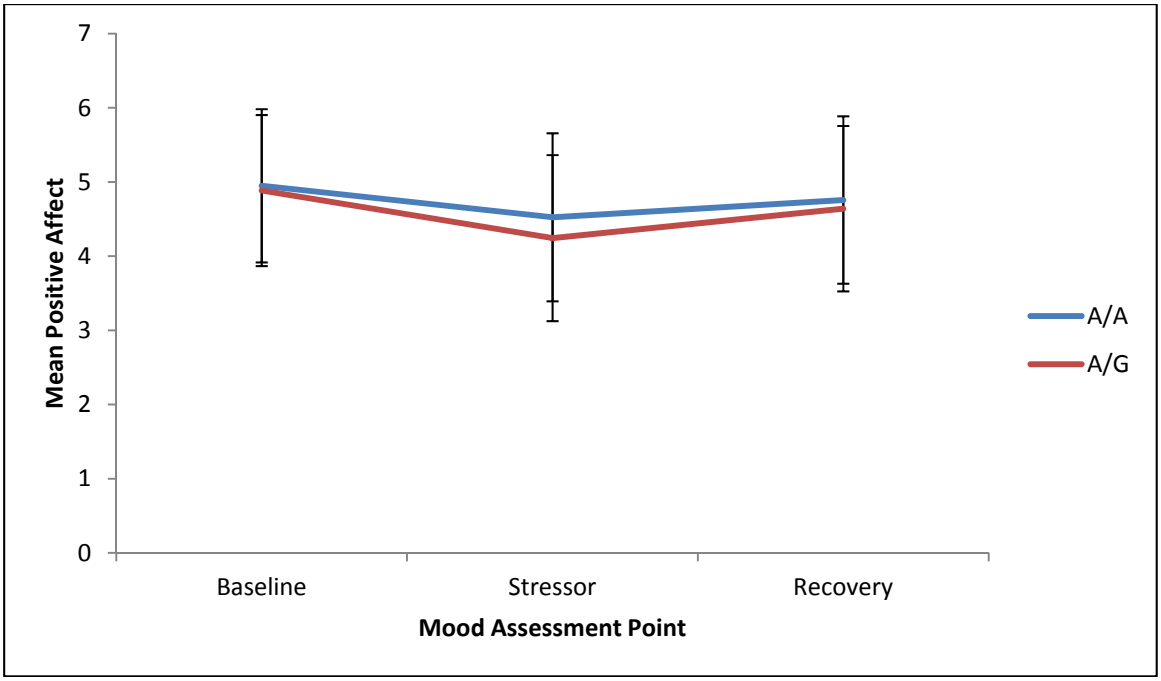

Figure 1. Mean positive affect by A118G SNP genotype in those who completed the academic failure recall task. Error bars represent standard deviation of the mean.

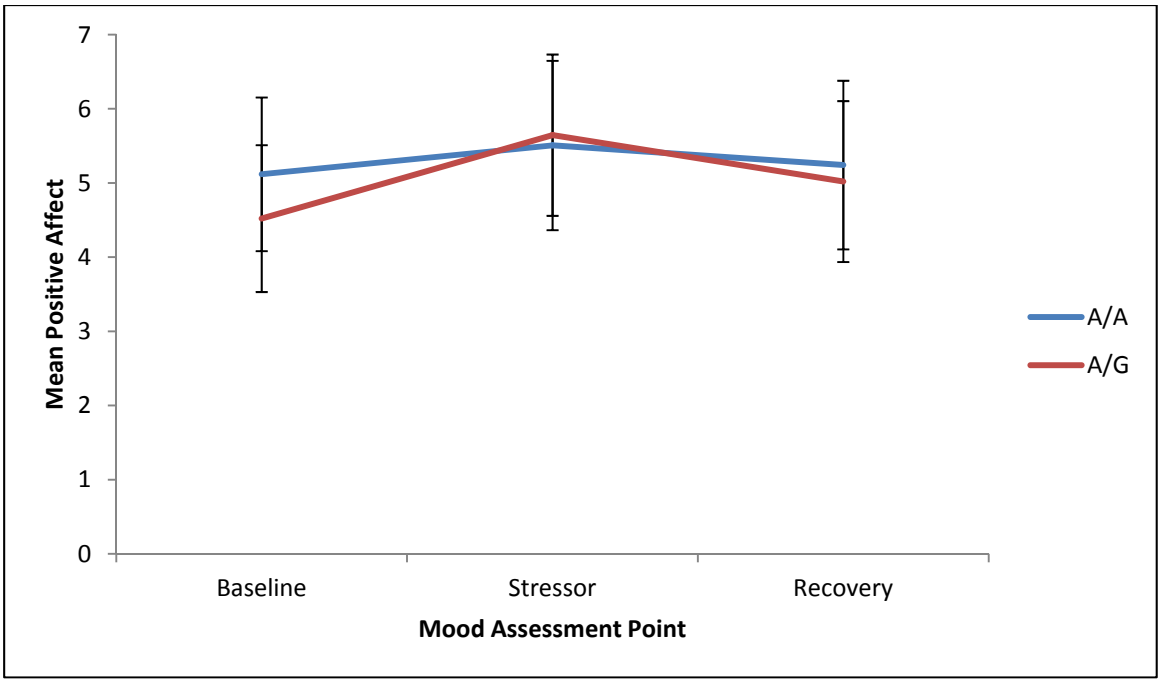

Figure 2. Mean positive affect by A118G SNP genotype in those who completed the neutral recall task. Error bars represent standard deviation of the mean.

Discussion

The positive affect of all of the participants increased after the neutral recall task, which indicates that the neutral recall was more positive than neutral with respect to its effects on mood. The mean positive affect of the G118 Group decreased to a greater degree in response to the academic failure recall task, and increased to a greater degree in response to the neutral recall task, than did that of the A118 Group. These findings suggest that those with the G118 allele are more sensitive to mood manipulation than those without the G118 allele.

The participants with the G118 allele had higher mean loneliness, rumination and baseline negative affect scores, and lower mean social support and baseline positive affect scores, than those without the G118 allele. Although these differences were not significant, it is possible that the small sample size provided insufficient power to detect effects; such analyses, in these alleles, are ordinarily conducted in samples with thousands of participants. The trends, however, suggest a possible association between the A118G SNP genotype and loneliness, social support and rumination. If the G118 allele is associated with these constructs we would expect it to be positively associated with loneliness and rumination, and negatively associated with social support. These trends support our hypotheses, to some extent, that those with the G118 allele are more likely to be lonely, have lower levels of social support and are more likely to ruminate, than those without the G118 allele. However, as the differences were not significant, we cannot make strong statements about the possible relationships.

One obvious limitation of the present study concerns the small sample size (n=107), as noted previously. A second limitation was the small number of participants with the G118 allele who completed the loneliness recall task. Ideally we would have had more participants assigned to this condition, but because we did not determine the genotypes until after the study was over we could not adjust for the low prevalence of the G118 allele. Another limitation concerns the lack of racial diversity in the sample population, which limited the generalizability of the results. An additional issue to address is the nature of the neutral recall task, which was designed to neither positively nor negatively affect the participant's mood, however, we found that the task positively impacted mood in all groups. Future studies should have larger sample sizes and should explore new neutral recall tasks.

In summary, while the findings relating trait loneliness, social support, rumination and baseline mood to the A118G SNP genotype were not significant, the present research

revealed trends that support a possible association between the A118G SNP of the mu-opioid receptor gene and social pain. Future research is needed to further assess the possible relationship between the A118G SNP and constructs related to social pain, including loneliness, social support, rumination and mood, using a larger, more racially diverse sample size. Future studies may also measure additional constructs related to social pain by including a sensitivity to social rejection scale and a perceived stress assessment, in addition to including measurements of sensitivity to physical pain.

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