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Oxytocin receptor gene variation predicts empathic concern and autonomic arousal while perceiving harm to others

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Abstract

Recent research indicates that the neuropeptide oxytocin and the gene for the oxytocin receptor (*OXTR*) have been implicated in the modulation of various social behaviors, including those related to empathy and sensitivity to others. In this study, we examine the hypothesis that genetic variation in *OXTR* is associated with autonomic reactions when perceiving others in distress. We also explore the possibility that individual disposition in empathic concern would differ by *OXTR* genotype. To address these questions, fifty-one male participants (18–35 years of age), genotyped for *OXTR* rs53576, viewed a social interaction containing high levels of individual distress and apparent physical pain. Electrodermal activity, a measure of sympathetic nervous system activity, was collected during the presentation of the stimuli. Participants also completed a self-report dispositional measure of empathy prior to starting the study and provided ratings of arousal while viewing the stimuli. *OXTR* variant rs53576 GG individuals showed increased levels of sympathetic and subjective arousal in response to the stimuli compared to A allele carriers. GG homozygotes also expressed greater levels of empathic concern. These findings support the importance of the oxytocin receptor variation in emotional and physiological reactions to the experiences of other conspecifics.

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Keywords

OXTR; electrodermal activity; empathy; arousal; empathic concern

Introduction

Oxytocin, a neuropeptide with widespread targets in both the brain and periphery, has been implicated in the regulation of various social behaviors ranging from social bonding and attachment to ally selection and intergroup cooperation (Bartz & Hollander, 2006; Carter, 1998; De Dreu et al., 2010; Ebstein, Knafo, Mankuta, Chew, & Lai, 2012; Kendrick, Keverne, & Baldwin, 1987; Ross & Young, 2009). Oxytocin modulates a variety of social behaviors, such as trust, generosity, and empathy (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Kogan et al., 2011; Rodrigues, Saslow, Garcia, John, & Keltner, 2009; Tost et al., 2010), as well as parental care (Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010; Neville, McFadden, & Forsyth, 2002). In addition to these pro-social behaviors, oxytocin administration has been found to increase aggression towards out-group members (De Dreu et al., 2010) and increase gloating and envy (Shamay-Tsoory et al., 2009). Additionally, some of the pro-social effects of oxytocin appear to be moderated by caregiving experiences during early development (Bartz et al., 2010; Riem, Bakermans-Kranenburg, Huffmeijer, & van Ijzendoorn, 2013; van Ijzendoorn, Huffmeijer, Alink, Bakermans-Kranenburg, & Tops, 2011). Recent work suggests that oxytocin's effects on social behavior may be a result of oxytocin modulating the salience of some forms of biological and socioaffective stimuli cues (Kéri & Benedek, 2009; Prehn et al., 2013).

Genetic variation in the oxytocin receptor (*OXTR*) has been associated with individual differences in the expression of various social behaviors including empathic concern and social cognition (Park et al., 2010; Rodrigues et al., 2009; Wu, Li, & Su, 2012). Furthermore, the A allele of *OXTR* rs53576 has been associated with decreased hypothalamus and amygdala volumes, areas of the brain extensively involved in regulation of social and emotional behaviors (Ebstein et al., 2012; Tost et al., 2010).

The present study explored the relationship between *OXTR* genetic variation, using a relatively common single nucleotide polymorphism (SNP; rs53576), dispositional empathy, and individual differences in physiological and subjective reports of arousal to a social interactions involving high levels of pain and distress. This was tested by having individuals view a Mixed Martial Arts (MMA) video, a full contact combat sport where fighters inflict and experience high levels of distress and pain. We predicted that *OXTR* variation would be associated with individual differences in sensitivity to the social stimuli, evidenced through differences in physiological responses and self-reported arousal as well as with differences in levels of dispositional empathy. There is now a converging agreement that empathy is not a single ability but a complex socio-emotional competency that encompasses different components including empathic arousal and empathic concern (Decety, Norman, Berntson, & Cacioppo, 2012). Empathic arousal, which refers to the unconscious contagious sharing of affect, is the first building block of empathy to appear during ontogeny (Decety & Michalska, 2010; Michalska, Kinzler, & Decety, 2013; Roth-Hanania, Davidov, & Zahn-Waxler, 2011). This gives rise to the hypothesis that individual levels of empathy may be associated with individual differences in arousal experienced while viewing others in physical distress. This study also examined the relationship between levels of dispositional empathy, sympathetic arousal, measured by electrodermal activity, and subjective arousal, in response to viewing the MMA match and whether this relationship was associated with variation in a common SNP (rs53576) located within the oxytocin receptor.

Methods and Materials

Participants

Fifty-one males aged 18 – 35 of mixed race (57% Caucasian, 35% African American, 5.9% Asian, and 7.8% other or multiple ethnicities) were recruited from the Chicago area and provided monetary compensation for their participation. Participants gave written informed consent, and this study was approved by the University of Chicago's Institutional Review Board and conducted in accordance with the Declaration of Helsinki.

Procedure

Electrodermal activity (EDA), a measure of sympathetic nervous system activity (Stern, Ray, & Quigley, 2001), was collected while participants viewed a 28-minute Mixed Martial Arts (MMA) fight consisting of five rounds of fighting. MMA is a popular full contact combat sport similar to boxing and was chosen because it is an evocative social stimulus with fighters exhibiting high levels of pain and distress. After each of the five rounds of the fight, participants were asked to rate how arousing they found the fight on a Likert scale from 1 – 9. Prior to viewing the fight, participants provided a buccal cell swab or saliva sample for DNA analysis, completed the Interpersonal Reactivity Index (IRI), a self-report measure of empathy (Davis, 1980, 1983), and provided information on how often they watch MMA.

Electrodermal Activity

EDA was recorded with a pair of Ag/AgCl electrodes filled with Biopac© isotonic electrode gel from the distal phalanges of digits II and III on the left hand (Stern et al., 2001) using AcqKnowledge data recording software (version 3.8.1), running on a Windows XP computer, connected to a set of Biopac © amplifiers connected to a Biopac © MP 100 A A/D digitization system (digitizing signals at 1kHz; Biopac © Systems, Inc., Santa Barbara, CA, USA). Electrodes were left undisturbed for 5 minutes before data were collected to ensure they reached stable impedance. After collection, AcqKnowledge was used to extract and count the skin conductance responses (SCRs) from the EDA recording using its automated SCR detector with an SCR threshold of 0.02 umho (Dawson, Schell, & Filion, 2000). This analysis was manually supervised to ensure proper SCR identification. Participants with recording artifacts were excluded, leaving 28 participants with complete SCR data. EDA data were split into 5.6 minute segments to correspond with the five rounds of the fight. A pre-fight measure was also extracted using the first 30s of the recording after the start of the video to ensure differences in physiological measures across genotypes were driven by viewing the fight.

Genotyping

DNA was collected with an SK-2 Isohelix swab kit for buccal samples and Salimetrics 2mL cyrovial for saliva samples. All samples were immediately frozen in a -20^0 C freezer upon collection and transferred to a -80^0 C freezer until analysis. DNA was purified from saliva samples using the Gentra Puregene Buccal Cell kit (Qiagen Inc., Valencia, CA) and genotyped for the SNP (rs53576) in *OXTR* using a Pyromark Q24 pyrosequencer and Pyromark Gold reagents (both from Qiagen, Valencia, CA). Genotype distribution (and frequency) obtained for rs53576 were as follows: 27 G/Gs (48.2%), 21 A/Gs (37.5%), and 8 A/As (14.3%). This distribution does not deviate from the Hardy-Weinberg equilibrium, $\chi^2 = 1.3$, df = 2, p = 0.52. Because of the uneven distribution, A/A and A/G genotypes (referred to as A allele carriers) were combined for the purposes of analysis, as in previous work (Rodrigues et al., 2009). *OXTR* rs53576 was chosen for analysis due to power limitations

and the small sample size, and because it has been previously researched in respect to social behavior, including dispositional empathy (Rodrigues et al., 2009).

Statistical Analysis

To determine whether levels of empathy as assessed by the IRI differed, independent sample t-tests were run comparing GG homozygotes to A allele carriers. For both physiological and arousal measures, repeated measures ANOVAs were run to assess change in arousal over time in response to viewing the fight. To determine if there was a relationship between empathy and arousal change by genotype, change scores were calculated for EDA and self-reported arousal and regressions were run and used to conduct simple slope analyses.

Results

Empathy

To assess whether individual variation in *OXTR* genotype accounts for individual differences in empathy, independent sample t-tests were run on the four factors of the IRI comparing GG homozygotes to A allele carriers. Empathic concern, defined as the capacity to experience feelings of compassion, warmth, and concern in response to other people, was the only factor to show a significant difference between genotypes ($t(49) = -2.480$, $p = .017$), with GG ($x = 20.96$, $sd = 4.894$) participants showing increased dispositional levels of empathic concern compared to A carriers ($x = 17.89$, $sd = 3.935$, Figure 1).

Physiological Measures

A one way repeated measures ANOVA was conducted to look at the effect of viewing the fight on EDA across the 6 rounds of the fight. There was a significant main effect of round on EDA ($F(5, 27) = 8.893$, $p < 0.001$. Post hoc comparisons indicated that there was a significant increase in electrodermal activity from pre-fight to round 1 ($t(27) = 4.831$, $p < 0.001$), and a continued significant elevation from pre-fight through rounds 2($t(27) = 3.275$, $p = 0.003$), 3 ($t(27) = 4.172$, $p < 0.001$), 4 ($t(27) = 2.290$, $p = 0.030$) and 5 ($t(27) = 2.326$, $p = 0.028$), suggesting that viewing the fight increased electrodermal activity across subjects. A 2 (*OXTR* rs53576: GG or AA/AG) by 6 (pre-measure and values for 5 rounds of the fight) repeated measures ANOVA was run to assess differences in physiological responses to viewing the fight by *OXTR* genotype. There was a significant main effect by genotype for EDA ($F(1,26) = 5.838$, $p = 0.023$). Individuals with the GG genotype had increased EDA while viewing the fight, indicative of increased sympathetic arousal, compared to those carrying an A allele (Figure 2). There was no significant genotype by time interaction ($F(1,26) = 0.897$, $p = 0.253$). Post hoc contrasts revealed that pre-fight EDA did not differ at baseline between groups (GG: $m = 0.04$, $sd = 0.04$; AA/AG: $m = 0.04$, $sd = 0.02$; $t = -0.294$, $p = 0.722$), although the groups did differ by the end of the fight (GG: $m = 0.06$, $sd = 0.03$; AA/AG: $m = 0.05$, $sd = 0.02$; $t = -2.427$, $p = 0.03$), indicating that the difference in physiological responding across genotype was driven by viewing the stimuli (Figure 2).

Subjective Measures of Arousal

A one way repeated measures ANOVA was conducted to look at the effect of viewing the fight on subject's subjective arousal ratings across the 6 rounds of the fight. There was a significant main effect of time on subjective ratings ($F(2.678, 46) = 7.881$, $p < 0.001$).[1] Post hoc comparisons indicated that there was a significant linear trend over time ($F(1, 46) = 15.541$, $p < 0.001$), suggesting that viewing the fight resulted in a linear increase of subjective arousal ratings over time. To examine whether participants differed by genotype in self-reported arousal while viewing the fight, participants' between rounds ratings were incorporated in a 2 (Genotype: GG or AA/AG) by 5 (rating from each round of fight)

repeated measures ANOVA. There was a significant main effect by genotype for arousal ratings ($F(1, 45 = 7.259$, $p = 0.010$), indicating that participants with the GG genotype had higher levels of reported arousal during the fight than A allele carriers. In addition, a trend towards a significant genotype by time interaction ($F(4, 45) = 2.078$, $p = 0.062$) was identified, suggesting that GG individuals' reported levels of arousal may have been increasing more rapidly than A carriers (Figure 3).

Relationship between Dispositional Empathy and Arousal

In order to test whether individual dispositional empathic concern were related to differences in EDA changes and subjective arousal ratings in response to the fight, EDA and self-reported arousal change scores were calculated for each round of the fight. EDA change scores were calculated by subtracting the pre-fight value from the value for each round, yielding 5 change scores representative of change from pre-fight for each round. Subjective arousal change scores were calculated by subtracting the arousal rating after round 1 from each of the ratings for the following rounds, representative of change in subjective arousal from the beginning of the fight for each round. Regression analyses were run testing whether dispositional empathic concern as measured by the IRI predicted change in EDA for each round from pre-fight or change in subjective arousal for each round from the first rating. There was no significant relationship for changes in either EDA or subjective arousal across all rounds (see Table 1).

Effects of Familiarity with Stimuli

As subjects' responses to the stimuli might be influenced by how often they consume MMA in daily life, participants were asked to rate how often they watched MMA prior to beginning the study on a scale from 1 – 5 with 1 being “never” and 5 being “> than 4 hours a week.” Controlling for how often subjects watch MMA did not alter the primary findings of this study.

Discussion

This study explored the relationship between a common SNP in the oxytocin receptor and individual differences in dispositional empathy as well as sympathetic nervous system responses and changes in subjective arousal to viewing a social interaction involving high levels of physical distress. The results revealed that individuals carrying an A allele for the rs53576 variant of the *OXTR* gene, compared to those homozygous for the G allele, demonstrated lower levels of dispositional emotional empathy, measured through empathic concern for others, along with decreased sympathetic arousal to a social stimuli, evidenced by decreased EDA and decreased subjective levels of arousal to viewing a violent video.

A number of studies have found that GG individuals show increased levels of empathy and prosocial behaviors (Kogan et al., 2011; Rodrigues et al., 2009; Tost et al., 2010). In particular, previous work has reported that GG individuals show significantly increased levels of other-oriented empathy (empathic concern, perspective taking, and fantasy) (Rodrigues et al., 2009). This study replicated this finding, demonstrating that *OXTR* variation was associated with increased levels of empathic concern, or the capacity to experience feelings of compassion, warmth, and concern in response to others (Davis, 1980). The IRI empathic concern subscale has many questions that require the individual to first evaluate the emotional state of another person such as “I often have tender, concerned feelings for people less fortunate than me” and imagine an approach-related behavior in response to the that evaluation, such as “When I see someone being taken advantage of, I feel kind of protective toward them”. Additionally, other work has shown a relationship between other-oriented empathy as measured by the IRI and variation in other *OXTR* SNPs

(Wu et al., 2012). While this study is not a direct replication of these results, it further implicates the potential involvement of *OXTR* variation in detection of other's emotional states.

In addition to reporting higher dispositional levels of empathic concern, GG individuals also exhibited increased levels of sympathetic arousal, as measured by EDA, and subjective reports of arousal to viewing the violent video as compared to AA/AG individuals. The ANS is involved in the stress response as well as regulating social behavior (Porges, 2011), and OT receptors are expressed throughout brainstem nuclei implicated in the regulation of the ANS (Gimpl & Fahrenholz, 2001). Specific modulation of the sympathetic branch of the ANS has previously been shown through increased sympathetic activity, measured using pre-ejection period (PEP), in GG individuals in response to social stress (Norman et al., 2012). Furthermore, *OXTR* variation has been demonstrated to influence the responsiveness of the amygdala and hypothalamus to social and emotional stimuli (Kogan et al., 2011; Tost et al., 2011).

One potential mechanism for the increased physiological and subjective arousal in GG participants may be an increased salience of social stimuli as compared to A carriers. GG individuals have previously been associated with increased response to distress signals in infants, where women homozygous for the *OXTR rs53576* G allele show increased heart rate in response to hearing an infant's cry (Riem, Pieper, Out, Bakermans-Kranenburg, & van Ijzendoorn, 2011) and overall increased maternal sensitivity (Bakermans-Kranenburg & Van Ijzendoorn, 2008; Sturge-Apple, Cicchetti, Davies, & Suor, 2012). In addition, variation in *OXTR* has been implicated in social information processing (Petrovic, Kalisch, Singer, & Dolan, 2008; Tost et al., 2010) and social communication, with GG individuals being better at detecting some emotions in others (Rodrigues et al., 2009).

On the surface, our findings seem to contradict previous work showing that *OXTR* GG individuals exhibit dampened physiological arousal, evidenced by a decreased startle response (Rodrigues et al., 2009). However, the stimuli used in Rodrigues et al (2009)—a startle anticipation task—and our stimuli—a 30min MMA fight—differ greatly, and this likely accounts for the inconsistent results. There is also evidence for increased autonomic arousal in response to a social stressor with GG adults showing increased sympathetic arousal during a speech task compared to A carriers (Norman et al., 2012) and GG women having increased heart rate in response to hearing infant cries (Riem et al., 2011). This suggests that the oxytocin receptor system's influence on autonomic responses is tied to a role in the perception of social cues in general. It is important to note when comparing results across studies using measures of autonomic nervous system activity, that there are various indices of sympathetic activity, and these different measures vary across temporal and contextual domains, and may not always be comparable. This study utilized EDA which is a single measure of sympathetic nervous system activity (Dawson, Schell, & Filion, 2000). Previous work has found relationships between the rs53576 SNP and other measures of sympathetic activity including pre-ejection period (Norman et al., 2012), a measure of sympathetic cardiac control (Berntson et al., 1997), and heart rate (Riem, Pieper, Out, Bakermans-Kranenburg, & van Ijzendoorn, 2011), a measure which includes both sympathetic and parasympathetic influences (Berntson et al., 1997). Future work will be necessary in order to determine whether the EDA findings in the present study can be extrapolated onto other measures of sympathetic nervous system activity.

One unanticipated finding in this study was the lack of a relationship between the self-report measure of dispositional empathic concern, taken prior to viewing the fight stimuli, and physiological or subjective measure of arousal by genotype. Empathic arousal provides a strong signal that can promote empathic concern and caring for others. To be motivated to

help another, one needs to be affectively, empathically aroused, and to anticipate the cessation of mutually experience personal distress (Decety, 2011). Research suggests that this sharing of affective states is supported by dedicated physiological and neural mechanisms. For example, concern for others' in distress has been associated to increases in autonomic arousal and activation of neural regions involved in individuals' own experiences of these states including the insula and anterior cingulate cortex (Decety & Jackson, 2004; Harrison, Singer, Rotshtein, Dolan, & Critchley, 2006). Because of this, it was expected that dispositional empathic concern would be related to sympathetic and subjective reports of arousal, but there was no evidence of this relationship. However, this study only measured dispositional empathy and did not measure changes in empathy and empathic components to viewing the fight. The lack of a relationship between self-reported empathic concern and physiological arousal to viewing the fight might be clarified if participants were asked to report their feelings of empathy and empathic concern specifically towards the fighters during the observation of the stimuli.

There are several important limitations in this study that need to be acknowledged. The first is the small sample size in the analysis for EDA (n = 28). These results should be replicated with a greater number of individuals. This study also utilized a sample consisting of multiple ethnicities which is a limitation, as there is some evidence that the allele frequencies and behavioral correlates of OXTR vary across ethnicities (Kim et al., 2010). Additionally, the study is limited in that it used only a self-report questionnaire to assess empathy and did not directly assess empathic responses related to the stimuli. However, the measure used in this study is one used previously and replicates previous results (Rodrigues et al., 2009). Future research should investigate the different components of empathy using behavioral as well as self-report measures since empathy is a construct that encompasses many different components (Decety & Svetlova, 2012; Singer & Lamm, 2009). Another limitation of the present study is that it evaluated only one OXTR SNP. As emphasized in a recent meta-analysis (Bakermans-Kranenburg & van Ijzendoorn, 2013), the functional significance of the respective OXTR SNPs are not well established, making it difficult to generate strong inferences regarding the precise relationship between genetic variation at this site and subsequent phenotypes. The goal of this study was to evaluate the relationship between a relatively common OXTR SNP previously shown to be related to aspects of empathy (Rodrigues et al., 2009) on the measures employed in this study. It is also important to note that the stimuli, an MMA fight, does not only contain high levels of pain and distress, but also involves a violent competition. There is a wealth of literature examining physiological and hormonal responding to competition, especially in males, demonstrating that these responses are influenced by a variety of factors including team affiliation, domination, and defeat (Carré, Putnam, & McCormick, 2009; Mehta & Josephs, 2006). These issues were not addressed in this study, but should be examined in future work. Finally, the population in this study was limited to males. There is evidence of gender differences in empathy(Decety & Svetlova, 2012; Schieman & Van Gundy, 2000), as well as systematic differences in aggression (Archer, 2004) which might suggest that a female population might show different patterns of responses to viewing a stimuli containing high levels of distress, pain, and violence, as well as aggression. Future research should explore these questions in a female population. Despite these limitations, this study provides valuable insight into the relationship between *OXTR* genotype and social behavior which should be explored in future research to more fully understand the role of oxytocin pathways in social behavior.

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Abbreviations

EDA	electrodermal activity
OXTR	oxytocin receptor gene
SCR	skin conductance response
MMA	Mixed Martial Arts

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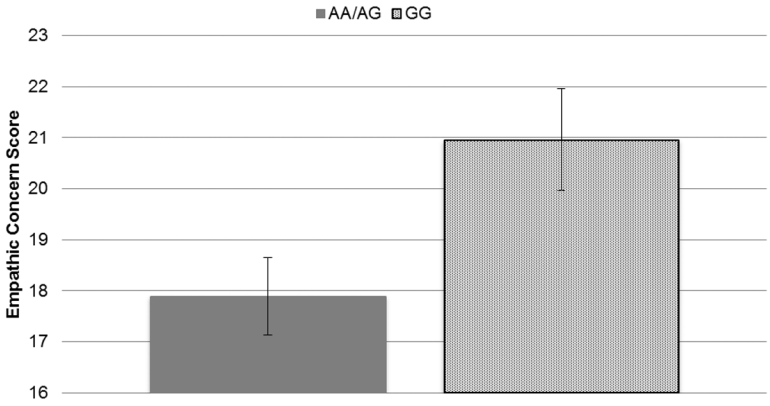

Figure 1. IRI Empathic Concern

Scores on empathic concern sub-scale of the interpersonal reactivity index for AA/AG (n = 27) and GG (n = 24) individuals, showing higher scores on empathic concern for GG (p = 0.017).

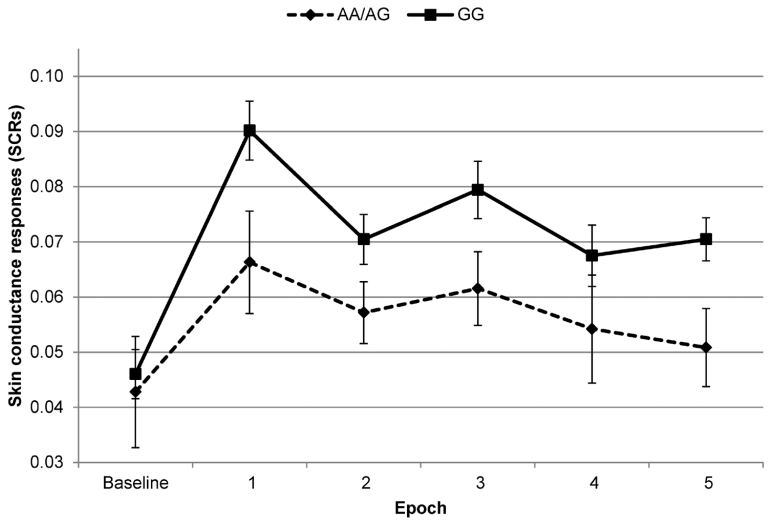

Figure 2. Change in electrodermal activity over time

Differences in electrodermal activity (EDA) over time, showing a greater increase ($p = 0.023$) in GG individuals ($n = 13$) EDA compared to AA/AG individuals ($n = 15$).

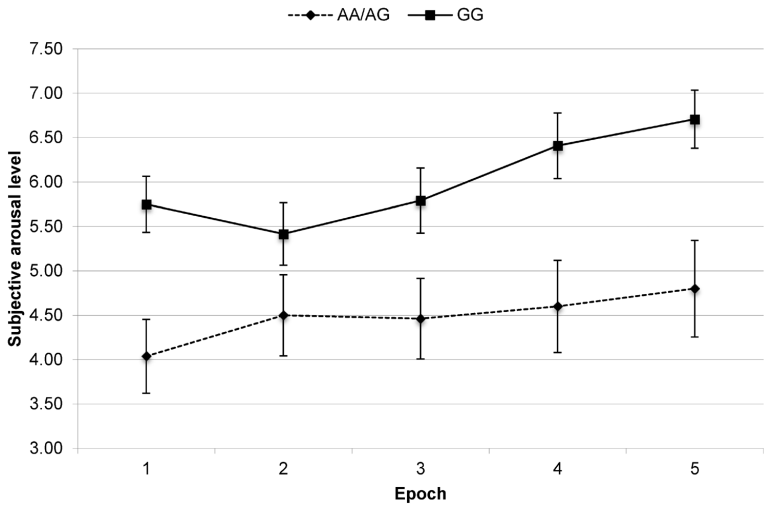

Figure 3. Change in subjective arousal over time

Subjective arousal ratings after each round for AA/AG (n = 25) and GG (n = 22) subjects, showing a greater increase over time in subjective arousal for GG individuals (p = 0.010).

Table 1

		β	SE	T(35)	p
EDA	Change 1 (EDA 1 – EDA Base)	.293	.001	1.864	.070
	Change 2 (EDA 2 – EDA Base)	.139	.001	.840	.406
	Change 3 (EDA 3 – EDA Base)	.275	.001	1.689	.100
	Change 4 (EDA 4 – EDA Base)	.100	.002	.587	.561
	Change 5 (EDA 5 – EDA Base)	.346	.001	2.021	.052
Subjective Arousal	Change 1 (Arousal 2 – 1)	−.162	.041	−1.150	.256
	Change 2 (Arousal 3 – 1)	−.088	.034	−.618	.540
	Change 3 (Arousal 4 – 1)	.171	.043	1.175	.246
	Change 4 (Arousal 5 – 1)	.058	.049	.403	.689

Regression statistics investigating whether scores on the empathic concern scale of the Interpersonal Reactivity Index (IRI) predicted change in electrodermal activity (EDA) for each round from pre fight levels or change in subjective arousal for each round from first arousal rating while viewing the fiffht.