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**Social anxiety and common OXTR gene variant are associated with
cortisol response following peer social challenge**

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Abstract

Background: Peer rejection and acceptance experiences are commonplace with potential to promote emotional and adrenocortical stress reactivity. Risk for heightened stress reactivity during these social challenges may be influenced by individual differences in social interaction anxiety (SIA) and the common gene variant, OXTR rs53576, but this relationship remains to be elucidated.

Methods: We tested the relationship between SIA, OXTR rs53576, and cortisol stress response over time in 53 young adults ($M_{age}=20.13$ yrs) using an experimental design. Participants were randomized to receive either scripted rejection or acceptance from a group of peer confederates. Saliva samples were collected pre- and post-evaluation and assayed for cortisol.

Results: In the peer rejection condition, participants showed significantly lower cortisol responses over time when social interaction anxiety levels were not elevated (versus elevated), and when possessing the GG genotype (versus AA/AG). In the peer acceptance condition, when SIA was not elevated, the GG genotype was associated with significantly lower cortisol responses than the AA/AG genotype.

Conclusion: Individual differences in SIA and OXTR 53576 are related to cortisol responses to peer social stressors, with non-elevated levels of SIA and the GG genotype generally contributing to reduced cortisol responsiveness.

Keywords: Anxiety; Stress; Cortisol; OXTR; Rejection; Acceptance; Peer Group

1. Introduction

Humans possess a powerful and persistent motivation to belong (Baumeister & Leary, 1995). The need for interpersonal acceptance and belonging transcends cultural, situational, and temporal boundaries and is so fundamental that it can be conceptualized as a core personality trait (DeWall et al., 2011). From an evolutionary perspective, this ubiquitous drive may have origins in the need for humans to form close relationships in an effort to improve survival and reproductive fitness (DeWall et al., 2011). The biological stress response system has been similarly fine-tuned by natural selection over time and serves to encode, filter, and adaptively respond to environmental information, including stimuli presenting as physical or social challenges (Del Giudice, Ellis, & Shirtcliff, 2011; Nesse, Bhatnagar, & Ellis, 2016).

Stimulation of the hypothalamic-pituitary-adrenal (HPA) axis and secretion of cortisol as its major glucocorticoid end product in humans, represents one of the major pathways through which individuals respond to environmental challenges (Smith & Vale, 2006). The HPA axis is particularly sensitive to social stimuli, evoking potent cortisol responses to social-evaluative threats (Dickerson and Kemeny, 2004), but also to positive events involving some measure of unpredictability or uncontrollability (Flinn, 2006). Threatening or challenging interpersonal situations have the potential to trigger both acute increases in cortisol (Kirschbaum, Pirke, & Hellhammer, 1993; Dickerson & Kemeny, 2004) and more chronic elevations in cortisol over time (Adam & Gunnar, 2001; Saxbe, Repetti, & Nishina, 2008; Sjögren, Leanderson, & Kristenson, 2006). Alternatively, positive social interactions and supportive relationships are well known for their ability to confer resilience to life stressors through moderation of the HPA axis response along with other putative mechanisms (Ozbay et al., 2007; Hostinar, Sullivan, & Gunnar, 2014).

While activation of the HPA axis is a powerful mediator of environmental adaptation to life challenges, chronic activation imposes significant physiological costs and risk for a wide range of physical and mental health problems (Evans, 2003; Flinn and England, 2003; Gunnar and Vazquez, 2006; Korte et al., 2005; McEwen and Wingfield, 2003). Given that social interaction is a regular facet of human life, it is important to understand how individual differences may influence vulnerability or resilience to common interpersonal challenges.

To this end, individual differences in fear related to social encounters (i.e., social interaction anxiety; Mattick & Clarke, 1998) are likely to contribute to divergent patterns of stress reactivity during challenging interpersonal experiences. Individuals with social interaction anxiety (SIA) frequently experience increased self-awareness and self-criticism following social interactions (Hirsch, Clark, Mathews, & Williams, 2003; Hofmann, 2007) and a marked fear of negative evaluation and interpersonal rejection (Clark & Wells, 1995; Hackmann, Surawy, & Clark, 1998; Hofmann, 2007; Rapee & Heimberg, 1997; Wells, Clark, & Ahmad, 1998; Wells & Papageorgiou, 1999). As social anxiety is also associated with heightened sensitivity and negative emotional reactivity to social stressors (Farmer & Kashdan, 2015), there is considerable potential for HPA axis dysregulation in this population. Indeed, there are some reports linking SIA to enhanced HPA axis reactivity and reduced cortisol recovery in the context of psychosocial stress (Furlan et al., 2001; Ketay et al., 2018; van West, Claes, Sulon, & Deboutte, 2008), though results have been mixed in this regard (e.g., Crişan, Vulturar, Miclea, & Miu, 2016; Krämer et al., 2012) and require further study.

Individual differences in genes that encode potential stress-modifying neurotransmitters and hormones or their receptors represent an additional tool for understanding vulnerability to social stressors. In particular, oxytocin has received considerable attention as neurotransmitter and

hormone that regulates a variety of social and emotional behaviors with documented potential to ameliorate stress reactivity, reduce anxiety, and support well-being (Kirsch et al., 2005; Uvnäs-Moberg et al., 2005; Campbell, 2010; Ishak, Kahloon, & Fakhry, 2011). As the oxytocin receptor appears to be an important mechanism connecting oxytocin to emotion (Ishak, Kahloon, & Fakhry, 2011), genetic variation in the oxytocin receptor gene (OXTR) may contribute to differences in stress reactivity between people. In particular, the common OXTR variant, rs53576 – a single nucleotide polymorphism located in intron 3 (Wu et al., 2005) – has been associated with several traits relevant to modulating stress reactivity to interpersonal challenges. For instance, relative to carriers of the minor A-allele (i.e., AA or AG genotype), the G-allele is associated with greater levels of positive affect (Lucht et al., 2009), greater sociality (Li et al., 2015), better discernment of emotional states (Rodrigues et al., 2009), and lower cortisol responses when provided social support prior to laboratory stressors (Chen et al., 2011).

Peer interactions represent one of the most common and potentially potent sources of interpersonal stress, with potential for gain (social acceptance) or loss (social rejection). We previously reported a relationship between OXTR rs53576 and rejection sensitivity on cortisol reactivity during laboratory peer social challenge (Auer et al., 2015). Critically, much like rejection sensitivity, social anxiety may be likely to influence responsiveness of the HPA axis during challenges interpersonal experiences. The goal of the present study was to extend our previous work by examining the relationship between SIA and OXTR rs5357 genotype on cortisol response to experimental peer rejection or acceptance among young adults, a population where social stressors may be especially salient. As elevated levels of social anxiety and the A allele of OXTR rs53576 appear to be independent risk factors for heightened stress reactivity and reduced recovery, we hypothesized that those with lower levels of social interaction anxiety and

homozygous carriers of the G allele would experience significantly reduced cortisol reactivity over time.

2. Methods

The present study involves a secondary analysis of experimental data related to peer rejection and acceptance (Auer et al., 2015). Protocols related to recruitment and experimental stress-induction are identical to previous reports; the sample characteristics are largely consistent as well, with the exception of a more limited sample size due a smaller number of participants completing measures of social interaction anxiety.

2.1 Participants

Participants were recruited through a university subject pool recruitment website. Exclusion criteria were use of alcohol or tobacco products, vigorous exercise within one-hour prior to participation, recent illness, and use of medications known to influence cortisol (no participants met exclusion criteria). A sample of 94 adults enrolled and completed study procedures approved by the Institutional Review Board, of which, a total of 53 adults (38 women, 15 men, $M_{\text{age}} = 20.13$ years, age range: 18–52 years) provided complete data for cortisol, social interaction anxiety, and OXTR rs53576, constituting the current sample. Participant characteristics are presented in Table 1.

2.2. Measures

2.2.1. Social Interaction Anxiety

Social interaction anxiety was assessed using the Social Interaction Anxiety Scale (SIAS; Mattick & Clarke, 1998). The SIAS is a commonly used 20-item self-report measure that asks respondents to rate their experiences across a range of social contexts associated with DSM-IV criteria for social phobia and social anxiety. Items were rated on a 5-point scale (0 = “Not at all

characteristic or true of me” to 4 = “Extremely characteristic or true of me”), with a total possible score of 60 (Mattick & Clarke, 1998). The SIAS has good psychometric properties, with high levels of internal consistency and discriminant validity (Heimberg et al., 1992; Mattick & Clarke, 1998).

2.2.2. *Salivary cortisol*

Following Granger and colleagues (2012), a total of three saliva samples were collected from each participant using the “passive drool” method, stored at -20°C , and assayed for cortisol using commercially available reagents (Salimetrics LLC, Carlsbad, CA) without modification to the manufacturer's protocols. There was a test volume of 25 μl , with a range of sensitivity from .007 to 3.0 $\mu\text{g dl}$, and inter- and intra-assay coefficients of variation below 10%. Raw cortisol values were square-root transformed to correct positive skew before analysis.

2.2.3. *Genotypes*

Following Nemoda et al. (2012), DNA was extracted from saliva. The SNP examined in this study consisted of either an adenine (A) or guanine (G) within intron 3 of the OXTR gene. Genotype distributions were in Hardy–Weinberg equilibrium, $\chi^2(2) = 1.157$, $p = 0.561$, and were distributed as: GG genotype $n = 24$ (45.3%), AG genotype $n = 21$ (39.6%), AA genotype $n = 8$ (15.1%). There were no genotype-by-gender differences, $\chi^2(2) = 1.255$, $p = 0.534$, or genotype-by-ethnicity differences, $\chi^2(12) = 12.670$, $p = 0.393$. We chose to compare individuals carrying at least one copy of the A allele (AA/AG) with GG individuals, consistent with several previous investigations of rs53576 (Li et al., 2015).

2.2.4. *Mood Manipulation Check, Number of Peer Evaluators, and Perceived Fairness*

Following collection of the final saliva sample, a brief single-item self-report assessment of mood was administered to assess efficacy of the experimental manipulation. Participants were

asked to rate how they currently felt on a scale ranging from 1 (“very poor”) to 5 (“very good”). To account for potential covariates beyond standard demographics, the number of peer evaluators – always two or three – was recorded and the perceived fairness (yes/fair versus no/not fair) of the evaluation was assessed following collection of the final saliva sample.

2.3. Procedure

The study protocol is previously described elsewhere (Auer et al., 2015). The experimental procedure was designed to elicit evaluative threat in participants by instructing them to complete an essay related to a social problem in society along with a proposed solution. To enhance task salience, each participant was asked to write about a problem that they personally cared about and were informed that their essay would be considered for a monetary award (\$150.00 USD) prior to study arrival. Specifically, participants received instruction that a committee of their student peers would judge their essay’s quality in consideration of the award. The experiment took place over approximately 90 minutes, separated by two phases. The first 60 minutes were spent completing study measures and sitting quietly; this was designed to encourage familiarity with lab space and lower baseline stress. Any remaining time following completion of measures was allotted to preparing for the committee evaluation, if desired. During this first phase, participants were randomized to receive scripted rejection or acceptance from the committee of peers by coin flip.

Next, the first of three saliva samples were collected to establish pre-evaluation cortisol. Participants were subsequently escorted to an experimental room where they were met by the peer committee, composed of 2-3 research confederates with each gender represented. The trained committee provided 10 continuous minutes of scripted negative or positive comments in the predetermined areas of essay quality (e.g., novelty, grammar, overall merit). Participants

assigned to the acceptance condition were informed that they were in contention for the award at the conclusion of the 10-minute evaluation, while participants assigned to the rejection condition were informed that their chances for receiving the award were low. The remaining two saliva samples were collected immediately after the evaluation and then 20 minutes post-evaluation.

2.4. Analytic Plan

All analyses were carried out using IBM SPSS Statistics 26.0 (Chicago, Illinois, USA). Following Pruessner and colleagues (2003), the area under the curve with respect to baseline (AUC_B), ground (AUC_G , with reference to the X-axis), and increase or decrease (AUC_I , with reference to the first value) were calculated to analyze cortisol responses. Participants were classified as having “non-elevated” or “elevated” levels of social interaction anxiety using a median split for the Social Interaction Anxiety Scale’s total score (e.g., Auer et al., 2018). Analysis of variance (ANOVA) was used to examine group differences in cortisol AUC_B , AUC_G , and AUC_I . The criterion level for significance was set at $p < .05$. When appropriate, data plots and follow-up analyses of simple effects were used to aid interpretation of significant interactions. The criterion level for significance was set at $p < .05$.

3. Results

Table 1

Characteristics of Study Participants

Participant Characteristics	Rejection	Acceptance	<i>p</i>
<i>N</i>	28	25	-
Women/Men	17/11	21/4	> .05
Non-elevated SIA/Elevated SIA	14/14	14/11	> .05
A carriers/GG	14/14	15/10	> .05

Age (SD)	19.9 (4.52)	20.36 (6.67)	> .05
Race/Ethnicity (N)			> .05
White, non-hispanic	18	16	
Black/African American	2	3	
Asian/Pacific Islander	3	1	
American Indian	0	1	
Other	5	4	

3.1. Manipulation check

Consistent with expectations, there were significant group differences in mood based on condition, $F(1, 46) = 97.88$, $p < .001$, partial $\eta^2 = .68$, with participants assigned to the acceptance group reporting feeling better than those in the rejection group following the peer evaluation period (See Figure 1).

Figure 1

Self-reported Mood Following Peer Rejection of Acceptance

Note. Mood ratings are on a 1–5 scale, with higher ratings reflecting more positive affect. Bars reflect standard errors.

3.2. Covariates

Pearson correlations were used to determine if potential confounding variables (i.e., number of evaluators, perceived fairness, age, gender, race/ethnicity) were related to cortisol AUC_{B,G,I} prior to group analyses. Perceived fairness was significantly related to cortisol AUC_I in the rejection condition, $r = -.403$, $p = .037$, but not the acceptance condition. No other variables were significantly related to cortisol outcomes.

3.3. Social interaction anxiety (SIA)

A chi-square test of independence was used to determine if SIA grouping (non-elevated versus elevated) varied by genotype (GG versus AA/AG). The SIA group-by-genotype interaction was not significant, $\chi^2(1) = .031$, $p = .859$.

3.4. Relationship between SIA, genotype, and condition

In order to test the relationship between SIA and genotype on cortisol response to peer evaluation, we began by conducting three-way ANOVA with SIA level (Non-elevated versus Elevated), Genotype (GG versus AG/AA), and Condition (Rejection versus Acceptance) as between subject factors. There was a significant three-way interaction for AUC_I, $F(1, 45) = 6.003$, $p = .018$, partial $\eta^2 = .118$. A follow-up two-way ANOVA examining the interaction between SIA level and genotype at each level of condition was significant for participants experiencing acceptance, $F(1, 21) = 6.55$, $p = .02$, partial $\eta^2 = .24$, but not rejection.

In the rejection condition, after controlling for perceived fairness of the evaluation as significant covariate ($p = .018$), there was a main effect of genotype, $F(1, 22) = 6.085$, $p = .022$, partial $\eta^2 = .217$, and SIA level, $F(1, 22) = 5.908$, $p = .024$, partial $\eta^2 = .212$. These results

indicate that participants with the GG genotype experienced significantly greater decreases in cortisol over time compared to AA/AG participants ($AUC_I = -.665$ versus $.003$) and that participants with non-elevated SIA experienced significantly greater decreases in cortisol compared to those with elevated SIA (cortisol $AUC_I = -.622$ versus $-.001$).

In the acceptance condition, follow-up analysis yielded a significant effect of genotype for those with non-elevated SIA, $F(1, 12) = 5.331$, $p = .040$, partial $\eta^2 = .308$, but not for those with elevated SIA. Specifically, participants with the GG genotype and non-elevated SIA experienced significantly lower cortisol responsiveness over time compared to those with AA/AG genotype and non-elevated SIA (cortisol $AUC_I = -.986$ versus $.411$). The impact of SIA level and genotype across evaluative conditions is illustrated in Figure 2. Mean values are reported in Table 2.

No significant group interactions or main effects were observed for AUC_B or AUC_G .

Table 2

Mean Cortisol AUC_I response to peer rejection or acceptance across genotype and SIA

Condition	Genotype	Non-elevated SIA	Elevated SIA
<i>Means (SD)</i>			
Rejection ^a	GG	-.951 (.734)	-.404 (.603)
	AA/AG	-.259 (.713)	.341 (1.021)
Acceptance	GG	-.986 (1.250)	.573 (1.951)
	AA/AG	.411 (.988)	-.471 (.622)

^aAccounting for perceived fairness of evaluation as covariate.

Figure 2*Stress Response to Peer Rejection and Acceptance as a Function of SIA and Genotype*

4. Discussion

Our results demonstrate the individual and interactive influence of SIA and a common polymorphism of the oxytocin receptor gene (rs53576) on HPA axis function among young adults exposed to two common, yet potent, social challenges: peer rejection and acceptance. We found that more normative (non-elevated) levels of SIA and the GG genotype were associated with less cortisol reactivity. To our knowledge, we report the first study examining the relationship between these individual differences in shaping the cortisol stress response to peer group rejection and acceptance in a laboratory setting.

Stress System Responsiveness to Social Challenges

The human need for interpersonal acceptance is powerful, likely shaped over the course of human evolution to facilitate life in small groups which was critical to survival and reproductive success (Baumeister & Leary, 1995; DeWall, Deckman, Pond Jr., & Bonser, 2011). Social rejection in this ancestral environment spelled serious danger, as consequences spanned from greatly diminished resources and meeting of basic needs to death. In light of such grave consequences, humans likely developed traits that would foster acceptance and reduce the odds of group rejection (DeWall, Deckman, Pond Jr., & Bonser, 2011). While the modern experience of rejection rarely leads to such serious consequences, threats to acceptance are likely to still activate the ancient biological stress response system whose basic structure has been conserved across species (Nesse, Bhatnagar, & Ellis, 2016; Del Giudice, Ellis, & Shirtcliff, 2011).

Humans have a powerful biological sensitivity to context, including a sensitivity to the social environment (Boyce & Ellis, 2005; Ellis et al., 2005, 2006, 2011). This biological sensitivity is reflected in part by activation of the HPA axis, which has been shown across a large number of studies to be responsive to psychosocial stressors over brief and extended periods of time (Adam & Gunnar, 2001; Dickerson & Kemeny, 2004; Kirschbaum, Pirke, & Hellhammer, 1993; (Saxbe, Repetti, & Nishina, 2008; Sjögren, Leanderson, & Kristenson, 2006). Importantly, individual differences may attenuate or enhance HPA axis response to psychosocial stressors, hence the inclusion of SIA and OXTR rs53576 in the current study.

The oxytocin receptor is a protein that functions as a receptor for oxytocin, a hormone and neurotransmitter widely expressed throughout the body and strongly associated with regulation of several complex functions such as affiliative behavior, bond formation, and reactivity to interpersonal stressors (Cataldo, Azhari, Lepri, & Esposito, 2018). While the exact function of rs53576 remains to be determined, evidence to date suggests that the G allele of rs53576 is

linked to more efficient oxytocinergic function, potentially accounting for a general boost to cortisol blunting observed in homozygous carriers in the current study. Similarly, lower levels of social interaction anxiety – and consequently, lower intrinsic levels of perceived threat related to social situations – may generally contribute to a quicker dampening of the HPA axis and cortisol response following stimulating social experiences, positive or negative. Importantly, the impact of individual differences may vary according to the nature of the socially challenging situation, in the case of the present study, group rejection or acceptance.

Peer Rejection and Acceptance

Given the importance of avoiding group rejection in human evolutionary history (DeWall, Deckman, Pond Jr., & Bonser, 2011), explicit and implicit communication of social rejection would be expected to trigger a robust stress response. Indeed, laboratory studies of stressors involving social-evaluative threat reliably increase cortisol in participants (Dickerson & Kemeny, 2004). However, when preexisting fears related social interactions also accompany social rejection experiences, activation of the HPA axis should be expected to be boosted even further. While not surprising, our finding that elevated levels of SIA were associated with greater cortisol responsiveness is consistent with previous studies linking elevated social anxiety to heightened HPA-axis responses in the context of psychosocial stress (e.g., Ketay et al., 2018; van West, Claes, Sulon, & Deboutte, 2008). Our finding that homozygous carriers of the G allele experienced greater cortisol declines over time relative to carriers of the A allele can also be considered consistent with previous reports (Chen et al., 2011). While Chen and colleagues (2011) organized their analysis of the rs5357 SNP in a different manner from the current study (comparing A allele homozygotes to G allele carriers), they similarly noted a benefit of the G allele, where its presence was associated with lower cortisol responses to stress after receiving

social support. As both lower SIA and the GG genotype were hypothesized as stress-protective factors in the context of interpersonal challenges, our finding that the combination of non-elevated SIA and GG genotype was associated with significantly lower cortisol responsiveness than normative SIA with the AA/AG genotype (only one protective factor) is also not unexpected.

Practical Implications

Positive peer relationships make critical contributions to healthy social-emotional development. All people experience some distress related to interpersonal interactions at times, but those exposed to chronic social stressors may be particularly susceptible to dysregulation of the stress response system. Results of this study suggest that carriers of the rs53576 A allele and those with elevated anxiety related to social interactions may be particularly susceptible to delayed physiological stress recovery following exposure to rejection experiences. While the genetic risk factor reported in this study cannot be changed, a wide range of psychological interventions have been shown to be effective in improving social anxiety in children, adolescents, and adults (Acarturk, Cuijpers, van Straten, & de Graaf, 2009; Yang et al., 2019). As genotype and SIA level accounted for roughly the same amount of variance in cortisol response to rejection in the current study, such intervention strategies appear to be an appealing tool to potentially mitigate overall vulnerability. Moreover, risk for dysregulated stress reactivity in the context of interpersonal challenges is assuredly multifactorial with several traits and situational factors contributing to responsiveness. For example, personality traits such as emotional stability and emotional intelligence (Matthews, Deary, & Whiteman, 2009) and situational factors such as availability of social support (Ozbay et al., 2007) are associated with improved adaptation to life stressors.

Limitations and Future Directions

Although this study is the first to our knowledge examining the combined impact of OXTR rs53576 and SIA on HPA axis stress response to peer rejection and acceptance among young adults, there were a few notable limitations. First, this study was limited by its relatively small sample and as such, the reported associations between OXTR rs53576 genotype and SIA should be considered preliminary and in need of replication in a larger investigation. This sample was also relatively homogenous with White and female individuals constituting the majority of participants. As there are some ethnic differences in the allele frequency distribution of rs53576, future studies should seek to build diversity into the next generation of studies on this topic. The focus on a single SNP of OXTR is also a limitation as complex human emotional and behavioral responses are likely to be polygenic in origin. An increasingly popular approach to the study of gene-environment interactions in the field of psychology and behavioral sciences includes the measurement of epigenetic marks (e.g., DNA methylation) to help elucidate the role of gene expression (Jones, Moore, & Kobor, 2018). Advances in salivary bioscience to facilitate measurement of epigenetic marks in oral fluid is a particularly promising future direction (Nemoda. 2020), with many additional advances on the horizon as well (for review, see Granger, Zalta, & Taylor, 2020).

This study did not include diagnostic assessments of social anxiety and the sample size was insufficient to delineate SIA groups by probable social phobia or social anxiety using the Social Interaction Anxiety Scale (SIAS; Mattick and Clarke, 1998). Alternatively, we adopted an approach using the SIAS to facilitate informative sample-specific comparisons between those with relatively high versus low levels of social interaction anxiety as done in previous studies

(e.g., Auer et al., 2018). However, assessment in a defined clinical sample with healthy controls would provide valuable information pertaining to how stress reactivity may vary as function of anxiety severity.

Conclusion

In conclusion, this study has found that social interaction anxiety and OXTR rs53576 are associated with HPA responses over time in young adults exposed to experimentally-induced peer rejection and acceptance. In general, lower social interaction anxiety and the GG genotype appear to be stress-protective with greater cortisol declines observed over time relative to elevated anxiety and the presence of the A allele. There is tentative evidence that the risk factors of social interaction anxiety and OXTR rs53576 interact to influence HPA function, but findings should be replicated in a larger clinical sample.

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