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Effect of the interaction between oxytocin receptor gene polymorphism (rs53576) and stressful life events on aggression in Chinese Han adolescents

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ABSTRACT

Objectives: Accumulating evidence suggests that stressful life events are associated with increased risk for aggressive behavior in adolescents; however, aggressive reactions to life stressors exhibit large individual differences. The present study sought to examine whether the interaction between a single nucleotide polymorphism (SNP [rs53576]) within the oxytocin receptor gene (*OXTR*) and stressful life events is related to aggression in Chinese Han adolescents.

Methods: A total of 197 Chinese Han adolescents (14–17 years of age) were included in this study. Aggression was assessed using the 12-item short version of Buss and Perry Aggression Questionnaire. Stressful life events during the past 12 months were assessed using the Adolescent Self-Rating Life Events Checklist. Genomic DNA was extracted from saliva and buccal cells from each individual.

Results: Multivariate analysis of variance yielded a significant interaction between *OXTR* rs53576 SNP and life stress ($F = 2.449$, $p = 0.043$, partial $\eta 2 = 0.051$) and of sex × SNP × life stress ($F = 3.144$, $p = 0.016$, partial $\eta 2 = 0.064$). High life stress during the past 12 months was associated with high levels of physical aggression and hostility in *OXTR* rs53576 homozygous AA adolescents but not in G-carrier adolescents. In boys, homozygous AA individuals in the high life stress group reported significantly higher levels of physical aggression than participants in the other three groups; the interaction, however, was not significant in girls.

Conclusions: This study, which analyzed a specific gene-environment interaction, demonstrated that AA *OXTR* rs53576 homozygosity may correlate with higher levels of aggression under high life stress conditions with a sample of healthy Chinese Han adolescents. These findings promote the etiological understanding of adolescent aggression, highlighting the complex effect of stressful life events on aggression, and adding evidence supporting the relationship between the oxytocin system and aggressive behavior in adolescents.

1. Introduction

Aggression is defined as overt or covert often harmful behavior or social interaction with the intention of inflicting damage or distress on others (de Almeida et al., 2015; Marcus, 2017). Human aggression is multi-dimensional and may be expressed physically, verbally, emotionally (e.g., anger), or cognitively (e.g., impulsivity, hostility) (Buss and Durkee, 1957; Buss and Perry, 1992). Adolescence is the transitional period between late childhood and the beginning of adulthood and is a time of dramatic physical, cognitive, emotional, and social changes such as rapid physical growth of the body, sexual maturation, increased self-consciousness, sensation seeking and risk taking, which contributes to a critical period of vulnerability for maladaptive behavioral and emotional development (Lerner and Steinberg, 2004; Sawyer et al., 2012; Steinberg, 2005). Neuroimaging studies looking at the development of brain throughout adolescence have found changes in the structure and function of brain regions that are implicated in executive function and social cognition, which supports the notion that adolescents experience heightened sensitivity and reactivity to social and emotional stimuli (Blakemore, 2008; Burnett and Blakemore, 2010; Choudhury et al., 2006; Dahl and Gunnar, 2009; Walker et al., 2004). These findings emphasize that the period of adolescence represents a key developmental window for understanding the emergence of aggression, yet they may also point to opportunities for early intervention.

The developmental approach to aggressive behavior addresses the key issue that the manifestations of aggression change dramatically

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throughout adolescence and that the changes may be sex dependent (Cleverley et al., 2012; Dodge et al., 2006; Loeber and Hay, 1997; Marcus, 2017). Research findings derived from national surveys and longitudinal studies on aggressive behavior in adolescence have converged on early adolescence as a time of increased prevalence of aggressive behavior (Marcus, 2007, 2017). Sex differences in aggression are minor during infancy and toddlerhood but tend to increase in adolescence (Card et al., 2008; Archer, 2004; Loeber and Hay, 1997). Direct aggression, such as physical and verbal aggression, both hostile and instrumental, is more common in teenage boys. However, indirect or relational aggression, such as deliberate social exclusion is more characteristic of teenage girls (Card et al., 2008; Heilbron and Prinstein, 2008). Numerous studies have also indicated the continuity in aggressive behavior over time, supporting that young people who exhibit aggressive behavior are at particular risk of retaining their violent behavior later into adulthood, which, consequently, has a long-lasting adverse effect on individual development (Huesmann et al., 2009; Loeber and Hay, 1997).

There are multiple risk factors that directly or indirectly influence aggression including age and sex, genetics, and psychopathological and environmental factors (Farrington, 1989; Valois et al., 2002). Environmental adversity (e.g., stressful life events) has long been implicated in the development of aggression (Timmermans et al., 2010). However, while stressful life events are common, the level of aggression shown by individuals usually varies. One plausible explanation for such variation is that individuals may have different sensitivities to environmental influences. It has long been acknowledged that some people are more likely to be affected by adverse environments due to an inherent vulnerability (e.g., the genotype) (Pluess, 2015). Thus, new efforts to understand the effects of environmental adversity on aggression have shifted focus to potential moderators of this association, such as the genotype (Rhee and Waldman, 2011). One such candidate is the *OXTR,* the receptor gene for the hormone oxytocin (Li et al., 2015).

Oxytocin is a peptide hormone and a neuropeptide. The physiologic effects of oxytocin are mediated through its specific receptor, which is expressed by neurons in several parts of the brain, including the hypothalamus and amygdala (Gimpl and Fahrenholz, 2001). Oxytocin and its receptor have been typically implicated in the regulation of prosocial behaviors and emotions, including trust, empathy, altruism, and affiliation behavior (Donaldson and Young, 2008; Neumann, 2008). Yet, accumulating evidence has revealed that the effects of oxytocin are not always positive and may induce antisocial behavior. The social salience hypothesis of oxytocin states that oxytocin may facilitate the social salience of certain social stimuli and that it can magnify prosociality when encountering close, familiar, or reliable others but diminish prosociality under conditions of uncertainty, competition, or interaction with out-group members (Shamaytsoory and Abuakel, 2016). Another social-approach and withdrawal theory suggests that the oxytocin system may facilitate social approach-related behaviors and emotions, including the “negative” states of jealousy, anger, and aggression, while inhibiting social withdrawal (Kemp and Guastella, 2011). Thus, accumulating studies are investigating a more complex role of the oxytocin system within a wide range of social behaviors, including its association with aggressive behavior in both animals and humans, rather than solely the prosocial role of oxytocin (Bartz et al., 2011; Campbell, 2011).

Recent studies have also focused on genetic variations in the oxytocinergic system, which may influence the number, organization, or functioning of oxytocin receptors that mediate oxytocinergic function that may modulate social behavior (Feng et al., 2015). The gene that encodes the oxytocin receptor *(OXTR)*, which is located on chromosome 3p25 and has four exons and three introns, is one such candidate. In particular, one SNP, rs53576, in the third exon of *OXTR* has been extensively studied and has attracted the most attention as a factor explaining the differences in oxytocinergic functioning (Li et al., 2015). Evidence has supported correlations between *OXTR* rs53576 and a range of behavioral outcomes, including dysfunctional emotional regulation, positive and negative affect, and stress reactivity (Li et al., 2015; Tost et al., 2010); however, the findings are heterogeneous. On one hand, studies have indicated that the A allele of *OXTR* rs53576 is a risk allele for impaired social functioning and that G-allele carriers tend to exhibit high empathy, greater social support, more emotional stability, and greater sociability (Lucht et al., 2009; Rodrigues et al., 2009; Massey-Abernathy, 2017). In contrast to these findings, others have reported that the rs53576 A-allele is associated with better social cognitive ability (Kim et al., 2010) and that the G-allele may contribute to the risk of developing emotional and behavioral problems by gene-environment interaction (Bradley et al., 2011). A meta-analysis failed to detect any association between the *OXTR* rs53576 genotype and social behaviors (Bakermans-Kranenburg and van IJzendoorn, 2014). The results of studies investigating the association between the *OXTR* gene and social behaviors have not been entirely consistent. Based on previous findings, it appears highly likely that the *OXTR* rs53576 polymorphism may interact with environmental adversity to potentially increase aggression.

Our study differs from previous reports in three respects. First, previous studies investigating associations between OXTR and aggressive behavior tended to focus on either adults or adolescents with a broad range of psychiatric diagnoses (e.g., bipolar disorder, alcohol dependence, and autism) (Olff et al., 2013). To date, this association has not been fully examined in healthy adolescents. Aggression is a prevalent externalizing behavior in healthy adolescents and has long-lasting adverse effects on individual development. It is necessary to explore the interaction effect of the *OXTR* genotype and stressful life events on aggression in healthy adolescents. Second, investigations of gene-environment interactions have largely—if not exclusively—been explored with Western samples. To our knowledge, this association has not been fully examined in Asian populations, especially in the Chinese Han population. The Chinese Han is one of the largest ethnic groups, and aggressive behaviors have been a major public health problem in China. Hence, it is necessary to explore whether the possible association between the *OXTR* genotype and aggressive behavior observed in Western populations also exists in the Chinese Han population (Leclair et al., 2016). Third, previous studies have mostly identified interactions between early environmental triggers (childhood adversity, early parenting style, and others) and genes that affect aggression. A previous study proposed that proximal environmental influences differentiate between distal factors and are specific social triggers that directly impact the individual. Given that few proximal variables have actually been measured, the present study aimed to fill this gap and investigate whether the effect of proximal environmental factors on aggression are moderated by genetic variants (Moffitt et al., 2006).

The present study was designed to examine the interaction effects of stressful life events and the *OXTR* rs53576 polymorphism on aggression in healthy Chinese Han adolescents. We hypothesized that there would be a significant interaction effect between *OXTR* rs53576 and stressful life events on aggressive behavior. Specifically, we proposed that stressful life events would be associated with high levels of aggressive behavior among *OXTR* rs53576 homozygous AA adolescents than among G-carriers.

2. Methods

2.1. Participants

The participants were a subset from the second wave data of the Genetics of Mental Health study. This study was performed in 2016 and involved Grade 10 and Grade 11 students from a public school in Shandong Province, China. These students had no self-reported history of mental illness or major somatic disease. Shandong is an eastern coastal province of the People's Republic of China and is typical in terms of its social and cultural life. The public school in Shandong was selected after taking into account prior study collaboration,