

Common oxytocin receptor gene (*OXTR*) polymorphism and social support interact to reduce stress in humans

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The neuropeptide oxytocin has played an essential role in the regulation of social behavior and attachment throughout mammalian evolution. Because recent studies in humans have shown that oxytocin administration reduces stress responses and increases prosocial behavior, we investigated whether a common single nucleotide polymorphism (rs53576) in the oxytocin receptor gene (*OXTR*) might interact with stress-protective effects of social support. Salivary cortisol samples and subjective stress ratings were obtained from 194 healthy male participants before, during, and after a standardized psychosocial laboratory stress procedure. Participants were randomly assigned either to prepare alone or to receive social support from their female partner or close female friend while preparing for the stressful task. Differential stress responses between the genotype groups were observed depending on the presence or absence of social support. Only individuals with one or two copies of the G allele of rs53576 showed lower cortisol responses to stress after social support, compared with individuals with the same genotype receiving no social support. These results indicate that genetic variation of the oxytocin system modulates the effectiveness of positive social interaction as a protective buffer against a stressful experience.

The quality of an individual's social relationships predicts a number of long-term health outcomes, and positive social interaction serves as an important buffer against everyday stress experiences (1–6). Whereas dysregulations of the hypothalamic–pituitary–adrenal (HPA) axis have been linked to the development of several stress-related disorders (7, 8), laboratory experiments on the psychobiological mechanisms underlying health-promoting effects of prosocial behavior have shown that social support from a partner or close friend during preparation for a stressful task reduces HPA axis responsiveness to social stress (9–12). This effect is so robust that even the act of imagining the support of a close other can be an effective buffer against stress (13).

Although for most individuals social support serves as a reliable protective factor against stress, significant differences also exist in individuals' responses to social interaction. For instance, insecure attachment is associated with reduced responsiveness to social support (9), and certain disorders, such as autism, are characterized by a general aversion to social interaction (14). Furthermore, cultural norms heavily influence how individuals seek and respond to social support; East Asians, for example, are less likely to seek explicit social support than European Americans and are more likely to experience negative emotions such as guilt in response to receiving explicit—as opposed to implicit—social support (13, 15).

In recent years, the human oxytocin system has been the subject of a rapidly growing area of research focused on elucidating the neuroendocrinological underpinnings of human prosocial behavior and stress buffering (for a review, see ref. 16). Oxytocin is a neuropeptide produced in the hypothalamus and released from axonal terminals as well as dendrites, resulting in both local action as well as diffusion through the brain to

a number of brain regions where the oxytocin receptor is found. It plays a critical role in mammalian social behaviors, including recognition of conspecifics, mother–infant attachment, and pair bonding (17, 18). In humans, oxytocin also plays an important role in social behavior and stress reactivity (19–21). After receiving a single dose of intranasally administered oxytocin, healthy adults show decreased reactivity to acute social stress (10) and increased trusting behavior (22). Intranasal oxytocin also dampens amygdala reactions to threatening faces (23–26), affects the recognition of social memory words (27, 28), and promotes more positive interpretations of ambiguous attachment-themed scenarios in insecurely attached adults (29). In addition, oxytocin administration improves emotion recognition, responsiveness to others, and social behavior in individuals with autism (30–32).

Because of the high degree of preservation of the oxytocin system across mammalian evolution and the known heritability of social behavior in humans (33, 34), variation in genes encoding oxytocin has the potential to shed light on individual differences in social behavior (16). Whereas studies of variation in the genes encoding neuropeptides themselves have been largely uninformative (35), a substantial body of evidence now implicates the genes encoding their receptors (16). The oxytocin receptor gene (*OXTR*) is located on chromosome 3p25, spans 17 kb, contains four exons and three introns (36), and encodes a 389-aa polypeptide with seven transmembrane domains belonging to the class I G protein-coupled receptor family (37).

One SNP in the third intron of *OXTR* has emerged as a particularly promising candidate in recent studies on human social behavior: rs53576 (G/A). In recent studies, the A allele of rs53576 has been associated with reduced maternal sensitivity to child behavior (38), lower empathy (39), reduced reward dependence (40), lower optimism and self-esteem (41), and, in men, negative affect (42). Moreover, the A allele has also been associated with a larger startle response (39) and reduced amygdala activation during emotional face processing (40). Associations have also been reported between other variants of *OXTR* and amygdala volume (43), risk for autism (44–47), the quality of infants' attachment bonds with their caregivers (48), attachment anxiety in adult females, and autistic-like social difficulties in adult males (49).

Recently, Kim et al. (50) reported that *OXTR* rs53576 genotype is associated with the tendency to seek emotional support during periods of distress in individuals for whom explicit sup-

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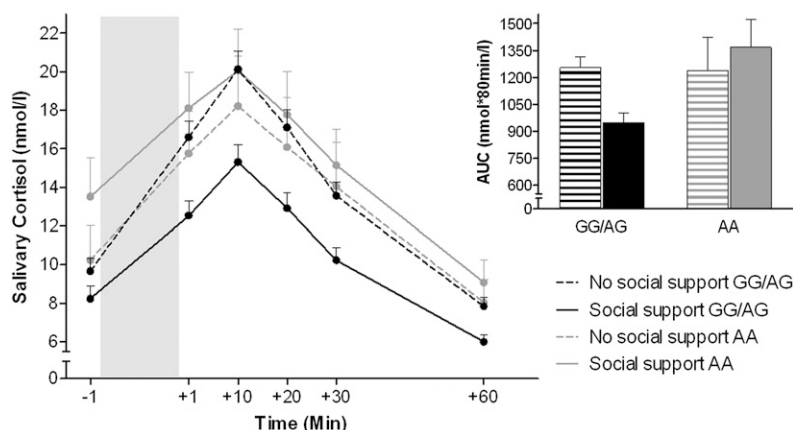


Fig. 1. Mean salivary cortisol levels before, during (shaded area), and after acute social stress in individuals receiving social support or no social support. Error bars represent SEM. *Inset:* Bar graph of area under the response curves (AUC), representing aggregated hormone levels through the six measurement points.

in basic emotional processing (52) and the regulation of complex social behavior (53). Rodent models have shown that oxytocinergic stimulation inhibits the amygdaloid efferents to the hypothalamus and brainstem that produce autonomic responses to social stimuli (54). Likewise, initial human studies have shown that intranasal oxytocin administration leads to a pronounced reduction in activation and amygdala–midbrain connectivity in response to fearful visual stimuli (23–26). Recent studies also suggest that oxytocin promotes responsiveness to social stimuli by reducing activation in the neural circuitry for anxiety and aversion and increasing activation in regions involved in empathy, specifically in response to infant crying (55). Interestingly, an increased functional coupling between hypothalamus and amygdala has been found in rs53576 A allele carriers during processing of emotionally salient social cues (40). Moreover, this allele was associated with morphometric alterations of the hypothalamus and amygdala. These results suggest altered top-down regulation of the hypothalamus in A allele carriers and are in line with the results of the present study, which suggests reduced HPA axis control in response to social support in rs53576 AA carriers.

Oxytocin is also known to be involved in social reward processing (17, 56). Thus, another plausible mechanism by which *OXTR* polymorphisms may influence the efficacy of social support is by influencing the reward value of social interaction early in development. Children who find social interaction more rewarding may be more likely to form positive associations with the experience of seeking social support; later in life, the cumulative effects of these experiences may manifest themselves as differential tendencies to seek and benefit from social support. Future developmental and longitudinal studies may help to shed some light on these issues.

An individual's beliefs and expectations about the general effectiveness of social support are likely to regulate that individual's tendency to seek social support. This evidence that a biological variable influences the effectiveness of social support provides one plausible mechanism for the group difference reported in Kim et al. (50)—namely, that within a single cultural group (Americans), individuals with the AA genotype are less likely to seek social support than those with the GG or AG genotypes. However, this interpretation does not preclude the converse and complementary possibility that an individual's history and experiences with social support influence physiological and psychological reactions to social support. Furthermore, the observed dissociation between perceived quality of social support and buffering of stress reactivity in individuals with the AA genotype is an issue worth future study. It is possible, for

instance, that these individuals' ratings of the quality of social support they received were more strongly influenced by social norms than by deliberate introspection.

Social support-seeking behavior and reactions to receiving social support are likely to be related through a feedback loop. Further research is needed to clarify the details of this relationship and to investigate, for instance, whether individuals with the AA genotype would begin to benefit more visibly from the type of social support offered in this study after repeated positive experiences of receiving it, or whether these individuals may instead benefit more strongly from implicit or other alternative forms of social support to those offered by the supporters in this study.

Because previous results have suggested sex differences in the effects of social support on the stress response (12, 57), as well as sex differences in associations between *OXTR* genotype and phenotype (49) and responses to intranasal oxytocin administration (26, 58), we decided to limit the present initial study to male participants. Follow-up studies testing women would be particularly informative given the potential for sex differences in this domain.

Our data were found to fit a recessive A-allele model (AA vs. G carriers); this particular grouping of genotypes has been used previously in research on rs53576 and social support-seeking behavior (50). However, given the relatively small number of individuals with the AA genotype in our study, replication of the results in a larger sample would be advisable. Other studies have

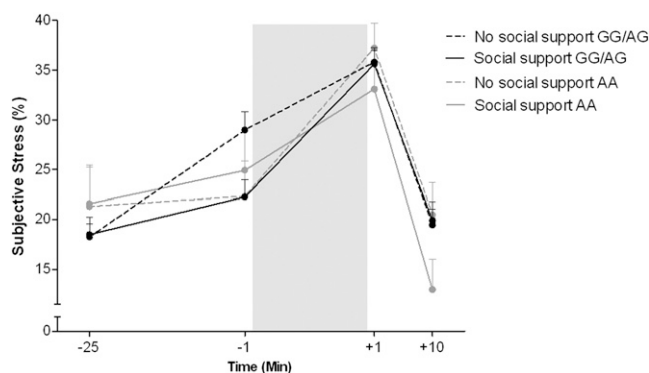


Fig. 2. Mean levels of subjective stress before, during (shaded area), and after acute social stress in individuals receiving social support or no social support. Error bars are SEM.

Stress Manipulation and Recovery. The group of participants was then led to the stress room. The 20-min stress induction protocol was conducted according to the original description of the TSST-G in ref. 51. The TSST-G consists of a mock job interview and an unanticipated mental arithmetic task, led by a panel of two evaluators who are seated at a table and flanked by two conspicuous video cameras. The evaluators are trained to maintain a neutral expression throughout the stress procedure and provide no positive feedback [e.g., verbal encouragement, nodding, smiling (51, 60)]. Moveable dividing walls separate the participants and prevent visual contact between them (Fig. 3B). Participants are informed that they will be called upon to answer questions in random order and may be repeatedly called upon at any time.

After the stress phase, the group of participants was led back to the waiting room, where additional cortisol and subjective stress measurements were taken. Participants in the social support condition also completed a questionnaire assessing how helpful, calming, and confusing they found the social support that they received. At the end of the study, participants were debriefed and thanked and received payment.

Stress Response Measures. Saliva samples were collected at six time points immediately before and after the stress manipulation (at -1, +1, +10, +20, +30, and +60 min relative to stress) using a commercially available sampling device (Salivette; Sarstedt). For biochemical analyses of cortisol concentration, saliva samples were spun at $2,000 \times g$ for 10 min to obtain 0.5–1.0 mL clear saliva with low viscosity. Salivary cortisol concentrations were determined by a commercially available chemiluminescence immunoassay (IBL International). Inter- and intrassay coefficients of variation were both <8%.

A subjective stress questionnaire was given at baseline, immediately after the preparation phase, and twice after the stress manipulation (at -25, -1, +1, and +10 min relative to stress). The subject indicated anxiety, physical discomfort, avoidance (desire to leave the situation), emotional arousal, and feelings of control on five visual analog scales ranging from 0 (not at all) to 100 (maximum) (51). Subjective stress was operationalized as the mean value of these five items (with the feelings of control scale reverse-coded) at each time point.

Genotyping. Buccal epithelial cells were collected in mouthwash samples, and DNA was isolated after a standard salting out method, using the Masterpure isolation kit (Epicentre). Genotyping of *OXTR* rs53576 was performed by 5'-nuclease assay. Primers and probes were from Applied Biosystems (TaqMan SNP Genotyping Assay). PCR was conducted with Hot Start Plus DNA polymerase and Q-solution (Qiagen) in a Bio-Rad C1000 machine with a CFX96 fluorescence reading module.

Statistics. Cortisol and psychological data were analyzed using three-way ANOVA with repeated measures [condition (two conditions: social support vs. no social support) by genotype (GG/AG vs. AA) $\times$ time (repeated factor: 6 for cortisol, 4 for subjective stress)]. Preliminary analyses showed that the recessive A allele model (AA vs. G carriers) provided best fit to the data; the same model has been used in previous research on rs53576 and social support-seeking behavior (e.g., ref. 50). The recessive model was therefore used in all subsequent analyses (Table 2 shows effect of social support on cortisol responses in GG, AG, and AA genotypes separately). Including the order in which participants were called upon to deliver their speeches as a covariate does not change the reported results; this variable was therefore dropped from the analyses. Because cortisol values showed approximately log-normal distributions, log-transformed cortisol values were used in the analyses. Where appropriate, Greenhouse-Geisser corrected values are reported. The areas under the individual response curves with respect to ground (AUC_G) of cortisol were calculated with the trapezoid formula, which allows a sensitive measure of physiological changes over time (61). To compare cortisol increases after stress, the prestress cortisol level was subtracted from the peak cortisol value for each individual participant. All analyses were conducted using SPSS18 (SPSS).

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