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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port-seeking is culturally normative. Specifically, individuals with the GG or AG genotypes self-reported on a free recall task a higher tendency to seek social support relative to those with the AA genotype. However, we are unaware of any studies that have specifically targeted the potential interaction between *OXTR* genotype and social support in a controlled laboratory setting on immediate physiological and psychological reactivity to psychosocial stress. Hence, we set out to study whether rs53576 might interact with stress-protective effects of social support in a naturalistic standardized psychosocial laboratory stressor in a group format (51). More specifically, we predicted that individuals with at least one copy of the G allele would benefit from social support during subsequent stress exposure, evidenced by significantly lower cortisol and subjective stress responses, more than individuals with two copies of the A allele (AA) of rs53576.

Results

The sample consisted of 173 (89%) participants of European descent, 15 (8%) of mixed descent, and 6 (3%) of other/unreported ethnicity. There were no significant main effects or interactions of ethnicity (European vs. Other) with other variables and no significant difference in the distribution of genotypes across ethnic groups ($\chi^2 = 0.31$; $P = 0.86$). Genotype frequencies for *OXTR* rs53576 were 78 (40%) GG, 87 (45%) AG, and 29 (15%) AA. This distribution was in Hardy-Weinberg equilibrium ($\chi^2 = 0.34$, $P = 0.56$). GG, AG, and AA carriers did not differ significantly in demographic and clinical characteristics (Table 1), including self-reported measures of trait anxiety and social anxiety. Stress responses during the group stressor were not influenced by the order in which participants were called upon to deliver their speeches (*Materials and Methods*).

Cortisol Responses to Stress. Replicating prior research, the psychosocial stress protocol induced significant increases in salivary cortisol levels in all participants [main effect of time: $F(1.79,328.98) = 127.84$, $P < 0.001$].

The interaction between genotype (AA vs. G carriers) and social support on cortisol responses [$F(1,184) = 4.83$, $P = 0.03$, partial $\eta^2 = 0.03$] was significant, indicating differential response patterns between the genotype groups depending on the presence or absence of social support. As predicted, 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 (Fig. 1). Post hoc analyses confirmed that in G allele carriers, the cortisol response to stress (expressed as the prestress to peak Δ) was significantly smaller in the social support compared with the no-support condition [$F(1,184) = 6.97$, $P < 0.01$], whereas there were no significant differences in the cortisol response between the social support and no-support condition in the AA genotype [$F(1,184) = 0.54$, $P = 0.46$]. In sum, only in G allele carriers was social support associated with reduced cortisol responsiveness.

In addition, there was a weak trend for a main effect of genotype [$F(1,184) = 3.19$, $P = 0.08$], with individuals with the AA genotype showing generally higher cortisol levels throughout the session than G carriers. A post hoc t test confirmed the group difference in prestress levels of cortisol, with individuals with the AA genotype exhibiting higher prestress levels than G carriers [$t(186) = 2.20$, $P = 0.03$].

Subjective Responses to Stress. Overall, the stress protocol induced subjective stress in participants [main effect of time: $F(2.84,525.62) = 71.26$, $P < 0.001$]. Stress ratings did not differ between the groups (AA vs. G carriers) at baseline [$F(1,187) = 1.20$, $P = 0.28$]. As predicted, the interaction between genotype and social support on subjective stress ratings through the session was significant [$F(3.37,623.50) = 4.77$, $P < 0.01$, partial $\eta^2 = 0.03$]. As shown in Fig. 2, social support attenuated anticipatory stress responses only in carriers of one or two G alleles but not in individuals homozygous for the A allele. Thus, G carriers benefited from social support during the anticipatory phase (the measurement taken 1 min before stress exposure), compared with individuals with the AA genotype. Interestingly, individuals with the AA genotype who received social support also reported the lowest levels of subjective stress 10 min after the end of the stress procedure, although it is unclear whether this effect indicates a greater recovery than that experienced by other participants from the social stress procedure itself (i.e., participants in the other groups also recovered to baseline subjective stress levels).

Notably, individuals with the AA genotype did not rate the social support they received as less helpful, less calming, or more confusing than G carriers. In fact, individuals with the AA genotype rated the social support slightly more favorably on each of these scales, although none of the differences reached statistical significance (all $t < 1.70$, all $P > 0.11$). Perceived quality of social support therefore does not explain the group difference in subjective stress ratings. Thus, despite being rated as relatively high in quality, subjectively beneficial social support did not provide an efficient buffer against stress reactivity in individuals with the AA genotype.

Discussion

We provide evidence that a common polymorphism of the oxytocin receptor gene mediates physiological and psychological benefits of social support in the context of psychosocial stress exposure. Specifically, rs53576 G carriers seemed to benefit more physiologically and psychologically from social support than individuals with the AA genotype, who showed nearly identical cortisol and subjective stress responses to acute psychosocial stress in both the support and no-support conditions. Because neurogenetic approaches can be used to indirectly assess the functioning of neurotransmitter systems (16), our results indicate that the oxytocin system plays a key role in the mediation of the effects of social support on psychological and physiological responses to acute stress.

Physiologically, it can be speculated that oxytocin released in the context of social support influences stress processing systems via oxytocin receptors in hypothalamic–limbic circuits (16). One likely important site of action is the amygdala, critically involved

Table 1. Characteristics of study groups

Characteristic	GG (n = 78)	AG (n = 87)	AA (n = 29)	Group comparison
Age (y)	23.1 (2.9)	23.3 (3.0)	23.4 (3.0)	$F(2,181) = 0.1$, ns
Verbal intelligence (Vocabulary Test)	34.1 (2.9)	33.4 (2.6)	33.4 (3.1)	$F(2,182) = 1.2$, ns
Trait anxiety (State Trait Anxiety Inventory)	36.1 (7.9)	36.3 (7.8)	35.4 (7.9)	$F(2,183) = 0.1$, ns
Social anxiety (Social Interaction Anxiety Scale)	18.0 (9.8)	20.0 (9.3)	18.4 (9.9)	$F(2,184) = 1.0$, ns
Empathy (Interpersonal Reactivity Index)	55.8 (8.3)	55.9 (11.3)	55.0 (7.8)	$F(2,184) = 0.1$, ns

Cell values indicate group means. In GG, AG, and AA columns, values in parentheses are SD. ns, nonsiginificant. The validated German versions of the following questionnaires were used: WST (62), STAI (63), SIAS (64), IRI (65).

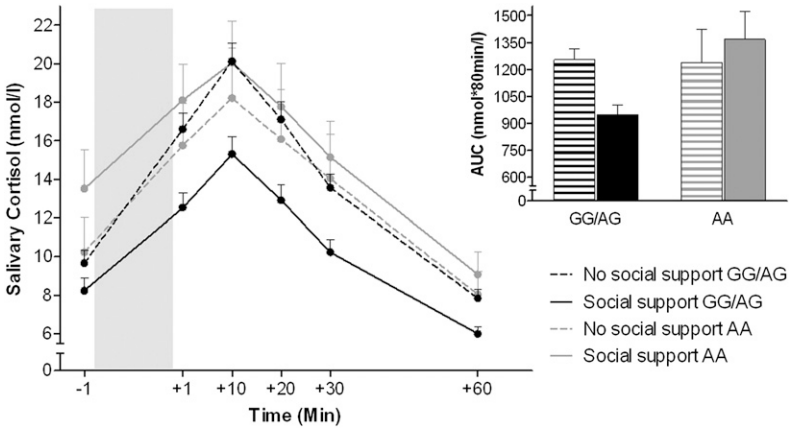

Fig. 1. Mean salivary cortisol levels before, during (shaded area), and after acute social stress in individuals receiving social support or no social support. Error bars represent SEM. *Inset*: Bar graph of area under the response curves (AUC), representing aggregated hormone levels through the six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

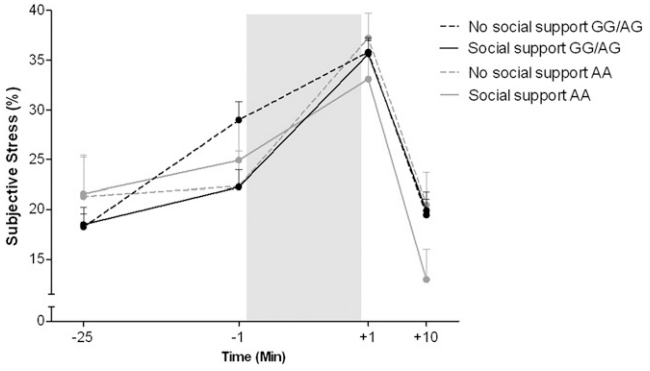

Fig. 2. Mean levels of subjective stress before, during (shaded area), and after acute social stress in individuals receiving social support or no social support. Error bars are SEM.

found links between rs53576 genotype and phenotype using, variably, additive (40) or dominant (38, 39) models. Because rs53576 is located in the intronic (noncoding) region of *OXTR* (36), the genetic variant investigated in this study is likely a marker for still-unidentified functional variants of the gene. Further research on the molecular level will be necessary to clarify the relationship between this intronic SNP and the functionality of the oxytocin receptor. Such research may also help reconcile previous results, which have variously used additive, dominant, and recessive models to describe effects of rs53576 on behavior.

Stress is a ubiquitous challenge across human cultures, affecting mental and physical health. The identification of factors that amplify or reduce stress and stress-related diseases represents a research priority. Research on how biological and environmental factors interact to influence individual responses to stress and social support is a critical component of a translational research program to advance clinical applications. Because the neuroanatomical distribution and sensitivity of oxytocin receptors may be guided by variations in the regulatory regions of their respective genes, further studies on the role of specific genetic variants in the behavioral and brain response to oxytocin administration will be crucial for decoding the neurobiology of the social brain and to tailor innovative strategies for prevention and therapy. For psychologists, health care practitioners, and the general public alike, a more nuanced understanding of these processes is expected to have broadly beneficial effects.

Materials and Methods

Participants. Two hundred three healthy males (mean age 23.2 y, SD 2.9 y) were recruited at the University of Freiburg, Germany, to participate in a study about "behavior in job interviews." Exclusion criteria included prior participation in a stress induction study, studying psychology, chronic or acute illness, current or previous psychiatric treatment, smoking more than five cigarettes per day, medication use, or substance abuse. Individuals were deemed eligible for participation if they stated that they would be able to bring a close female social supporter with them to the experimental session; eligible participants were then randomly assigned to the social support condition (instructed to bring a companion to the session) or to the no social support condition (instructed to arrive at the session alone).

Participants were instructed to abstain from caffeine, alcohol, and drug or medication use 24 h before the session. They were asked to eat standard meals on the day of participation and then abstain from food 2 h before the session. One participant was excluded for not understanding the instructions because of limited German comprehension. One group consisted of only three instead of four to six participants (*Preparation and Social Support Manipulation*, below), resulting in substantially shorter stress exposure; therefore, these three participants were excluded. Inclusion of these four additional participants does not significantly change the results of any reported analyses. Genetic samples were not collected for five participants. Results are therefore reported for the remaining 194 (social support $n = 79$; no social support $n = 115$ participants). All participants gave informed consent and were paid 25 euros for participation. Female social supporters were given a small gift of candy for participation in the first phase of the session. The study was approved by the institutional review board of the University of Freiburg.

General Procedure. The 2-h sessions were all conducted in the late afternoon to control for diurnal variations in cortisol secretion. The Trier Social Stress Test for Groups [TSST-G (51)] was used to induce moderate psychosocial stress. This protocol has been found to induce reliable psychobiological stress responses (51, 59, 60). Physiological and psychological measures (cortisol and subjective stress) were taken throughout the session. A timeline of the experimental procedure is depicted in Fig. 3*A*.

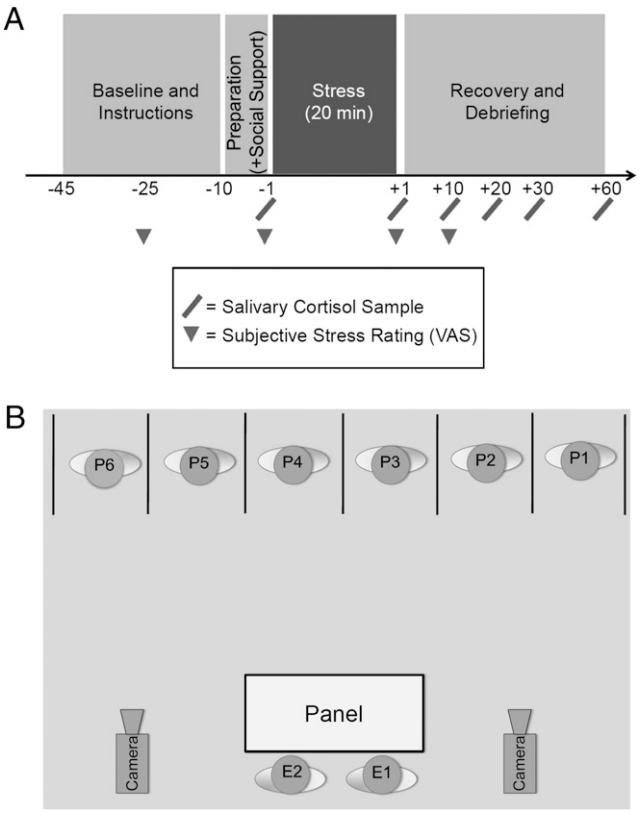

Fig. 3. (*A*) Sequence of events and timeline of the study protocol. (*B*) Layout of stress room, depicting six participants (P) and two evaluators (E). VAS, visual analog scale.

Preparation and Social Support Manipulation. Participants arrived at the laboratory in groups of four to six. Half were instructed to arrive alone and half with a female social supporter. The social supporters were each immediately directed to separate rooms ("support rooms"), where they were instructed that their task would be to be as helpful as possible to their companion as he prepared for a mock job interview (instructions adapted from ref. 10).

In a separate room ("waiting room"), the participants themselves were instructed not to communicate with one another for the duration of the study. They provided baseline measures of cortisol and subjective stress and then received information about the upcoming mock job interview task. Immediately before the stress manipulation, participants were given 10 min to prepare for the interview. Participants in the social support condition spent these 10 min in one of the three support rooms with their social supporters. Participants in the no social support condition prepared on their own. After the 10-min task preparation phase, the social supporters were thanked and dismissed.

Table 2. Differences between social support and no social support condition in cortisol responses for GG, AG, and AA genotypes

Variable	GG	AG	AA
Aggregated cortisol levels (AUC)	−292.4 (128.8)	−303.1 (120.5)	129.1 (212.6)

Values are mean (SD). Areas under the individual response curves (AUC) aggregate the six cortisol levels during the stress protocol. Negative values represent a relative decrease in cortisol release (i.e., protective effect of social support).

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. 3*B*). 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 × *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) × 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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