Available online at www.sciencedirect.com

SciVerse ScienceDirect

Current Opinion in Neurobiology

Oxytocin, stress and social behavior: neurogenetics of the human oxytocin system

Robert Kumsta[1] and Markus Heinrichs[1,2]

The neuropeptide oxytocin has had key roles throughout mammalian evolution in the regulation of complex social cognition and behaviors, such as attachment, parental care, pair-bonding, as well as social exploration and recognition. Recently, studies have begun to provide evidence that the function of this neuropeptide is impaired in mental disorders associated with social deficits. In this review, we focus on the genetic mechanisms of inter-individual variation in the social neuropeptide signaling. We discuss molecular genetic studies which identified variations in specific genes contributing to individual differences in social behavior and cognition, with a focus on the gene coding for the oxytocin receptor (*OXTR*) emerging as a particularly promising candidate. We conclude that molecular studies are warranted to elucidate functional consequences of variants that have shown stable associations with sociobehavioral phenotypes. With regard to the variability in individual responses to oxytocin administration, we advocate the need for pharmacogenetic approaches in order to test how the efficacy of oxytocin administration is modulated by genetic variation of *OXTR* or other genes involved in oxytocin signaling.

Addresses
[1] Department of Psychology, Laboratory for Biological and Personality Psychology, University of Freiburg, D-79104 Freiburg, Germany
[2] Freiburg Brain Imaging Center, University Medical Center, University of Freiburg, D-79106 Freiburg, Germany

Corresponding authors: Kumsta, Robert (robert.kumsta@psychologie.uni-freiburg.de) and Heinrichs, Markus (heinrichs@psychologie.uni-freiburg.de)

Current Opinion in Neurobiology 2013, **23**:11–16

This review comes from a themed issue on **Neurogenetics**

Edited by **Ralph Greenspan** and **Christine Petit**

For a complete overview see the Issue and the Editorial

Available online 4th October 2012

0959-4388/$ – see front matter,

http://dx.doi.org/10.1016/j.conb.2012.09.004

Introduction

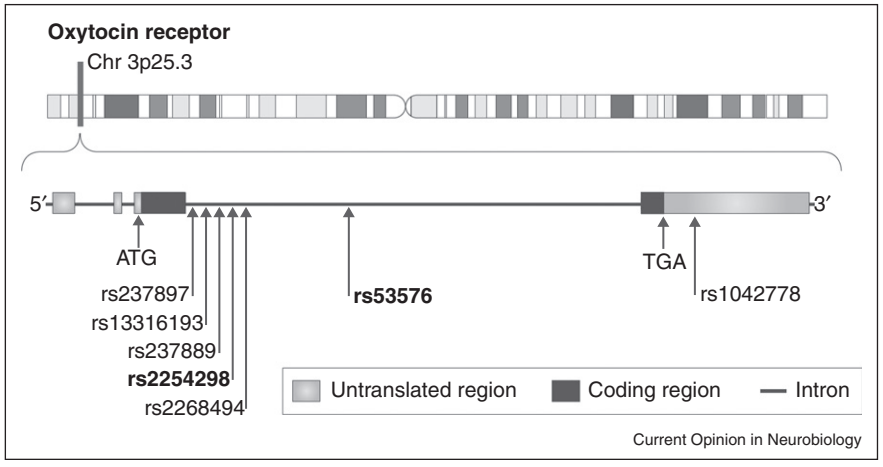
Research in the social neurosciences has made considerable progress in identifying the neurobiological underpinnings of complex social behavior. Investigations across species have shown that the neuropeptide oxytocin, together with arginine vasopressin, plays a key role in encoding information relevant to social interactions and is critically involved in the regulation of complex social cognition and behavior, including attachment, social recognition, social exploration, as well as anxiety and fear-related behaviors (for review, see [1••]). Twin studies have provided evidence that social phenotypes show considerable heritability [2••]. Recent studies have investigated the genetic mechanisms of inter-individual variation in the social neuropeptide signaling. In particular, molecular genetic studies have identified variations in specific genes contributing to individual differences in social behavior and cognition, and the gene coding for the oxytocin receptor (*OXTR*) has emerged as a particularly promising candidate.

The aim of this review is to provide an overview of recent association studies involving *OXTR* single nucleotide polymorphisms (SNP) (Figure 1) with a focus on sociobehavioral phenotypes in healthy individuals. These include prosocial behavior, parenting, empathy, positive affect, social auditory processing, and sensitivity to social support or support seeking during stress. Recent imaging genetics findings and gene by environment interactions will be discussed, followed by a brief account on other genes involved in oxytocinergic signaling. Studies investigating associations between genetic variation of *OXTR* and autism spectrum disorder or autistic traits will not be covered here, and the reader is referred to Ebstein *et al.* [3] for a comprehensive account of the role of *OXTR* in autism.

General social phenotypes

Several molecular genetic studies in nonclinical subjects have shown associations between *OXTR* and general sociobehavioral phenotypes. Concerning prosocial behavior, Kogan *et al.* [4] showed that a single intronic *OXTR* SNP, rs53576, previously associated with autism [5] plays an important role in the regulation of prosocial behavior, with G homozygotes displaying higher prosociality in nonverbal displays, as judged by outside observers' ratings of silent behavior. In a laboratory-based experiment which included a two-person investment game measuring trust, trustworthiness behavior, and risk behavior, Krueger *et al.* [6] showed that the rs53576 GG genotype was associated with higher trust but was not related to a general increase in trustworthy or risk behaviors. In a study on real world prosocial behavior (i.e. volunteer work, charitable activities and commitment to civic duty), no main effect of *OXTR* rs53576 was observed. However, genotype interacted with perceived threat to predict charitable activities, such that the GG genotype buffered the negative association between threat and prosocial behaviors [7]. An effect of another *OXTR* SNP

Figure 1



Genetic variants in the oxytocin receptor gene (*OXTR*). The (*OXTR*) gene is located on chromosome 3p25-3p26.2, spans 17 kb, and contains three introns and four exons. The 389 amino acid polypeptide with seven transmembrane domains belongs to the class I G protein-coupled receptor. Two single nucleotide polymorphisms (SNPs) in the third intron of *OXTR* have emerged as particularly promising candidates in the study of sociobehavioral phenotypes (indicated in bold): rs53576 (G/A) and rs2254298 (G/A). The main SNPs with their location and rs number are shown above. Exons are indicated by the darkershaded boxes, and the untranslated regions are shown by the lighter boxes. Variants in the gene are shown by arrows. Chr, chromosome.
Figure modified, with permission, from [1••].

(rs1042778) on prosocial behavior in an economic exchange game [8] could not be replicated in a subsequent study [9].

Two studies found associations between *OXTR* SNPs and sensitive parenting. In particular, mothers who carried at least one *OXTR* rs53576 A allele showed lower levels of sensitive responsiveness to their toddlers [10]. Interestingly, A allele carriers also showed reduced physiological reactivity to repeated infant cry sounds [11]. Feldman *et al.* [12] showed that the TT genotype of another *OXTR* SNP (rs1042778) was associated with less parental touch (and also with lower plasma oxytocin levels). Further association studies on *OXTR* rs53576 report that A allele carriers exhibited lower empathy [13], lower positive affect scores [14], and more self-reported difficulty in hearing and understanding people under background noise [15].

To summarize, these studies suggest that polymorphisms in the OXTR gene (Figure 1), particularly rs53576 (but also rs2254298 and rs1042778), contribute to the modulation of social behavior in healthy subjects.

Social stress and social support

In addition to its role in social behavior and social cognition, oxytocin has been found to dampen the stress response in humans (for review, see [16]). Intranasal administration of oxytocin has been shown to attenuate neuroendocrine stress reactivity [17] and has been associated with decreased amygdala activation in response to threatening stimuli [18,19]. Rodrigues *et al.* [13] showed a link between *OXTR* rs53576 and dispositional as well as physiological stress reactivity. A allele carriers reported higher levels of reactivity across a range of stressful contexts, and greater cardiovascular reactivity indicated by heart rate during a startle anticipation task (but see also Norman *et al.* [20], who found that individuals with the GG genotype showed higher levels of sympathetic reactivity to psychological stress). On the basis of the findings that oxytocin administration, in particular when combined with social support, reduces the neuroendocrine and subjective stress response, a study from our laboratory investigated whether *OXTR* rs53576 might interact with stress-protective effects of social support [21•]. It was shown that social support by the partner before a standardized laboratory stressor was associated with reduced cortisol and subjective stress responses in male G allele carriers. Conversely, individuals with the rs53576 AA genotype did not benefit from social support. Interestingly, Kim *et al.* [22•] showed that in Americans (but not Koreans), AA genotype carriers are less likely to seek social support compared to G allele carriers during times of distress. These results show that genetic variation of *OXTR* influences sensitivity to social context, thereby modulating the effectiveness of positive social interaction as a protective buffer against a stressful experience.

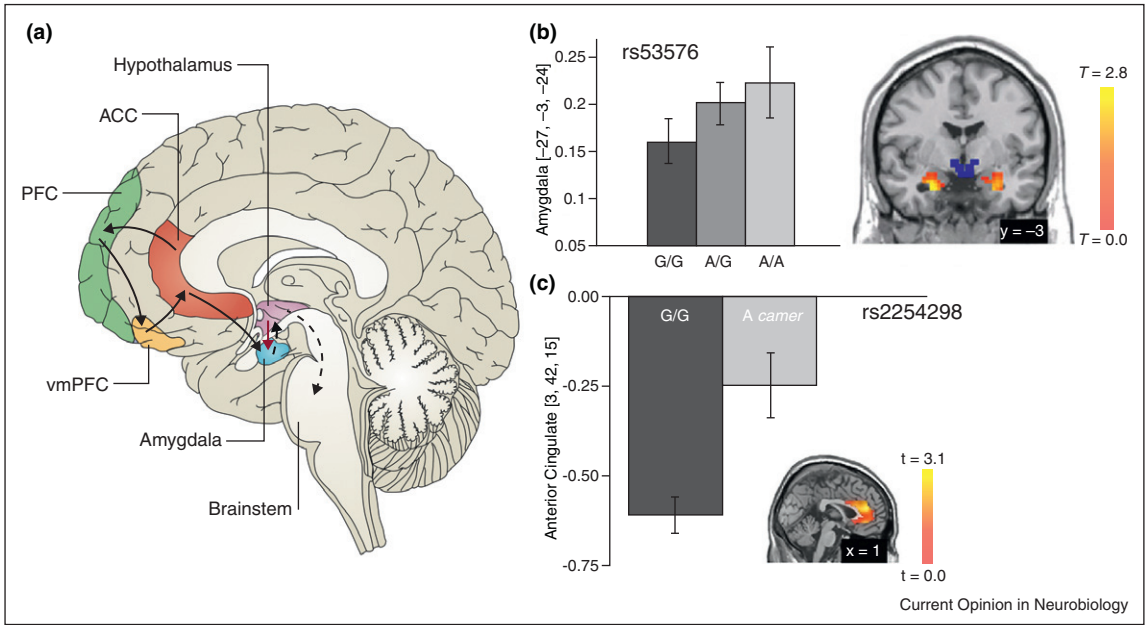
Psychological resources such as optimism, mastery, and self-esteem are also discussed as stress buffers and are predictors of long-term health outcomes. Saphire-Bernstein *et al.* [23•] reported that rs53576 A allele carriers

had lower levels of optimism, mastery, and self-esteem. The observed association with depressive symptoms seems to be largely mediated by the influence of *OXTR* variation on psychological resources. However, the association between rs53576 and optimism could not be replicated in a large sample of Caucasian women [24].

Neurogenetics: structural and functional neuroimaging

The imaging genetics approach, which relates genetic variants to brain structure and function, can be employed to come to a better understanding of the neurobiology underlying the observed associations between *OXTR* variants and social behavior and cognition phenotypes. It has been suggested that so-called endophenotypes (or intermediate phenotypes) can provide a bridge between genotype and behavioral phenotype. Several studies have shown associations between *OXTR* SNPs and morphometric alterations as well as differences in activity of key limbic structures involved in social behavior and in the pathophysiology of psychiatric disorders characterized by impaired social functioning. For instance, an increased functional coupling between hypothalamus and amygdala during processing of emotionally salient social cues was observed in rs53576 A allele carriers. Moreover, this allele was associated with morphometric alterations of the hypothalamus and amygdala, and was related to reduced reward dependence scores of the Tridimensional Personality Questionnaire in males [25•]. Three other studies found that the rs2254298 SNP is associated with amygdala volume. In a large Japanese sample, Inoue *et al.* [26] reported larger bilateral amygdala volume in rs2254298 A allele carriers, which was also found in a sample of adolescent girls of mixed ethnicity [27]. Tost *et al.* [28] extended these findings by investigating structure and function of emotion regulatory circuits including the hypothalamus, amygdala, and the dorsal anterior cingulate gyrus (dACG) in a large Caucasian sample. While no effects of rs2254298 on amygdala volume were observed, a significant decrease in hypothalamus gray matter volume was observed in rs2254298 A carriers, an effect driven mainly by males. Similar to findings on rs53576, an increase in the structural coupling of hypothalamus and dACG was observed in rs2254298 A carriers. Finally, the rs2254298 A allele was associated with deficient deactivation of dACG during emotional face processing (see Figure 2).

Figure 2



Neuropeptides and social-emotional information processing in humans. Oxytocin receptor SNPs have been associated with structural and functional changes in brain regions involved in a regulatory circuit of social–emotional information processing. **(a)** Top-down control of the amygdala (shown by black arrows) arises from the anterior cingulate cortex (ACC) and ventral medial prefrontal cortex (vmPFC). Bottom-up modulation of the amygdala (shown by the red arrow) arises from neurons in the hypothalamus that express the neuropeptides OXT and AVP, which target distinct neuronal populations in the central amygdala. Projections from the amygdala to the brainstem, via the hypothalamus, regulate the expression of autonomic reactions to social signals (shown by dotted arrows). **(b)** An increase in the functional correlation of the hypothalamus and amygdala has been observed in rs53576 A allele carriers. The blue region illustrates the hypothalamus seed region of the analysis [25•]. **(c)** rs2254298 has been associated with amygdala volume in two studies [26,27]. Furthermore, decreased hypothalamus gray matter volume and an increase in functional coupling of hypothalamus, dACG and amygdala was observed in rs2254298 A carriers [28], shown in panel (c).Part (a) modified, with permission, from [1••], part (b) modified, with permission, from [25•], part (c) modified, with permission, from [28].

Taken together, these imaging studies suggest that genetic variation of *OXTR* affects a limbic circuit involving the amygdala, the hypothalamus, and the cingulate gyrus. The findings provide support for the notion that *OXTR* SNPs mediate their effects on social cognition and behavior by modulating neural circuits for processing of social information and negative affect [29].

Gene–environment interaction

It is well documented that early environmental factors can have long-lasting influences on health outcomes. For instance, there is a strong link between adverse childhood experience (such as sexual/physical abuse, emotional neglect, or being reared in institutions) and mental health problems in adulthood [30]. Neurobiological mechanisms underlying this relationship involve alterations of stress response systems, and also deficits in emotion processing and emotional regulation [31], an effect that might be mediated through oxytocin functioning [32]. Indeed, the developing central nervous oxytocin system represents a target for the effects of early adversity. For instance, in a sample of adult women with a history of early abuse, Heim *et al.* [33] found decreased oxytocin concentrations in cerebrospinal fluid (CSF) in women reporting moderate to severe exposure to various forms of childhood abuse or neglect as compared to women with none or mild forms. Bradley *et al.* [34] provided evidence for a gene-environment interaction involving *OXTR*. They showed that the relationship between childhood maltreatment and both emotional dysregulation and attachment style was moderated by *OXTR* SNP rs53576. A sample of low-income, African American male and female G allele carriers were at increased risk for emotional dysregulation when exposed to multiple categories of childhood abuse, and exhibited enhanced disorganized adult attachment compared to A allele carriers. It is of note that it was the G allele carriers who showed both increased vulnerability towards emotion and attachment problems following childhood maltreatment, and benefited from stress buffering effects of social support. This might be explained by the differential susceptibility theory recently proposed by Belsky *et al.* [35], in which those most susceptible to adversity are simultaneously the most likely to benefit from supportive experiences, and supports the notion that genetic variation of *OXTR* influences sensitivity to social context.

Further evidence for gene-environment interactions was found in a sample of adolescent girls with respect to symptoms of depression and anxiety. Girls who had both high early adversity and were heterozygous for the *OXTR* rs2254298 polymorphism reported the highest levels of symptoms of physical and social anxiety and depression [36•]. These findings strengthen the notion that the relationship between childhood adversity and risk for mental health problems involves oxytocin neurobiology, and that part of the outcome heterogeneity is explained by genetic variation at *OXTR*.

Other oxytocin pathway genes

Whereas a large number of investigations have focused on the receptor for oxytocin and its relation to social phenotypes, little attention has been paid to other players involved in the oxytocin pathway. These include the gene for oxytocin (*OXT*; coding for the precursor protein oxytocin-neurophysin-I), the gene encoding the enzyme that metabolizes oxytocin, oxytocinase (human leucyl/cystinylaminopeptidase; LNPEP), as well as CD38, a key mediator of oxytocin brain release. For all these genes, associations with autism have been reported (for review, see [3]). Regarding LNPEP, no associations with behavioral phenotypes have been reported, and only one study involving *OXT* SNPs has been published in a healthy subject sample. Love *et al.* [37], using [^{11}C]raclopride positron emission tomography, found that *OXT* SNP rs4813625 (located upstream of the gene) was associated with dopamine responses to a standardized stressor (moderate levels of sustained pain) in a sex-specific manner. In a recent study, rs3796863 of CD38 was associated with neural processing of social stimuli. Homozygotes for the C allele showed slower reaction times and higher activation of the left fusiform gyrus during face matching and gaze processing, an effect that was modulated by intranasal oxytocin administration [38].

Conclusions

These investigations show that *OXTR* SNPs are important in explaining variability of human social behavior and social cognition, and that these effects might be mediated by modulation of neural circuits underlying processing of social information. It has to be kept in mind that most of the investigated *OXTR* SNPs are located in introns or intergene regions, with unclear functionality. To our knowledge only one presumably functional SNP in the promoter region (rs2268498) has been associated with behavioral phenotypes, that is negative affect [39] and moral judgments [40].

Molecular studies are warranted to elucidate functional consequences of variants that have shown stable associations with sociobehavioral phenotypes. With regard to clinical utility, it has been proposed that patients with mental disorders associated with severe deficits in social interactions might profit from therapy approaches where oxytocin administration is combined with interaction-based psychotherapy [1••,16,32]. Considerable variability in individual responses to oxytocin has been documented, suggesting that intranasal oxytocin administration interacts with genetically influenced differences in the oxytocin system, for instance in the number, organization, or functioning of *OXTR*s. Future studies using a pharmacogenetic approach will shed light on whether the efficacy of exogenous oxytocin administration is influenced by genetic variation of *OXTR* or other genes involved in oxytocin signaling.

Acknowledgement

The authors gratefully acknowledge grant support from the Deutsche Forschungsgemeinschaft (DFG, HE 5310/1-1, KU 2479/3-1).

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Meyer-Lindenberg A, Domes G, Kirsch P, Heinrichs M:
•• **Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine**. *Nat Rev Neurosci* 2011, **12**:524-538.
This perspective review assesses the socially relevant neuropeptides oxytocin and vasopressin in the human brain from a translational viewpoint. Besides summarizing the state of the field with regard to social behavior, genetics, systems-level neuroscience, neuroendocrinology and clinical studies, it also highlights data that are lacking and incompletely understood mechanisms that should be the focus of research with the goal of seeing neuropeptide treatments enter clinical practice.

2. Ebstein RP, Israel S, Chew SH, Zhong S, Knafo A: **Genetics of**
•• **human social behavior**. *Neuron* 2010, **65**:831-844.
A comprehensive review that covers both twin studies and molecular genetic approaches with a focus on the genetics of the arginine vasopressin and oxytocin receptor genes and their role in social behavior.

3. Ebstein RP, Knafo A, Mankuta D, Chew SH, Lai PS: **The contributions of oxytocin and vasopressin pathway genes to human behavior**. *Horm Behav* 2012, **61**:359-379.

4. Kogan A, Saslow LR, Impett EA, Oveis C, Keltner D, Rodrigues Saturn S: **Thin-slicing study of the oxytocin receptor (OXTR) gene and the evaluation and expression of the prosocial disposition**. *Proc Natl Acad Sci USA* 2011, **108**:19189-19192.

5. Wu S, Jia M, Ruan Y, Liu J, Guo Y, Shuang M, Gong X, Zhang Y, Yang X, Zhang D: **Positive association of the oxytocin receptor gene (OXTR) with autism in the Chinese Han population**. *Biol Psychiatry* 2005, **58**:74-77.

6. Krueger F, Parasuraman R, Iyengar V, Thornburg M, Weel J, Lin M, Clarke E, McCabe K, Lipsky RH: **Oxytocin receptor genetic variation promotes human trust behavior**. *Front Hum Neurosci* 2012, **6**:4.

7. Poulin MJ, Holman EA, Buffone A: **The neurogenetics of nice: receptor genes for oxytocin and vasopressin interact with threat to predict prosocial behavior**. *Psychol Sci* 2012, **23**:446-452.

8. Israel S, Lerer E, Shalev I, Uzefovsky F, Riebold M, Laiba E, Bachner-Melman R, Maril A, Bornstein G, Knafo A *et al.*: **The oxytocin receptor (OXTR) contributes to prosocial fund allocations in the dictator game and the social value orientations task**. *PLoS One* 2009, **4**:e5535.

9. Apicella CL, Cesarini D, Johannesson M, Dawes CT, Lichtenstein P, Wallace B, Beauchamp J, Westberg L: **No association between oxytocin receptor (OXTR) gene polymorphisms and experimentally elicited social preferences**. *PLoS One* 2010, **5**:e11153.

10. Bakermans-Kranenburg MJ, Van Ijzendoorn MH: **Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting**. *Soc Cogn Affect Neurosci* 2008, **3**:128-134.

11. Riem MM, Bakermans-Kranenburg MJ, Pieper S, Tops M, Boksem MA, Vermeiren RR, van Ijzendoorn MH, Rombouts SA: **Oxytocin modulates amygdala, insula, and inferior frontal gyrus responses to infant crying: a randomized controlled trial**. *Biol Psychiatry* 2011, **70**:291-297.

12. Feldman R, Zagoory-Sharon O, Weisman O, Schneiderman I, Gordon I, Maoz R, Shalev I, Ebstein RP: **Sensitive parenting is associated with plasma oxytocin and polymorphisms in the OXTR and CD38 genes**. *Biol Psychiatry* 2012, **72**:175-181.

13. Rodrigues SM, Saslow LR, Garcia N, John OP, Keltner D: **Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans**. *Proc Natl Acad Sci USA* 2009, **106**:21437-21441.

14. Lucht MJ, Barnow S, Sonnenfeld C, Rosenberger A, Grabe HJ, Schroeder W, Völzke H, Freyberger HJ, Herrmann FH, Kroemer H *et al.*: **Associations between the oxytocin receptor gene (OXTR) and affect, loneliness and intelligence in normal subjects**. *Prog Neuro-Psychopharmacol Biol Psychiatry* 2009, **33**:860-866.

15. Tops M, Van Ijzendoorn MH, Riem MME, Boksem MAS, Bakermans-Kranenburg MJ: **Oxytocin receptor gene associated with the efficiency of social auditory processing**. *Front Psychiatry* 2011, **2**:60.

16. Heinrichs M, von Dawans B, Domes G: **Oxytocin, vasopressin, and human social behavior**. *Front Neuroendocrinol* 2009, **30**:548-557.

17. Heinrichs M, Baumgartner T, Kirschbaum C, Ehlert U: **Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress**. *Biol Psychiatry* 2003, **54**:1389-1398.

18. Domes G, Heinrichs M, Glascher J, Buchel C, Braus D, Herpertz S: **Oxytocin attenuates amygdala responses to emotional faces regardless of valence**. *Biol Psychiatry* 2007, **62**:1187-1190.

19. Kirsch P, Esslinger C, Chen Q, Mier D, Lis S, Siddhanti S, Gruppe H, Mattay VS, Gallhofer B, Meyer-Lindenberg A: **Oxytocin modulates neural circuitry for social cognition and fear in humans**. *J Neurosci* 2005, **25**:11489-11493.

20. Norman GJ, Hawkley L, Luhmann M, Ball AB, Cole SW, Berntson GG, Cacioppo JT: **Variation in the oxytocin receptor gene influences neurocardiac reactivity to social stress and HPA function: a population based study**. *Horm Behav* 2012, **61**:134-139.

21. Chen FS, Kumsta R, von Dawans B, Monakhov M, Ebstein RP,
• Heinrichs M: **Common oxytocin receptor gene (OXTR) polymorphism and social support interact to reduce stress in humans**. *Proc Natl Acad Sci USA* 2011, **108**:19937-19942.
This paper provides first evidence that only individuals with one or two copies of the G allele of rs53576 show lower cortisol responses to stress after social support, indicating that genetic variation of the oxytocin system modulates the effectiveness of positive social interaction as a protective buffer against a stressful experience.

22. Kim HS, Sherman DK, Sasaki JY, Xu J, Chu TQ, Ryu C, Suh EM,
• Graham K, Taylor SE: **Culture, distress, and oxytocin receptor polymorphism (OXTR) interact to influence emotional support seeking**. *Proc Natl Acad Sci USA* 2010, **107**:15717-15721.
This study strengthens the notion that *OXTR* rs53576 is sensitive to input from the social environment, in this case, sensitivity to cultural norms regarding emotional support seeking. It was shown that among distressed American participants, G allele carriers of the rs53576 reported seeking more emotional social support, compared with those with the AA genotype, whereas Korean participants did not differ significantly by genotype. No differences were observed between *OXTR* genotype groups under conditions of low distress in either cultural group.

23. Saphire-Bernstein S, Way BM, Kim HS, Sherman DK, Taylor SE:
• **Oxytocin receptor gene (OXTR) is related to psychological resources**. *Proc Natl Acad Sci USA* 2011, **108**:15118-15122.
This paper shows that rs53576 A allele carriers have lower levels of optimism, mastery, self-esteem, and depression relative to GG homozygotes. The effects of *OXTR* on depressive symptoms seem largely mediated by the influence of rs53576 on psychological resources.

24. Cornelis MC, Glymour MM, Chang SC, Tchetgen EJ, Liang L, Koenen KC, Kang JH, Pasquale LR, Rimm EB, Kawachi I *et al.*: **Oxytocin receptor (OXTR) is not associated with optimism in the Nurses' Health Study**. *Mol Psychiatry* 2012 http://dx.doi.org/10.1038/mp.2011.178. [Epub ahead of print].

25. Tost H, Kolachana B, Hakimi S, Lemaitre H, Verchinski BA,
• Mattay VS, Weinberger DR, Meyer-Lindenberg A: **A common allele in the oxytocin receptor gene (OXTR) impacts prosocial temperament and human hypothalamic-limbic structure and function**. *Proc Natl Acad Sci USA* 2010, **107**:13936-13941.
This study shows that common genetic variants in *OXTR* that have been associated with autism, are also linked to variations in hypothalamic, amygala and cingulate structure and function in healthy individuals.

26. Inoue H, Yamasue H, Tochigi M, Abe O, Liu X, Kawamura Y, Takei K, Suga M, Yamada H, Rogers MA *et al.*: **Association between the oxytocin receptor gene and amygdalar volume in healthy adults**. *Biol Psychiatry* 2010, **68**:1066-1072.

27. Furman DJ, Chen MC, Gotlib IH: **Variant in oxytocin receptor gene is associated with amygdala volume**. *Psychoneuroendocrinology* 2011, **36**:891-897.

28. Tost H, Kolachana B, Verchinski BA, Bilek E, Goldman AL, Mattay VS, Weinberger DR, Meyer-Lindenberg A: **Neurogenetic effects of OXTR rs2254298 in the extended limbic system of healthy Caucasian adults**. *Biol Psychiatry* 2011, **70**:e37-e39 author reply e32–e41.

29. Meyer-Lindenberg A, Tost H: **Neural mechanisms of social risk for psychiatric disorders**. *Nat Neurosci* 2012, **15**:663-668.

30. Paolucci EO, Genuis ML, Violato C: **A meta-analysis of the published research on the effects of child sexual abuse**. *J Psychol* 2001, **135**:17-36.

31. Repetti RL, Taylor SE, Seeman TE: **Risky families: family social environments and the mental and physical health of offspring**. *Psychol Bull* 2002, **128**:330-366.

32. Heinrichs M, Domes G: **Neuropeptides and social behaviour: effects of oxytocin and vasopressin in humans**. *Prog Brain Res* 2008, **170**:337-350.

33. Heim C, Young LJ, Newport DJ, Mletzko T, Miller AH, Nemeroff CB: **Lower CSF oxytocin concentrations in women with a history of childhood abuse**. *Mol Psychiatry* 2009, **14**:954-958.

34. Bradley B, Westen D, Mercer KB, Binder EB, Jovanovic T, Crain D, Wingo A, Heim C: **Association between childhood maltreatment and adult emotional dysregulation in a low-income, urban, African American sample: moderation by oxytocin receptor gene**. *Dev Psychopathol* 2011, **23**:439-452.

35. Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R: **Vulnerability genes or plasticity genes?** *Mol Psychiatry* 2009, **14**:746-754.

36. Thompson RJ, Parker KJ, Hallmayer JF, Waugh CE, Gotlib IH:
• **Oxytocin receptor gene polymorphism (rs2254298) interacts with familial risk for psychopathology to predict symptoms of depression and anxiety in adolescent girls**. *Psychoneuroendocrinology* 2011, **36**:144-147.

This study provides a good example of a gene by environment interaction. It was shown that girls who both were heterozygous for *OXTR* rs2254298 and had high early adversity reported the highest symptom levels of depression, physical anxiety, and social anxiety.

37. Love TM, Enoch MA, Hodgkinson CA, Pecina M, Mickey B, Koeppe RA, Stohler CS, Goldman D, Zubieta JK: **Oxytocin gene polymorphisms influence human dopaminergic function in a sex-dependent manner**. *Biol Psychiatry* 2012, **72**:198-206.

38. Sauer C, Montag C, Worner C, Kirsch P, Reuter M: **Effects of a common variant in the CD38 gene on social processing in an oxytocin challenge study: possible links to autism**. *Neuropsychopharmacology* 2012, **37**:1474-1482.

39. Montag C, Fiebach CJ, Kirsch P, Reuter M: **Interaction of 5-HTTLPR and a variation on the oxytocin receptor gene influences negative emotionality**. *Biol Psychiatry* 2011, **69**:601-603.

40. Walter NT, Montag C, Markett S, Felten A, Voigt G, Reuter M: **Ignorance is no excuse: moral judgments are influenced by a genetic variation on the oxytocin receptor gene**. *Brain Cogn* 2012, **78**:268-273.