Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine

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Abstract | The neuropeptides oxytocin (OXT) and arginine vasopressin (AVP) are evolutionarily highly conserved mediators in the regulation of complex social cognition and behaviour. Recent studies have investigated the effects of OXT and AVP on human social interaction, the genetic mechanisms of inter-individual variation in social neuropeptide signalling and the actions of OXT and AVP in the human brain as revealed by neuroimaging. These data have advanced our understanding of the mechanisms by which these neuropeptides contribute to human social behaviour. OXT and AVP are emerging as targets for novel treatment approaches — particularly in synergistic combination with psychotherapy — for mental disorders characterized by social dysfunction, such as autism, social anxiety disorder, borderline personality disorder and schizophrenia.

For social neuroscience, few molecules could be more important and exciting than the neuropeptides oxytocin (OXT) and arginine vasopressin (AVP) (FIG. 1). These peptides have had key roles throughout mammalian evolution in the regulation of complex social cognition and behaviours[1], such as attachment[2], social exploration, recognition[3] and aggression[4], as well as anxiety[5–7], fear conditioning[8] and fear extinction[9]. Recently, studies have begun to provide evidence that the function of these neuropeptides is impaired in mental disorders associated with social deficits. Through the discovery that neuropeptides can be non-invasively delivered to the brain in humans[10], with clear behavioural- and neural systems-level consequences, this work now acquires a possible translational dimension. This clinical translation, if proven to be feasible, would constitute a substantial development as currently no robust empirical evidence exists for effective treatments of severe social impairments such as autism. The uniqueness of, and challenges posed by, human 'social disorders' was described by Thomas R. Insel: "We are, by nature, a highly affiliative species craving social contact. When social experience becomes a source of anxiety rather than a source of comfort, we have lost something fundamental — whatever we call it"[11].

The goal of this Review is to assess the OXT and AVP systems in the human brain from a translational viewpoint. Besides summarizing the state of the field with regard to social behaviour, genetics, systems-level neuroscience, neuroendocrinology and clinical studies (including behavioural and functional imaging studies into the effects of intranasal OXT and AVP administration in humans (Supplementary information S1,S2 (tables)), we will highlight unanswered questions, data that are lacking and incompletely understood mechanisms that should be the focus of research with the goal of eventually seeing neuropeptide treatments enter clinical practice.

Behavioural studies in humans

Correlational studies: peripheral levels and behavioural markers. A number of studies report correlations between peripheral levels of OXT and AVP and behaviour. For example, high levels of plasma OXT have been associated with trust and trustworthiness[12], positive physical contact with a partner[13], reduced hormonal responses to a psychosocial stressor[14] and lower levels of anxiety in patients with depression[15]. By contrast, attenuated peripheral levels of OXT have been found in patients with depression[16], schizophrenia[17,18] and autism spectrum disorders (ASDs)[19]. However, it is unclear whether peripheral levels of OXT and AVP are closely related to CNS neuropeptide function, which is more directly relevant for behavioural effects or psychopathology[20]. The validity of the assessment and interpretation of peripheral neuropeptide levels with respect to CNS availability of these neuropeptides and their effects on behaviour is highly controversial and needs further

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Event-related brain potentials
Electrical potentials that are generated in the brain as a consequence of the synchronized activation of neuronal networks by external stimuli. These evoked potentials are recorded at the scalp and consist of precisely timed sequences of waves or 'components'.

Trier Social Stress test
(TSST). A standardized psychosocial laboratory stressor that includes public speaking and mental arithmetic.

investigation[21–24]; this is an important issue that needs to be resolved for translational success to be achieved. A straightforward alternative approach is to measure neuropeptides from cerebrospinal fluid, which might better reflect their availability in the brain[10]. However, this invasive method is not feasible for routine use in humans. Thus, most studies have used intranasal delivery of peptides to investigate the central actions of neuropeptides in humans, as this provides a direct pathway to the brain[1,10].

Basic cognitive processes. Among the first studies using intranasal neuropeptide administration were experiments on cognitive processes such as memory and attention, and associated brain responses. Some of these studies reported enhancing effects of AVP on cognitive functioning in healthy young participants[25] and the elderly[26]. Another study showed that AVP administration increases the amplitude of several components of the late event-related brain potentials, which are thought to reflect higher order cognitive processing[27]. Furthermore, intranasal AVP delivery enhanced performance and associated event-related potentials in a simple reaction time task[25,28]. Results from studies that directly compared the effects of OXT and AVP suggest that the two might have opposite roles, with the former impairing memory and learning processes and the latter improving cognitive performance[29].

Social stress. Stressful social interactions normally trigger behavioural and physiological responses to adapt to these situations. Activation of the hypothalamus–pituitary–adrenal axis, with the secretion of corticotrophin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol, is a major endocrine component of this adaptive stress response. One study showed that healthy males who received social support and a single dose of OXT during preparation for the Trier Social Stress test (TSST)[30] showed the lowest cortisol response to the TSST, whereas subjects who received no social support

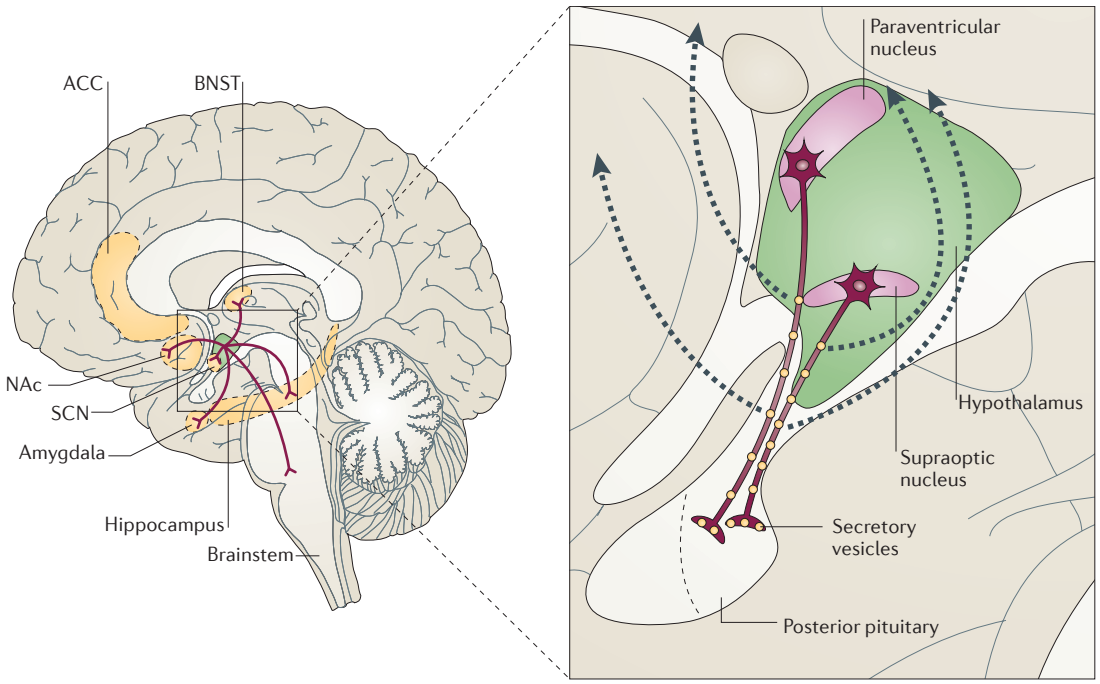

Figure 1 | **Neurophysiology of OXT and AVP.** Oxytocin (OXT) and arginine vasopressin (AVP) are synthesized in magnocellular neurons in the paraventricular and supraoptic nuclei of the hypothalamus, and are processed along the axonal projections to the posterior lobe of the pituitary, where they are stored in secretory vesicles and released into peripheral circulation (inset). In addition to this release from axonal terminals, there is dendritic release of OXT and AVP into the extracellular space, resulting not only in local action but also in diffusion through the brain to reach distant targets (shown by the dotted arrows)[186]. Furthermore, smaller parvocellular neurons in the paraventricular nucleus also produce OXT and AVP and project directly to other regions in the brain. As is the case for all eutherian mammals, humans have four receptors for OXT and AVP: OXT receptor, AVP receptor 1A (AVPR1A), AVPR1B and AVPR2. In the brain, OXT and AVP travel along the axonal projections from parvocellular neurons of the hypothalamus to different areas — including the amygdala, hippocampus, striatum, suprachiasmatic nucleus, bed nucleus of stria terminalis and brainstem — where they act as neuromodulators or neurotransmitters, and thereby influence neurotransmission in these areas. For example, OXT and AVP modulate neural populations in the central amygdala[43]. AVP also binds to AVPR1B in the anterior pituitary, fostering (together with corticotropin-releasing hormone (CRH)) the secretion of adrenocorticotropic hormone (ACTH) and hence, promoting the secretion of cortisol. Thus, both peptides have peripheral and central functions. However, the central and peripheral release are not necessarily associated and the distribution of OXT and AVP receptors in the human brain has not been fully explored so far. ACC, anterior cingulate cortex; BNST, bed nucleus of the stria terminalis; NAc, nucleus accumbens; SCN, suprachiasmatic nucleus.

and a placebo showed the highest response[31]. Notably, the group receiving social support and OXT also had lower levels of anxiety and higher ratings of calmness during the test. Another study showed that intranasal OXT increased positive communication behaviour in both men and women during a couple conflict, and reduced plasma cortisol levels during the conflict[32] — which is in line with animal studies indicating that central OXT facilitates pair bonding behaviour[33] . Likewise, breastfeeding women, in whom the endogenous secretion of OXT is increased, also showed attenuated cortisol responses to psychosocial stressors[34,35]. The stress buffering effect of OXT has been replicated in other recent studies[36,37]. Experiencing early parental separation stress has been shown to reduce the suppressing effect of OXT on cortisol levels, suggesting that the sensitivity of the central OXT system might be set in early life[38].

Although these findings suggest that OXT enhances the buffering effect of positive social interactions on stress responsiveness, the underlying biological mechanism remains to be investigated[39,40]. This could be of translational relevance as social stresses increase risk for many psychiatric disorders[41], whereas positive social interactions decrease it. Animal experiments have shown that, in contrast to the stress-reducing effects of OXT, AVP promotes the secretion of ACTH[42] and neural transmission in the amygdala[43], and thereby presumably increases the endocrine stress response in humans. Indeed, two studies showed that, compared to a placebo, intranasal administration of AVP resulted in a significant increase in salivary cortisol and heart rate in the TSST[44], specifically under conditions of socio-evaluative threat by others[45].

Emotion recognition and beyond. A number of recent studies have addressed the role of OXT in decoding subtle social signals such as facial expressions. One study used the Reading the Mind in the Eyes test, which has been developed to assess the social cognitive abilities of adults with ASD[46]. Here, participants were shown photos depicting the eye region and were asked to indicate what the person in the photo was thinking or feeling. Compared to a placebo, intranasal OXT administration in this test improved the performance of healthy men, particularly for difficult stimuli[47]. Other studies that investigated whether OXT selectively improves the recognition of specific emotions revealed mixed results. Some authors reported improved processing of positive facial expressions[48,49] and decreased aversion to angry faces[50], whereas others reported improved recognition only of fearful faces[51], increased recognition of sex- and relationship-related words[52], or no effect of OXT on emotion recognition in a visual search task[53]. A recent study showed enhanced emotion recognition for both happy and angry faces even at very short presentation durations of 17 to 83 ms, suggesting that OXT also promotes the early stages of visual processing of emotional stimuli[54]. OXT may also have a role in inter-individual differences in emotion recognition accuracy[55]. In a task that measured 'empathic accuracy' (based on correlations between participants' ratings of the affect that they perceived an individual in a film clip to have experienced and that individual's own ratings of the affect that they experienced), intranasal OXT administration improved empathic accuracy (compared to a placebo) only in participants with high levels of autistic traits, who presumably have low baseline empathic abilities.

In contrast to studies of emotion recognition, which is generally thought to represent the cognitive facet of empathy, studies into the effects of OXT on emotional empathy — that is, the vicarious feeling of an emotion — are rare[56,57]. Nevertheless, recent studies have reported positive effects of intranasal OXT administration on emotional empathy but not cognitive empathy[56], and positive effects on 'compassion-focused imagery'[58]. Likewise, a single intranasal administration of OXT increased the subjective experience of attachment security in males with an insecure attachment pattern[59]. As secure attachment in humans is associated with lower stress reactivity and a better ability to interact socially[60], understanding the role of OXT in attachment may have clinical implications for several mental and developmental disorders that are associated with stress and impaired social behaviour.

It is generally assumed that visual attention plays a crucial part in the recognition of facial emotions[61]. So far, four studies have examined the effects of OXT on visual attention to faces and, with one exception[62], have reported increased gazing time on the eye region (compared to other parts of the face) when observing neutral and emotional facial expressions[63–65]. Although the results suggest that improved facial emotion recognition after OXT treatment might be due in part to increased eye gaze, this hypothesis has not yet been explicitly tested.

Memory for social information. Early studies on the cognitive effects of OXT suggested an OXT-induced impairment of semantic memory[29]. More recently, it has been demonstrated that OXT can selectively modulate social memory. One study showed that intranasally administered OXT selectively reduced implicit memory of socially relevant words, but not neutral words, in males[66]. Another study showed that post learning intranasal OXT administration enhanced immediate (30-min) and delayed (24-h) recognition of face identities. Specifically, memory was improved for faces with angry or neutral expressions but not for faces with happy expressions[67], even though there was no effect of OXT on memory for associations between specific faces and specific facial expressions. However, it has also been shown that intranasal OXT given before learning enhances memory for happy faces, compared to angry and neutral faces[68]. Importantly, a recent study showed that intranasal OXT specifically improves recognition memory for faces but not for non-social stimuli[69]. Finally, intranasal OXT seems to modulate recollections of maternal care and closeness as a function of attachment security: after OXT, securely attached males remembered their mother as more caring and close, whereas in anxiously attached males OXT had the opposite effect[70].

With regard to AVP administration, a recent study showed that intranasal AVP given before encoding

Reading the Mind in the Eyes test
Participants are presented with 36 pictures of the eye region of faces and are asked to decide which of four words best describes what the person in the picture is thinking or feeling.

enhances the feeling of familiarity with images of positive and negative faces compared to neutral faces[71] and, in males, enhances the recognition of sexual cues in images[72]. Taken together, the evidence so far suggests that elevated levels of OXT and AVP during memory encoding of social stimuli promote the subsequent feeling of familiarity with these stimuli.

Social interaction. In the rodent literature, OXT emerges as a neuropeptide that promotes social approach behaviour and helps rodents to overcome any avoidance of proximity. Trusting other people could be considered an indicator of social approach in humans. In the first study that investigated the role of OXT in interpersonal trust[73], the authors assessed the participants' willingness to take social risks (in a trust game) compared to non-social risks (in a lottery game). Participants who received OXT showed higher levels of trust compared to the placebo group, a result that has been replicated in follow-up experiments[74,75]. Importantly, OXT did not increase the participants' willingness to take risks in general but only within social interactions. A subsequent study investigated whether OXT modulates trusting behaviour in response to a betrayal of trust[76]. After a number of initial trials of a trust game, the participants received information about the responses of a 'trustee' (which were disadvantageous to the participant) before they continued with the second half of trials. Participants in the placebo group adjusted their behaviour in the later phase, whereas participants who had received intranasal OXT continued to show trusting behaviour even though their trust had been betrayed.

The effect of OXT on cooperative behaviour seems to be critically dependent on the presence of prior social information, at least brief prior face-to-face contact[77], suggesting that the social context modulates the effect of OXT on social interaction. In addition, OXT increased the perceived trustworthiness and attractiveness of faces showing various expressions[78]. A set of studies support the hypothesis that OXT specifically promotes generosity[79] and in-group but not out-group trust and cooperation[80–82]; however, enhanced envy and gloating in a social game after OXT administration has also been reported[83]. Using an explicit social exclusion paradigm (a virtual ball-tossing game, 'cyberball'), another experiment showed that OXT increased the desire for future social interactions but did not buffer against social rejection in an explicitly aversive context[84]. In the context of parenting, OXT also positively affects the responsiveness of fathers towards their toddlers, and might thereby promote positive interactions[85]. However, OXT did not affect appetitive, consummatory and refractory sexual behaviour in men[86].

Notably, only a small number of experimental studies have investigated the effects of AVP on human social interactions. Recent findings in males suggest that intranasal AVP has similar effects to OXT on emotion recognition and memory encoding[71,72]. A study using electromyographic recordings showed enhanced subtle frowning (assessed by corrugator supercilii muscle activity) in response to neutral facial expressions after intranasal AVP treatment, suggesting an enhanced negative emotional response to ambiguous social cues[87]. Interestingly, there is evidence for sexually dismorphic effects of intranasal AVP on social perception: intranasal AVP decreased the perception of friendliness in males, but increased it in females[88].

In conclusion, it is difficult to draw a coherent picture of the social effects of OXT and AVP in humans, owing to the heterogeneous behavioural paradigms that have been used to investigate them. Nevertheless, results from the studies that have been performed so far are consistent with the view that OXT enhances the motivation to engage in social interactions, by improving decoding of emotional cues and promoting the willingness to take risks in terms of cooperative and trusting behaviours. Only a few studies have used social and non-social stimuli to assess the specificity of these effects, and they suggest that the effects are more pronounced for social stimuli[89,90]. With regard to the effects of AVP, the few published findings suggest that AVP might have opposite effects to OXT in the context of social stress and cognitive performance, at least in males. Nevertheless, given the convergent evidence for behavioural effects of OXT and — to a lesser extent — AVP, elucidation of the neurogenetic mechanisms supporting these effects are necessary for translating them for clinical use.

Human genetics of OXT and AVP

There is a high degree of preservation of the neuropeptide system across mammalian evolution and the heritability of social behaviour in humans[91,92], including autistic traits[93], is well known. Hence, variation in genes that encode neuropeptides may shed light on individual differences in social behaviour and heritable disorders, such as ASD, that are characterized by impaired social behaviour. Although studies into the effect of variation in the genes encoding OXT and AVP on social behaviour have been largely uninformative[94], a substantial body of evidence now implicates the genes that encode their receptors (FIG. 2). The oxytocin receptor (*OXTR*) gene is located on chromosome 3p25, spans 17 kb, contains four exons and three introns[95], and encodes a 389-amino-acid polypeptide with seven transmembrane domains belonging to the class I G protein-coupled receptor family[96]. The AVP receptor in the human brain that is the most strongly implicated in neuropsychiatric phenotypes is encoded by the gene AVP receptor 1A (*AVPR1A*), which is located on chromosome 12q and contains two exons that are separated by a 2.2-kb intron. The type 1B receptor, encoded by the gene *AVPR1B,* is also expressed in the brain and is involved in the stress response as it mediates the stimulatory effects of AVP on ACTH release[97]. Because a selective AVPR1B antagonist had anxiolytic- and antidepressant-like effects in rodents[98] and as some genetic associations with mood[99,100] and anxiety[101] disorders have been described, this receptor has translational interest. However, this translational potential is not yet supported by behavioural or neuroimaging studies in humans.

Linkage
A technique for identifying candidate chromosomal regions that underlie a particular trait based on the extent to which that trait is co-inherited with certain genetic markers.

Haplotype
A combination of alleles at different loci in the genome that tend to be inherited together because they show high linkage disequilibrium (often because they are physically close).

Reward dependence
A personality measure that quantifies sociability and the interest in, as well as reliance on, social approval.

Association with ASD. A role for OXT in genetic risk for ASD is supported by linkage data[102] and disease association with common variants in *OXTR*[94,103–107]. Two single nucleotide polymorphisms (SNPs) in the third intron of *OXTR* have emerged as particularly promising candidates in the recent ASD literature: rs53576 (G to A) and rs2254298 (G to A) (FIG. 2). In several studies, these polymorphisms were overtransmitted in families to offspring with ASD[105], and formed a central component in ASD-related haplotypes[105,106]. By genotyping all haplotype tagging SNPs (htSNPs) across the *OXTR* region[107], an association between SNPs (or haplotypes) and measures of social skills in individuals with ASD was observed. These association results are not wholly consistent[103]; however, understanding inter-individual variation in the OXT system is important considering the current interest in treating ASD with OXT[108–110]. It is unfortunate, therefore, that rs53576A is not present on many currently available chips that are used for genome-wide association studies of ASD.

Evidence for an involvement of the AVP system in ASD comes from genetics studies of polymorphic microsatellite repeats[111] in the 5′ flanking region of *AVPR1A* (FIG. 2). Of these, RS3, a complex repeat upstream of the transcription start site and with 16 different alleles in the population, and RS1, a repeat located 553 bp from the start site and with nine alleles, have alleles that have been differentially transmitted to individuals with ASD[112–114]. Specifically, overtransmission of the 334- and 340-bp alleles of RS3 (REF. 114) and undertransmission of the 312-bp allele of RS1 (REF. 113) have been found. Another study[112] found no association of specific *AVPR1A* alleles with ASD, but significant associations of haplotypes consisting of RS1, RS3 and an intronic microsatellite. These findings provide evidence for a contribution of genetic variation in *AVPR1A* to risk for ASD, and this evidence is further supported by linkage of markers in the 5′ region of the gene in ASD families[113] and the social dysfunction (reminiscent of ASD) found in *Avpr1a* knockout mice[115]. Interestingly, microsatellite repeats are also found upstream of *Avpr1a* in prairie voles, a commonly used animal model for affiliative social behaviour related to neuropeptide signalling. In these animals, some but not all[116] studies have found an association of these repeats with prosocial behaviours[117].

Further evidence for the important role of the OXT system in autism comes from recent work on CD38, a transmembrane protein that is involved in oxytocin secretion in the brain and strongly influences social behaviour[118]. Interestingly, several genetic variants on the CD38 gene were identified that show a significant association with high functioning autism[119]. Furthermore, individuals affected by autism also show a significant reduction of CD38 expression in lymphoblastoid cell lines[120]. These findings already represent a translational success in that they have initiated the search for a treatment aimed at increasing OXT secretion by influencing CD38 expression using all-trans retinoic acid, a known inducer of CD38 expression[121,122].

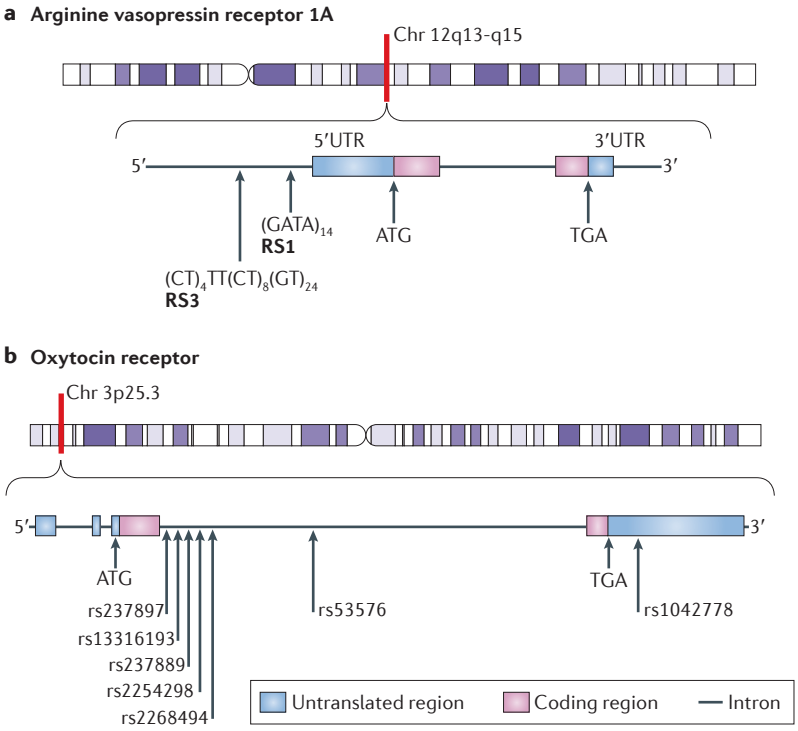

Figure 2 | **Genetic risk variants in the gene for vasopressin receptor 1A and the oxytocin receptor. a** | Arginine vasopressin receptor 1A (AVPR1A) is the main vasopressin receptor in the brain. It is encoded by *AVPR1A*. Three polymorphic microsatellite repeats[111] (RS1, RS2 and RS3) in the 5′ flanking region of *AVPR1A* have been found. Of these, RS1 and RS3 are of relevance for genetic association studies. RS1 is a repeat located 553 bp from the start site, in which nine alleles have been identified in humans. RS3 is a complex repeat upstream of the transcription start site and has at least 16 different alleles in the population. **b** | For the oxytocin receptor, the main genetic variants that are implicated are single nucleotide polymorphisms (SNPs; shown with their location and rs number). Exons are shown by the pink boxes, and the untranslated regions near the genes are shown by the blue boxes. Variants in the gene are shown by arrows. Chr, chromosome.

Association with general social phenotypes. Studies have provided evidence that *OXTR* rs53576A is associated with deficits in sociobehavioural domains such as a mother's sensitivity to her children's behaviour[123], empathy[124], reward dependence[125] and positive affect (found only in males[126]). Likewise, rs2254298A has been associated with emotional deficits[126] — although less consistently so[107] — and with altered performance on the social value orientation task, an economic exchange game in which a participant's behaviour differs depending on his or her concern for the well-being of others, or his or her concern for equality[127]. A recent study revealed a gene–environment association for this SNP; girls who are heterozygous for the rs2254298 polymorphism and who have a history of adversity early in life (in this case, a mother with a history of depression) had the highest levels of depression and anxiety[128]. Associations were also found between a microsatellite marker near the *OXTR* gene and a tendency to parent children at an earlier age in females[129]. An effect of SNPs in *OXTR*, most notably rs1042778, on prosocial behaviour in an economic exchange game[127] was not replicated in a subsequent study[130].

In terms of AVP, the amount of money given to the opposing player in the Dictator Game was related to the

length of the *AVPR1A* RS3 promoter repeat[131]. *AVPR1A* haplotypes also differed between dancers and athletes[132], and were associated with musical ability[133], suggesting a role of this gene in modulating musical expression, which is considered to be a component of human social behaviour. Furthermore, associations between the *AVPR1A* RS3 repeat polymorphism and pair bonding behaviour (specifically, fidelity) in men[134] and age of first sexual intercourse in men and women[129] have been observed. Interestingly, in females the age of first intercourse was associated with the *AVPR1A* RS1 polymorphism[129]. The personality measures 'novelty seeking' and 'harm avoidance' — which contribute to impulsivity and anxiety during social interactions, respectively — were also associated with the RS1 genotype[135].

Impact of genetic variation on intermediate phenotypes. Understanding the neurobiology that underlies these complex — and often not fully consistent — associations is a major research goal. This begins on the cellular level: the most strongly implicated polymorphisms in *OXTR* and *AVPR1A* do not change the amino acid sequence of the encoded protein, and thus must exert their effects in ways that are discussed below or through a coding variation in linkage disequilibrium. Whereas no evidence exists for this possible coding variation, the length of *AVPR1A* RS3 has been associated with hippocampal *AVPR1A* mRNA levels in humans[131], indicating a possible role for this polymorphism in modulating gene transcription. Further work is necessary to determine a possible functional role for the other polymorphisms in *AVPR1A* as well as for the common variants in *OXTR*.

On the neural systems level, imaging genetics is a method by which common genetic variants can be related to brain structure and function (FIG. 3). So-called intermediate phenotypes highlight systems that mediate the effect of the genetic variants under study, providing a bridge between genotype and behaviour. This approach has revealed that in healthy subjects, RS1 and RS3 *AVPR1A* polymorphic microsatellite repeats that are linked to ASD were associated with differential activation of the amygdala[135] (FIG. 3c), a key neural structure in the circuit that regulates fear responses[136] and social information processing[137]. The direction of the association differed between RS1 and RS3, perhaps paralleling the hyper-[138,139] and hypoactivation[140,141] of the amygdala during face processing in individuals with ASD. Furthermore, this study[135] found evidence that the long and short forms of the RS1 and RS3 microsatellite repeats had different impacts on amygdala activity, reminiscent of findings in voles[117]. A possible electrophysiological correlate is the finding that longer *AVPR1A* RS3 alleles were associated, particularly in males, with greater levels of prepulse inhibition of the startle response[142], a neural response that is important for the filtering of affective and social stimuli that are processed through limbic system structures, including the amygdala. The effect of these genetic variants on brain structure has not been investigated.

Regarding *OXTR*, a recent study found that the rs53576 genotype was associated with morphometric alterations of the hypothalamus and amygdala[125] (FIG. 3b). The risk allele-load dependent decrease in hypothalamic volume predicted reduced reward dependence in males. Moreover, the correlation between grey matter volume of the hypothalamus and that of the dorsal cingulate gyrus and amygdala was greater in *OXTR* risk allele carriers. In two other studies, the rs2254298A *OXTR* risk alleles were associated with larger amygdala volume[143,144], and allelic variation in *OXTR* also influenced amygdala activity[125], indicating a convergent impact of *OXTR* polymorphisms on this key limbic structure. As in the case of *AVPR1A*[135], the directionality in neuropeptide-related genetic associations differed between the variants examined[125,135].

One study[125] showed evidence of sexual dimorphism for the effect of *OXTR* (but not for *AVPR1A*[135]) polymorphisms: first, the *OXTR*-related decrease in hypothalamus volume was, for the most part, driven by male risk allele carriers[125]; second, there was a gene-by-sex interaction effect on grey matter volume in the right amygdala — male carriers of rs53576A had an increased amygdala volume that was consistent with the presumed dose of *OXTR* risk alleles[125]; and third, a cross correlation[125] of grey matter volume and personality measures revealed that lower hypothalamus volume predicted lower sociability in male, but not female, subjects.

Taken together, these studies suggest that a limbic circuit involving the amygdala, the cingulate gyrus and the hypothalamus is affected by genetic variation in neuropeptide receptors, at least in humans. As the involvement of these brain areas has emerged from imaging genetics evidence, we can invoke previous evidence of their functional interactions and their involvement in both normal behaviour and psychiatric conditions to understand how genetic variation influences psychiatric phenotypes in humans. Prior evidence implicates this circuitry in social behaviour[2,135,137] (FIG. 3a) and in the pathophysiology of ASD[138–141] and of psychiatric disorders that are characterized by impaired social functioning. Thus, results from imaging genetics studies support a model in which *OXTR* and *AVPR1A* variants mediate their associated increased disease risk by modulating circuits for processing of social information and negative affect[145].

Interactions with other neurotransmitter systems. A large body of work suggests that there are functional interactions between OXT and AVP and other hormonal and neurotransmitter signalling systems, including gonadal hormone, dopamine and serotonin systems. For example, in animals, the expression of *OXTR* in the limbic system is sensitive to the level of gonadal steroids[146]. Oestrogens upregulate *OXTR* expression[147], stimulate OXT release from hypothalamic neurons[148] and increase OXT receptor binding in the amygdala[149]. In addition, the effects of OXT on processing of affect and anxiety are mediated through serotonergic neurons[150]. In addition, hypothalamic OXT cells express dopamine receptors[151], and dopaminergic and OXT pathways converge in the medial prefrontal cortex[152] and the ventral striatum — which regulate social behaviours, including

Dictator Game
An economic exchange game in which a player (the 'dictator') splits up an asset, such as money, between him- or herself and another player. The amount of money or asset given to the other player is a measure of altruism.

Linkage disequilibrium
The non-random association (that is, correlation) of alleles at two or more loci, so that certain combinations of alleles occur together more frequently than would be expected by chance. This means that a true causative locus might in fact be one that is in linkage disequilibrium with the one that is under investigation in a genetic association study.

Prepulse inhibition of the startle response
Electrophysiological paradigm in which a relatively weak sensory event (the prepulse) is presented 30–500 ms before a strong stimulus, which induces startle. The reduction of the magnitude of the startle response following the prepulse is measured.

pair bonding — and this interaction may be crucial for the reinforcing and/or rewarding properties of these behaviours, although this has not been specifically investigated.

Formal genetics studies can search for interactions between variants in candidate genes in the various neurotransmitter and neuropeptide systems in association with relevant phenotypes. A widely studied variant near the promoter region of solute carrier family 6 member 4 (*SLC6A4*), the gene that encodes the serotonin transporter, showed such an interaction[123]. After controlling for differences in maternal education, depression and marital discord, this study found that parents with both the low activity variant of *SLC6A4* (5-HTTLPR) and an *OXTR* SNP (rs53576) were less sensitive to their children's needs and less effective in helping them when needed. Furthermore, an interaction between a variant of *SLC6A4* and *OXTR* rs2268498 was associated with negative emotionality, a personality measure related to fear and sadness[153]. Associations between *AVPR1A* polymorphisms and musical ability were also conditional on the *SLC6A4* genotype[132].

These associations are especially interesting because imaging genetics studies have shown an effect of *SLC6A4* genotype on amygdala activation[154] and structure, and on the interaction (measured using functional and structural connectivity) between the amygdala and a region of the cingulate cortex[145] (FIG. 3d). Moreover, this amygdala–cingulate circuit is modulated by acute treatment with serotonergic drugs. Of note, this amygdala–cingulate circuit may mediate the increased risk of depression[145] (FIG. 1) and violence[155] (FIG. 3e) resulting from (gene–environment) interactions between serotonin system-related genes and early life adversity. Behaviourally, such gene–environment interactions have now been observed for *OXTR* variation as well[128]. Recently, early-life exposure to environmental risk factors with a social component, urban upbringing, was found to impact the same circuit during evaluative social stress[156]. Thus, the amygdala–cingulate circuit is modulated by variations in, and manipulations of, both the serotonin system and the OXT system, and may therefore be an area in which the actions of the two social behaviour systems converge.

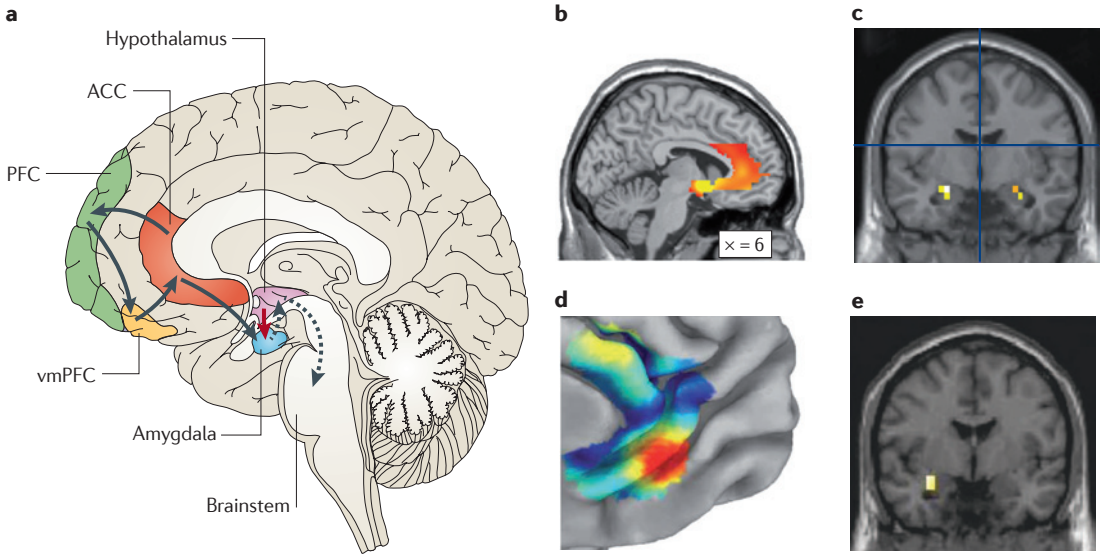

Figure 3 | **A proposed regulatory circuit of social–emotional information processing in humans.** The proposed circuit includes areas in which effects of oxytocin (OXT) and arginine vasopressin (AVP) system-related gene variants (which affect social behaviours and are associated with increased risk for autism spectrum disorder (ASD)) and serotonin system-related gene variants (which are associated with risk for depression) converge. **a** | Top-down control of the amygdala (shown by black arrows) arises from the anterior cingulate cortex (ACC) and ventral medial prefrontal cortex (vmPFC), with the latter being particularly important for the regulation of moral behaviours. 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** | MRI studies have shown volume reduction in the hypothalamus and ACC in carriers of the oxytocin receptor (*OXTR*) allele rs53576A, which is associated with increased risk for ASD[125] (bright colours indicate stronger reduction). **c** | Functional MRI studies have shown that RS3 *AVPR1A* risk variants are associated with increased amygdala activation during an emotional face matching paradigm[135]. **d** | MRI studies have shown structural reduction in the ACC in carriers of the risk allele for solute carrier family 6 member 4 (*SLC6A4*), 5-HTTLPR[145] (red indicates stronger reduction). **e** | Carriers of the monoamine oxidase type A (MAOA) variable number of tandem repeat (vNTR) risk allele (which is associated with increased impulsivity and violence) show increased amygdala activation during an emotional face matching paradigm[155]. ×, *x* coordinate. Part **a** is modified, with permission, from REF. 187 © (2010) National Academy of Sciences. Part **b** is reproduced, with permission, from REF. 125 © (2010) National Academy of Sciences. Part **d** is reproduced, with permission, from REF. 145 © (2005) Macmillan Publishers Ltd. All rights reserved. Part **e** is reproduced, with permission, from REF. 155 © (2006) National Academy of Sciences.

Evaluative social stress
A form of social stress that is induced by one's performance being observed and criticized by others.

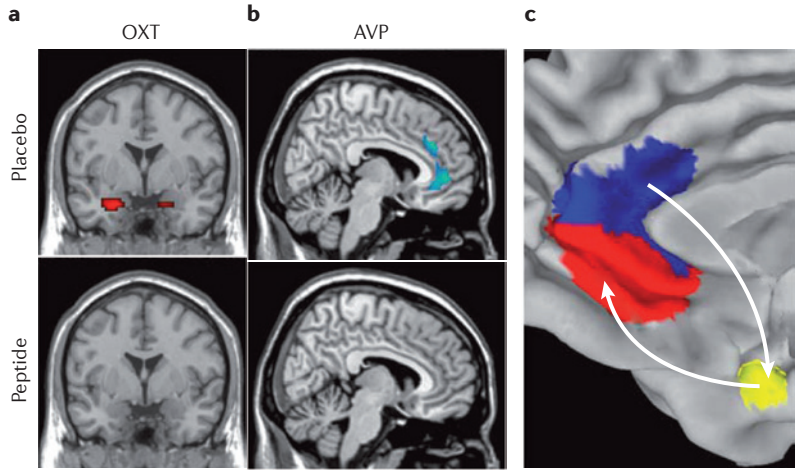

Figure 4 | **Intranasal OXT and AVP administration influences the amygdala–cingulate circuit. a** | Compared to a placebo condition (top panel), in healthy male subjects an acute intranasal challenge with oxytocin (OXT)[158] (bottom panel) modulates the activity in components of the amygdala–cingulate circuit for the regulation of negative affect[145] during the processing of unpleasant faces and scenes. Fear-inducing visual stimuli activated the amygdala in the placebo condition (shown in red) but not after OXT administration. **b** | By contrast, activity in the subgenual and supragenual cingulate cortex (shown in blue) was reduced during a face-matching task in the placebo condition (top panel) but not after intranasal arginine vasopressin (AVP)[167] administration (bottom panel). **c** | A schematic of the amygdala–cingulate circuit, showing areas of the cingulate that exhibited negative functional connectivity (the perigenual cingulate, shown in blue) and positive functional connectivity (the subgenual cingulate, shown in red) with the amygdala (shown in yellow)[145]. Part **a** is reproduced, with permission, from REF. 158 © (2005) Society for Neuroscience. Part **b** is reproduced, with permission, from REF. 167 © (2010) Society for Neuroscience.

The hypothalamus seems to be an area where genetic effects (on *OXTR*) and gonadal steroids converge. It would be of great interest to see if dopaminergic core circuits in ventral and dorsal striatum, midbrain and prefrontal cortex also show such convergence, as animal studies suggest[157]. Even now, the remarkable convergence of formal genetic and neural systems-level data further strengthens the role of a cingulate–hypothalamic–amygdala circuitry as a key target for translational efforts directed at neuropeptide-associated disorders. For translational success, it must be shown that the circuit that is implicated by imaging genetics is also affected by acute neuropeptide administration. As the following section shows, this is largely borne out by the available data.

Neuroimaging studies

Initial neuroimaging work focused on the effect of OXT administration on the amygdala, on the basis of findings from animal neurochemistry[43] and human behavioural studies[31,73]. The first brain imaging study[158] used an implicit emotion recognition task requiring visual processing of threatening stimuli of different social valence (faces and scenes) that had been shown to reliably engage the amygdala[159]. Intranasally administered OXT had no effect on task performance, anxiety ratings or arousal, but it reduced the strong, right-lateralized activation of the amygdala to both classes of stimuli (FIG. 4). Furthermore, OXT reduced the functional coupling between the amygdala and brain stem regions that mediate autonomic and behavioural aspects of fear. The results of this study provided initial evidence that the prosocial effect of OXT might be secondary to an anxiolytic effect that involves modulation of amygdala responsivity. Additional brain imaging studies using different stimuli and experimental approaches replicated the dampening effect of OXT on amygdala activity in males[57,76,160,161]. A study employing a passive viewing paradigm using pictures of emotional facial expressions also showed that intranasal OXT attenuated the reactivity of the right amygdala to pictures of angry and fearful faces, but also to happy ones[160]. Again, no effect on the behavioural level was observed. This result demonstrates that the prosocial effect of OXT seems not to be restricted to threatening situations but might occur through a reduction of the uncertainty about the predictive value of any kind of socially relevant stimulus. This assumption is additionally supported by results from a subsequent fear conditioning study in which neutral face stimuli were associated to an aversive experience (electric shock)[161]. Here, the authors applied OXT to healthy males after the conditioning procedure. OXT administration resulted in a lower difference in valence ratings between faces paired with an electric shock during conditioning and the same faces presented alone after conditioning. Importantly, this modulation of valence ratings was not accompanied by general changes in valence ratings, demonstrating the specificity of the effect of OXT. Administration of the neuropeptide also reduced activation of the right amygdala and right fusiform face area in response to face pictures paired with a shock. However, this dampening effect was only present for faces showing direct gaze[161], supporting the idea that OXT influences brain activity specifically in response to socially significant stimuli.

These initial brain imaging studies seemed to provide concurrent evidence for the amygdala as one of the core points of OXT action in the human brain. However, a crucial issue is that these studies all used face stimuli to probe amygdala responses. Although the first study also found an effect for emotional scenes (such as depictions of accidents and disasters)[158], it could not be ruled out that the OXT effect on the amygdala is restricted to a very specific type of visual stimuli. Subsequently, Singer and colleagues[57] found that intranasal OXT administration reduced the amygdala response to images of people receiving a painful stimulus in male participants, providing initial evidence that the OXT effect on the amygdala may extend to a broader range of visual stimuli. However, this effect was mainly driven by a small number of participants exhibiting selfish traits, making it difficult to interpret the results in the context of prosocial behaviour.

Clearer support for the idea of a more general, rather than face-specific, prosocial effect of OXT mediated by attenuated amygdala activation comes from a study using an economic trust game[76]. Here, participants who received a placebo showed a decrease in trust after experiencing breach of trust, and intranasal OXT administration increased tolerance for this betrayal. On

the neural level, the reduction in trust was accompanied by increased amygdala activation, but this did not occur after OXT administration. Interestingly, OXT administration not only modulated activity in areas that mediate emotional processing (the amygdala and midbrain) but also in the caudate[76], a region that has been linked to reward processing and behavioural adaptation[162]. This result could be the first brain imaging indicator of interactions of the OXT system with other neurotransmitter systems, in this case the dopaminergic system. Such an interaction has been repeatedly demonstrated in animal studies[163]. Converging evidence for the modulating effect of OXT on amygdala reactivity points to a potential role of intranasal administration of this peptide in the treatment of amygdala-related psychiatric disorders, as discussed below.

Although recent studies support the general hypothesis that the amygdala is the main target region of OXT, it also indicates that a simple model cannot explain the complex mechanisms that underlie the prosocial effect of OXT. This was shown recently by an elegant study using high-resolution functional MRI of different amygdala subregions[65]. The authors pointed to the contradictory fact that OXT administration increases the number of times that a participant looks at the eye region on images of human faces[64], a behaviour that is associated with increased amygdala activation[164]. The authors proposed that different amygdala subregions might be differentially influenced by OXT depending on the stimulus context[65]. Participants who received intranasal OXT showed an increased probability of fixating the eye region even if they had been instructed to fixate the mouth. This behaviour was accompanied by increased activation of right posterior amygdala, also known as the basal nucleus of the amygdala[65]. Furthermore, activation of the superior colliculi — which are known to be involved in the initiation of saccades and attentional shifts[165] — increased. The authors[65] also found an interaction between the emotional content of the depicted faces and the effect of OXT administration on an anatomically distinct subregion of the left amygdala, with an OXT-induced attenuation of activation in this subregion to fearful faces and an increase in activation to happy faces, thus contradicting the general 'amygdala attenuation' effect described previously.

Taken together, accumulating evidence from recent brain imaging studies shows that the prosocial effect of OXT administration on brain systems, particularly on the amygdala, is more complex than initial studies suggested. Besides subregional processing in the amygdala, other subcortical targets, especially the midbrain and striatum, have been implicated.

Notably, all of the studies that we have referred to so far have investigated male subjects only. A recent brain imaging study focused on the effect of intranasal OXT application on brain activation in females[62]. Controlling for potential confounding factors such as the menstrual cycle, hormonal contraception or gaze fixation pattern, the authors found a specific increase of left amygdala activation in response to fearful images after administration of OXT, as well as in the fusiform gyrus, the medial temporal lobe, the inferior frontal lobe and the superior temporal gyrus, implicating increased activation of a network that overlaps with the brain network involved in social cognition[166]. This suggests a sexual dimorphism that might reflect an interaction between the effects of steroid hormones and the effects of OXT, although the present data are not sufficient for conclusive interpretations. As in other areas of neuropeptide research, there is a great need for studies on gender differences in neuropeptide actions. An elegant way to investigate the interaction of gonadal steroids and the OXT system on brain activation would be to pharmacologically manipulate specific sex steroid levels and/or to include postmenopausal women and women in different phases of their menstrual cycle.

In contrast to OXT, imaging studies using AVP challenges are rare so far. Only two studies have investigated the influence of AVP administration on brain activity[167,168]. In both studies, healthy male individuals received AVP or a placebo intranasally before being scanned. In the first study[167], subjects performed an emotional face-matching task. Although AVP treatment had no detectable effects on amygdala activity, it abolished the typical deactivation of the subgenual cingulate cortex, a region that is known to be involved in the modulation of amygdala activation (FIG. 4). Furthermore, structural equation modelling revealed an influence of AVP on the effective connectivity between the subgenual and supragenual cingulate and the amygdala, further emphasizing the effect of AVP on the circuitry that modulates emotion processing (see FIG. 4 for a more detailed description of these circuitries). In the second study[168], AVP induced a regionally specific alteration in the left temporoparietal junction — a key node of the theory of mind network — during an implicit social recognition matching task in which either familiar or unfamiliar faces and scenes were shown. Jointly, these two studies identify a predominantly cortical effect of AVP application in humans, with effects on a key region for social cognition in humans and a key regulatory region of the limbic system, whereas the effect of OXT might be focused mainly on the amygdala.

Taken together, most brain imaging studies support the view that the effects of OXT and, with less evidence, AVP on social processing are mediated by limbic circuitry with the amygdala as a core structure. In addition, imaging genetics studies have shown a preferential impact of the neuropeptide system on cingulate and hypothalamus activity, whereas the striatum and parts of the so-called 'social brain', such as the amygdala, seem to be reactive to acute OXT administration, in a network also implicated by imaging genetics (FIG. 4). It is also noteworthy that gene–sex interactions seem to be present both in imaging genetics and pharmacological fMRI studies. If replicated, these results would support a model in which genetic effects (on neuropeptide receptors) and acute effects (on neuropeptide levels) impact regulatory circuits for social and emotion processing at different time courses while converging on the amygdala. Notably, the brain imaging research that is summarized above is restricted by the selective usage

Emotional face-matching task
An experimental paradigm that is used to evoke emotional responses implicitly by presenting the participants with a task in which they have to match one of two emotional faces to a target face.

Social recognition matching task
An experimental paradigm that is used to evoke social information processing implicitly by presenting the participants with a task in which they have to match one of two socially relevant pictures (faces or scenes) to a target picture.

of task paradigms. Because a potential modulation of brain systems can only be observed in structures that are functionally involved in the tasks, it cannot be ruled out that OXT and AVP influence a number of other brain regions. Thus, future studies should explicitly investigate the effects of neuropeptides on functional connectivity of other potential candidate areas. In addition, more sophisticated experimental paradigms that probe different aspects of social cognitions should be used in future studies. Lastly, more knowledge about the distribution of OXT and AVP receptors in the human brain using positron emission tomography would be helpful to guide imaging studies.

Treatment implications for OXT and AVP

Taking into consideration the effects of OXT and AVP on social behaviour and the association of genetic variants in the OXT and AVP systems in mental disorders that are characterized by severe social deficits, an obvious next step is to consider the possible therapeutic value of neuropeptides in such disorders. To evaluate such a therapeutic value, challenge studies that systematically manipulate the CNS availability of OXT and AVP are indispensable. As only a small fraction of the neuropeptide passes the blood–brain barrier after intravenous administration[169], and intravenous infusion could potentially have side effects due to effects on hormone systems — for example, uterus contraction in females — a potential clinical use of neuropeptides requires a more direct pathway to the human brain, namely through intranasal administration[10].

Few clinical studies into intranasal AVP administration have been conducted, but selective V1a and V1b receptor antagonists, which have been used in animal studies[170,171], might be promising targets for human neuropsychopharmacology. AVP antagonists have been considered for the treatment of major depression[172] and may also be helpful in the treatment of stress-related disorders and disorders that are characterized by interpersonal violence, such as antisocial personality disorder[173].

Although there are currently no systematic, randomized control trials on the therapeutic effects of intranasal OXT treatment, preclinical studies in patients with different mental disorders have shown promising results from a single dose of intranasal OXT. Below, we provide a synthesis of recent advances that have been made in the effort to use OXT and AVP in the treatment of psychopathological states. For an overview of studies on endogenous levels of OXT and AVP in different disorders, see a recent review[10].

ASD. ASD is a prototypical disorder of social dysfunction. It is a neurodevelopmental disorder that is characterized by alterations in three core symptom domains: speech and communication deficits, repetitive or compulsive behaviours with restricted interests, and social impairment. In one study[110] OXT nasal spray or a placebo was administered to male youths aged 12 to 19 who have ASD. OXT administration improved performance on the Reading the Mind in the Eyes task[46] in all participants, suggesting that early treatment with intranasal OXT might improve social functioning in young individuals with ASD. Another study[63] in individuals with ASD showed that intranasal OXT increased social interactions and feelings of trust in a simulated ball game that involved interactions with fictitious partners. OXT administration also increased patients' gazing time on the eye region of pictures of faces. Although only a small fraction of intravenously administered OXT infusion is expected to pass the blood–brain barrier, peripheral infusion has also been shown to induce subtle behavioural effects, including enhanced emotional understanding of speech intonation and decreased repetitive behaviours in individuals with ASD[174]. Together, these studies indicate that intranasal OXT administration improves emotion recognition, responsiveness to others and social behaviour, suggesting a therapeutic potential of OXT through its effects on core dimensions of ASD.

Social anxiety disorder. Social anxiety disorder (SAD) is characterized by clinically significant anxious reactions and extreme discomfort in anticipation of — or following — exposure to social settings, including performance and test situations. SAD ranks as the third most common mental health disorder after depression and alcoholism[175], and as such has major public health implications. In one study, OXT was administered intranasally to patients with SAD, in combination with five weekly sessions of brief exposure therapy[176]. OXT administration improved speech performance as exposure sessions progressed. However, presumably owing to the low frequency of sessions, these effects did not generalize to other treatment outcomes. Another study[177] examined the effects of intranasal OXT on amygdala activity in patients with generalized SAD and control subjects during performance of an emotional face matching task that involved pictures of fearful, angry and happy faces. Both groups activated bilateral amygdala to all emotional faces after placebo treatment, but patients with SAD showed hyperactivity to fearful faces in bilateral amygdala compared with the control group. OXT administration had no effect on amygdala activity in response to emotional faces in the control group, but attenuated the heightened amygdala reactivity to fearful faces in the SAD group[177]. These findings suggest that OXT has a specific effect on fear-related amygdala activity, particularly when the amygdala is hyperactive.

Borderline personality disorder. Borderline personality disorder (BPD) is characterized by affective instability, impulsivity, identity diffusion and interpersonal dysfunction. Perceived rejection and loss often serve as triggers to impulsive, suicidal and self-injurious behaviour, affective reactivity and angry outbursts, suggesting that the attachment and affiliative system may be implicated in this disorder[178].

Despite the potential promise of psychopharmacological treatment options using OXT, there has been surprisingly little investigation in this area. One recent pilot study showed a stress buffering effect of OXT in

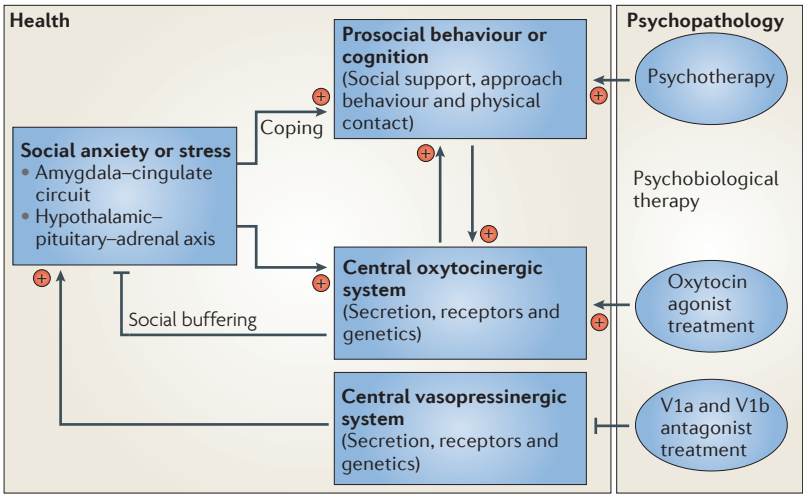

Figure 5 | **An integrative translational model of the interactions of OXT, AVP, social approach behaviour and social stress.** Social stress and social anxiety stimulate the amygdala–cingulate circuit and the hypothalamus–pituitary–adrenal (HPA) axis, which is enhanced by arginine vasopressin (AVP). In healthy individuals, stress and anxiety encourages social approach behaviour as a coping strategy. It also stimulates oxytocin (OXT) release, which also promotes social approach behaviour. In addition, positive social interaction (for example, physical contact) is itself associated with OXT release, which in turn further promotes social approach behaviour. OXT reduces amygdala and HPA axis reactivity to social stressors (shown by the inhibitory arrow) and as such it is an important mediator of the anxiolytic and stress-protective effects of positive social interaction ('social buffering'). Patients with mental and developmental disorders that are associated with severe deficits in social interactions (for example, autism, social anxiety disorder and borderline personality disorder) may benefit from novel 'psychobiological therapy' approaches in which psychotherapy is combined with administration of OXT (or OXT receptor agonists). Selective V1a and V1b receptor antagonists might be a promising target for reducing the anxiogenic and aggression-related role of AVP (shown by the inhibitory arrow). Figure is modified, with permission, from REF. 20 © (2008) Elsevier.

BPD patients undergoing the TSST[179]. Although intranasal OXT decreased cooperative responses in a social dilemma game in a recent experimental study with a modest sample size of 14 adult patients (four of whom were males) with BPD[180], several clinical trials using adequate sample sizes are currently being carried out to investigate the therapeutic value of OXT in BPD (see the ClinicalTrials website).

Schizophrenia. Animal models of schizophrenia showed that increasing endogenous OXT levels or systematic OXT administration seems to have antipsychotic-like effects, such as reversed prepulse inhibition deficits induced by amphetamine or the phencyclidine analogue MK 801 (REF. 181). In addition, schizophrenia patients have been found to have altered plasma OXT levels[1]. In one study[182], schizophrenia patients received 3 weeks of daily intranasal OXT (40 IU twice a day) and a placebo adjunctive to antipsychotics. OXT reduced positive and negative symptoms of schizophrenia compared with the placebo. Another recent study explored whether 10 or 20 IU of intranasal OXT reverses the impaired discrimination of facial affect in schizophrenia patients[183]. Emotion recognition fell in patients with schizophrenia following 10 IU of OXT owing to an increased propensity to identify all emotions regardless of whether they were displayed. By contrast, emotion recognition improved following 20 IU of OXT in polydipsic relative to non-polydipsic patients.

Future directions

As intranasal OXT administration in social interaction experiments reduces behavioural and endocrine responses to social stress[31], mediates stress-protective effects of social support ('social buffering')[31], attenuates amygdala reactivity to social stimuli[65,76,158,160] and improves social cognition, emotion recognition, secure attachment and empathy[32,47,59,64,66,69] in humans, a pharmacological intervention in the OXT system might be a target for novel therapeutic approaches (FIG. 5). Specifically, a combination of OXT administration (including selective and longer acting OXTR agonists such as carbetocin) with interaction-based psychotherapy might provide new avenues for a better treatment of mental disorders that are characterized by early attachment disruption or social interaction pathology — for example, social anxiety disorder, ASD, borderline personality disorder and schizophrenia[1]. It is important to note that these social disorders are exceptionally difficult to treat or cannot be effectively treated at all (for example, ASD).

The initial results of experimental neuropeptide administration in patients are promising, and several clinical trials are being carried out (see the ClinicalTrials website), aimed at developing and evaluating new clinically relevant approaches for using neuropeptide administration. In particular, intranasal OXT treatment is expected to improve the readiness to interact socially (for example, in cognitive behavioural group therapy) and to facilitate more active and successful engagement in confronting feared social situations outside of therapy sessions. FIGURE 5 shows an integrative model of the interactions between social anxiety and stress, social approach behaviour and the central OXT and AVP systems in humans. In this model, the key route to translational success involves a systematic inquiry into 'propsychotherapeutic' neuropharmacology, which is designed to support and enhance psychotherapeutic interventions rather than provide an alternative or additional route to a cure. We therefore propose the term 'psychobiological therapy' for this new approach (FIG. 5).

The model indicates areas in which further research is needed to clarify optimal strategies to manipulate neuropeptide availability or to use neuropeptide levels as potential markers of beneficial treatment effects. In particular, more research is required into the mechanism by which OXT and AVP (and receptor agonists and antagonists) penetrate the brain following different methods of administration. Given the unclear pharmacodynamics of intranasal administration, a focus on the development on non-peptidergic drugs[173] acting on these receptors will be an important goal. Furthermore, the relationship between peripheral and central OXT and AVP (including the crosstalk between the neuropeptides at their receptors in the CNS) warrants

further investigation. In addition to *in vitro* studies on OXT and AVP binding sites in the human brain[184] and recent fMRI studies that have identified areas of neural activity induced by OXT and AVP[20,185], the development of specific radioactive labelling of neuropeptides in positron emission tomography may provide a better understanding of the location of OXT and AVP receptors in the human brain — particularly the brain circuits that are related to the processing of social information. As the neuroanatomical distribution and sensitivity of OXT and AVP 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 behavioural and brain responses to OXT administration will be crucial for decoding the neurobiology of the social brain and to tailor new treatment strategies.

In the past decade, one of the most exciting areas on the frontier of social neuroscience has been the opportunity to bridge the insights that are emerging from studies of prosocial behaviour in animals to preclinical human research using brain imaging, behavioural genetics and social interaction experiments. The perspective for the next decade is to further span this translational bridge from human neurobiology — based on mechanistic animal models — to potential treatment developments. Although this research period has just begun, the tremendous growth in this research field offers a promising new path for exploring the neuroendocrinology of the social brain.

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Competing interests statement
The authors declare no competing financial interests.

FURTHER INFORMATION

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