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A Precision Medicine Approach to Oxytocin Trials

Elissar Andari,

Division of Behavioral Neuroscience and Psychiatric Disorders, Yerkes National Primate Research Center, Center for Translational Social Neuroscience, Emory University, Atlanta, GA, USA

Rene Hurlemann, and

Department of Psychiatry, Medical Psychology Division, NEMO (Neuromodulation of Emotion) Research Group, University of Bonn, Bonn, Germany

Larry J. Young

Department of Psychiatry, Center for Translational Social Neuroscience, Division of Behavioral Neuroscience and Psychiatric Disorders, Yerkes National Primate Research Center, Emory University, Atlanta, GA, USA

Abstract

In this chapter, we introduce a new area of social pharmacology that encompasses the study of the role of neuromodulators in modulating a wide range of social behaviors and brain function, with the interplay of genetic and epigenetic factors. There are increasing evidences for the role of the neuropeptide oxytocin in modulating a wide range of social behaviors, in reducing anxiety, and in impacting the social brain network. Oxytocin also promotes social functions in patients with neuropsychiatric disorders, such as autism and reduces anxiety and fear in anxiety disorders. In this chapter, we will emphasize the importance of integrating basic research and clinical human research in determining optimal strategies for drug discoveries for social dysfunctions and anxiety disorders. We will highlight the significance of adopting a precision medicine approach to optimize targeted treatments with oxytocin in neuropsychiatry. Oxytocin effects on social behavior and brain function can vary from one individual to another based on external factors, such as heterogeneity in autism phenotype, childhood experiences, personality, attachment style, and oxytocin receptor polymorphisms. Hence, targeted therapies for subgroups of patients can help alleviating some of the core symptoms and lead to a better future for these patients and their families.

Keywords

Anxiety disorders; Autism; Oxytocin; Precision medicine; Social salience network; Targeted therapies

Correspondence to: Elissar Andari.

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1 A New Area of “Social Pharmacology”

Ten thousand years ago, humans were predominately hunter-gatherers relying on natural resources in order to survive. Today, we use highly sophisticated technology to generate more optimal resources to support our longer life span and advanced population of 7.125 billion people. Humans evolved by living in groups, sharing and producing food items, discovering upgraded communication tools (Egyptian papyrus, Phoenician alphabet, printing press, radio, cinema, and internet), revolutionizing health-related technologies (anesthesia, pharmaceutics, surgeries, antibiotics, and deep brain stimulation), and developing advanced scientific tools [genome sequencing, gene editing via CRISPR (clustered regularly interspaced short palindromic repeats) and optogenetics]. Our neurobiology shapes the complexity of social adaptations within and between species, and provides at the same time an evolved foundation for a socio-emotional and cognitive intelligence. Despite the significant evolution in cognitive and linguistic human aptitudes, we share several of our social rules and emotional capacities with nonhuman species. Social cooperation and reciprocity, kinship recognition, punishment, a sense of fairness, empathy, parental care, and pair bond formation are documented in several nonhuman species. Whereas some social behaviors have remained conserved across evolutionary lineages, others differ between and within species; and while some parts of our neuronal and genetic repertoire might be shared across million years of evolution, other biological systems are highly plastic and change dramatically.

For the past two decades, there has been a revolution in social neuroscience with the discovery of the role of the neuropeptide and neuromodulator oxytocin (OT) in initiating and modulating a wide range of social behaviors, from reproduction and mating to maternal care, pair bonding, and empathy. This nine amino acid molecule became the darling of researchers in the domain of behavioral neuroscience, molecular biology, psychopharmacology, endocrinology, and clinical neuropsychiatry. This huge expansion of interest in OT is due in part to its proposed crucial role in our basic emotional responses towards social encounters, coworkers, friends, partners, family members, and even our pets, *a role that is essential for well-being and survival*. We now know that love and attachment and any other form of sociality stems from neurobiological roots, and that reciprocally, our actions can impact our brain function and neuronal systems. Today, love and passion are not solely written in poems and expressed in arts as spiritual feelings that originate from the heart or the soul, but are also discussed in scientific reports as emotional states that are biologically orchestrated by hormonal factors, physiological states, genetics, and brain function. The study of the effects of neuromodulators on behavior and brain function and the interplay between these effects with genetic and molecular background lead to the creation of a new era of “social pharmacology” in the twenty-first century.

The neuropeptide OT is a fundamental biological element of sociality and affect. The peptide structure and the neuronal system of oxytocin along with its homologs remained relatively conserved across species over 600 million years, but its receptor expression is evolutionarily diverse and varies in relation to socio-behavioral diversity. The expression of OT receptor (OTR) is highly plastic and can be tuned up or down within specific neural systems based on species-dependent adaptive needs. It has been shown that the difference in

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sociality between and within animal species is in part explained by a substantial difference in OTR density and distribution within the social brain network. For instance, social rodents such as prairie voles and naked mole rats show a greater density of OTR in reward brain regions (such as the nucleus accumbens (NAcc)), compared to nonsocial meadow voles (during summer season) and cape mole rats (Kalamatianos et al. 2010). While rhesus macaques exhibit OTR expression in areas relevant to visual processing (such as the nucleus basalis of Meynert or NBM), the more highly social marmoset macaques have dense OTR in reward brain regions such as the NAcc (Freeman and Young 2016). This shows that social species differ from nonsocial species in their brain responsiveness to centrally released OT. The plasticity of OTR expression is critical for shaping a diversity of social behaviors across and within species. Importantly, our group has recently demonstrated that the density of OTR variability between individuals within the prairie vole species in the ventral striatum is the result of gene polymorphisms in the OTR gene (King et al. 2016). Further, individual variation in OTR density in the NAcc predicts how early life social experiences shape later social attachment behaviors (Barrett et al. 2015).

Oxytocin has been strongly implicated in sociality in humans in an adaptive and context-dependent fashion. Sociality is frequently confused with positive and affiliative behaviors such as love and morality. Sociality consists also of non-affiliative or agonistic behaviors that are essential for the foundation and maintenance of social structure. For instance, aggression and exclusion are necessary for the establishment of social hierarchies and the maintenance of territory in response to outsiders. Researchers have found that OT increases cooperation and trust in others, but also envy and gloating during the experience of loss and defensive responses and punishment for the out-group during threatening conditions (De Dreu et al. 2010; Kosfeld et al. 2005; Shamay-Tsoory et al. 2009). Thus, the function of oxytocin is not a simple formula that leads to one outcome with a positive valence or a negative valence: $f(OT) = X_i + R^+$ or $f(OT) = X_i + R^-$ (in which X stands for subject and R for response). Instead, we can define oxytocin's functions in a more complex equation that accounts for multiple factors that affect the outcome: $f(OT) = X_i + R(S_i \times GN_i \times MS_i \times P_i \times D_i \times Clt_i \times Cxt_i) + ft$ [in which the response is weighed by several factors: S for species, GN for genetic and neurobiological predispositions; MS for mental state; P for personality; D for development and age; Clt for culture; Cxt for context (baseline situation, type of outcome measure, history of the interaction, gain, loss, unfairness, etc.); and ft for fitness and adaptive response]. This function takes into account the diversity of social phenotypes, the interindividual heterogeneity, and the importance of selecting objective outcome measures while investigating the role of OT.

We hypothesize that OT modulates social behavior by impacting the activity and connectivity of the social salience network (SSN) that includes regions involved in fundamental processes such as perception and affect. OTR are found in sensory associative areas such as the olfactory bulb in rodents and visual associative areas in rhesus macaques and humans (Freeman and Young 2016). They are also found in regions involved in attention such as the basal nucleus of Meynert and the diagonal band of Broca that have a high number of cholinergic neurons (Freeman et al. 2014). In rodents, OTR are also found in amygdala, anterior cingulate cortex (ACC), insula, prefrontal cortex (PFC), and NAcc, which are regions of the salience and reward network. OT is known to reduce fear and

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anxiety by reducing the activity of amygdala. We hypothesize that OT modulates social behavior by enhancing attention to relevant social cues, reducing anxiety, and reinforcing the reward value of these cues, via the interaction with other neurotransmitters and hormones such as dopamine, vasopressin (AVP), serotonin, opioids, and corticotropin-releasing factor (CRF) (Bosch et al. 2016; Burkett et al. 2011; Burkett and Young 2012; Dolen et al. 2013; Young et al. 2014).

In light of seminal evidence on the role of OT in sociality and its effect on the SSN, researchers started investigating the baseline concentration of this hormone in individuals diagnosed with social disorders such as Autism Spectrum Disorder (ASD). Exogenously, oxytocin is administered intranasally (IN-OT) to humans given that this is likely the most efficient route for OT to penetrate the brain and bypass the blood–brain barrier (BBB) (Lee et al. 2017). The noninvasive intranasal delivery has been used as a treatment for several neurological disorders and it has a great potential in psychiatry. Intranasal delivery is used for administering larger molecules than OT, such as insulin and horseradish peroxidase. Today, we have accumulated evidence for the effects of IN-OT in promoting social functioning in ASD (Andari et al. 2010, 2016) and in reducing anxiety in patients with anxiety-related disorders.

In this chapter, we highlight the relevance of fundamental research in animals and clinical research in humans in determining optimal strategies for drug discoveries for social dysfunctions. Understanding the brain mechanisms and genetic underpinnings of normative social functioning is essential for unraveling key dysfunctions and potential therapies for neurodevelopmental disorders. The first section will describe the evolutionary origin of OT peptide, its synthesis and mode of release and receptor distribution. The second section comprises the different methods used to investigate the role of OT in animals and humans and in particular, the intranasal mode of delivery. The third section highlights the diversity of neurobehavioral functions of OT in humans and animals including maternal attachment, pair bond formation, prosociality, and social cognition. The fourth section incorporates the promising implications of OT in psychiatric disorders that are characterized by social dysfunctions and anxiety disorders. We also highlight the significance of adopting a precision medicine perspective that accounts for translational approaches to optimize targeted therapies with OT in neuropsychiatry.

2 Oxytocin System, Origin, Structure, Synthesis, and Release

2.1 Ancestral Oxytocin

The neuropeptide signaling system of OT, which is at least 600 million years old, has remained relatively conserved across species and its homologs are documented in invertebrates such as worms, insects, and vertebrates, shaping conserved functions such as reproduction (Gruber 2014). AVP is also an old neurophysiological nonapeptide that has a very similar structure to OT with a known role in water retention and vasoconstriction. It is documented that OT-like and AVP-like peptides originated from one ancestral arginine vasotocin gene that duplicated before vertebrate divergence 450 million years ago. The most common OT homologs are isotocin, which can be found in bony fish, and mesotocin, which can be found in lungfish, amphibians, reptiles, and birds (Stoop 2012). The general

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physiological function of this neurohypophysary system remained partly conserved across species. The OT – and AVP – like peptides coordinate reproductive behavior in nematodes (*Caenorhabditis elegans*), worms (Beets et al. 2012), leeches, earthworms, and snails (Gruber 2014). In nonmammalian vertebrates, these peptides and their homologs play a role in reproductive behavior, social communication, affiliation behaviors, and stress responses (Donaldson and Young 2008; Gimpl and Fahrenholz 2001; Goodson et al. 2015; Knobloch and Grinevich 2014). In mammals, OT is involved in the induction of vocalization, courtship behavior, female sexual receptivity, alternative mating, and maintenance of social-related behaviors (ovulation, parturition, lactation, sexual behavior, suppression of food intake, and social interactions). Most mammals today express OT and AVP, which differ mainly at the third and eighth position. The structure of the neuropeptide OT consists of a disulfide bridge between Cys residues 1 and 6 and contains a six-amino acid cyclic part and a C-terminal three-residue tail. The human gene for OT-neurophysin I encoding the OT pre-propeptide is mapped to chromosome 20p13 and consists of three exons. Despite some conserved functions of the OT system, it underwent several adaptive transformations in its axonal projections and its receptor distribution in the brain, shaping the evolution of complex social behaviors.

2.2 Synthesis and Release

The central oxytocin system has undergone macro-anatomical and cytological transformations during evolution. In more basal vertebrates such as fish and amphibians, homologs of oxytocin such as mesotocin and isotocin reside in the magnocellular neurons of the ancestral preoptic nucleus of the hypothalamus. This nucleus diverged in advanced vertebrates such as reptiles, birds, and mammals, into the paraventricular and supraoptic nuclei with accessory nuclei between them. Also, the hypothalamic magnocellular neurons went through several modifications in terms of location and cytological organization from uni- or bipolar neurons into highly differentiated neurons with elaborated dendritic tree. One of the most fascinating advancements is the expansion of oxytocin axonal projections to fore-brain regions, which could be related to the increased complexity of social behaviors (Knobloch and Grinevich 2014).

In mammals, oxytocin is synthesized by magnocellular neurons of the paraventricular (PVN) and supraoptic (SON) as well as in the accessory nuclei that are situated between the PVN and SON of the hypothalamus (Farina Lipari et al. 2005). The release of the final nonapeptide involves a calcium-dependent fusion of the granules with the nerve terminal. With the presynaptic release, dendritic release is dependent on the increase and mobilization of intracellular calcium that is stored in the soma and dendrites but not in nerve terminals. There are several factors that contribute to the mobilization of these Ca^{2+} stores that lead to OT release, including the α-melanocyte stimulating hormone (α-MSH). α-MSH originates from proopiomelanocortin-producing neurons in the arcuate nucleus and acts on melanocortin 4 (MC4) receptors in OT neurons (Sabatier et al. 2003). Interestingly, the behavioral effects of α-MSH are very similar to OT in terms of food inhibition, sexual stimulation, and pair bond formation (Modi et al. 2015; Penagarikano 2016; Penagarikano et al. 2015) It is possible that α-MSH exerts these neurobehavioral effects by stimulating endogenous OT release. These findings are translational in terms of future use of targeted

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drugs and small molecules (such as selective MC4 receptors agonists) that can cross the BBB, stimulate endogenous central OT release, and enhance social cognition.

OT is released in the blood and in the brain by the magnocellular neurons of the hypothalamus. The magnocellular OT neurons send axonal projections to forebrain regions where axonal release of OT can reach OT sensitive regions far away from the hypothalamus (such as amygdala, ventral striatum, hippocampus, and other regions rich in OT receptors).

OT is also released in the brainstem and hindbrain by parvocellular neurons of the hypothalamus. The magnocellular neurons of the hypothalamus project axons to posterior pituitary to release oxytocin into circulation. These large neurons also provide innervation to the forebrain by axonal release of OT containing fibers specifically targeting the brain areas expressing the oxytocin receptor. Also, local release from dendrites and continuous diffusion has been suggested as a route of action (Leng et al. 2008; Ross and Young 2009). These neurons can release OT peripherally and centrally at the same time in response to physiological or behavioral stimulation such as vaginocervical stimulation during copulation or suckling during breast-feeding. This suggests that there is likely a coordinated evoked release of OT in the brain and the periphery, and that peripheral measurements of OT levels during social or sexual events can, to some extent, reflect OT function in the brain. There is an increased interest in studying the relationships between human peripheral OT levels and socio-emotional behaviors. OT concentration is likely to be a biomarker of sociality.

2.3 Oxytocin Receptors

In mammals, there are four neurohypophysial peptide receptors: a single OT receptor (OTR) and three subtypes of AVP receptor (V1A, V1B, and V2). All these receptors belong to the G protein-coupled receptor superfamily that appeared early in evolution. Given the similarity in the structure of OT and AVP, OT can bind to AVP receptors with a lower affinity compared to OT receptors and vice versa. V1A is expressed in the forebrain and is the receptor that is most often linked to the regulation of social behavior. V1B is expressed in the anterior pituitary and restricted brain areas. V2 is expressed in the kidney and regulates the antidiuretic properties of AVP. OTR is expressed in the brain and in the periphery. In the periphery, OTR are found in the uterus, ovary, testis, prostate gland, mammary tissues, kidney, heart and cardiovascular system, pancreas, adrenal gland, fat cells, and thymus, supporting the close dialogue between the neuroendocrine system and the immune systems.

In contrast to the conserved nature of the peptide across vertebrates, OTR expression in the brain varies tremendously across and within species. More importantly, the diversity in OT receptor distribution is associated with variations in species-specific social behavior. *In rodents*, OTR are found in the olfactory system (olfactory bulb and accessory nucleus), striatum, BNST (bed nucleus of the stria terminalis), basolateral and medial amygdala, hippocampus, insula, ACC/mPFC (medial PFC), hypothalamus, in addition to the brainstem and spinal cord (Tribollet et al. 1989). Rodent species rely heavily on olfactory investigations to process social information and recognize social partners. Therefore, it is possible that OT acts on OTRs in olfactory areas as well as the other subcortical and striatal regions in order to enhance attention to relevant social cues and increase reward sensitivity to these cues. However, *primate species* rely mainly on visual investigation to detect and

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process social cues. Similar to humans, faces and the eyes are crucial for social communication between primates. Accordingly, OTR expression is found in areas important for visual processing and allocation of attention and saccades among primates and humans. In primates, OTR has been detected in the superior colliculus, the pulvinar, and the primary visual cortex (Freeman et al. 2014). OTR was also observed in the brainstem nuclei relevant for the control of the muscles of the eyes such as the oculomotor nucleus (III) and the nucleus prepositus, and OTR expression has also been found in NBM, which is an important source of cholinergic release in the brain. *In humans*, OTR are observed in abundance in the NBM and diagonal band of Broca, with less intense binding in the medial septal nucleus, globus pallidus, and ventral pallidum. There is OT binding in the hypothalamus, superior colliculus and in the brainstem, midbrain pontaine tegmentum and spinal cord. Moderate densities of OT were detected in the nucleus of the solitary tract and spinal trigeminal nucleus. High densities were observed in the medio-dorsal region of the nucleus of the solitary tract (Loup et al. 1989). Researchers also found OT receptors in olfactory nucleus suggesting that OT may also modulate the processing of olfactory cues in humans (Boccia et al. 2013). Given that primates and humans are visual, OT might act on OTRs in attention and visual areas to increase attention to social cues. The difference in OTR distribution in the brain between different species shapes behavioral aptitudes in processing social cues. Our knowledge about OTR distribution in human brains relies solely on postmortem studies and autoradiography. There is a substantial need for the discovery of specific radio-ligands, small antagonists, or agonists of OTR that could penetrate the brain and that we can use to image OTR in vivo in the human brain using positron emission topography. Our group evaluated a potent and selective oxytocin receptor antagonist in nonhuman primate and showed that it mildly penetrated the brain (Smith et al. 2016). These results are promising and further research on small potent molecules that penetrate the brain can be important to pursue in the human population.

3 Methodology of OT Research, IN-OT, and the Human Brain

While there are several invasive methods that can be used in order to investigate the effects of OT on behavior in animal models, there are only a few noninvasive methods that can be used in human research studies. In rodents for instance, there is a possibility of directly injecting OT agonists or antagonists into the brain and studying the direct functionality and causality of OT in a particular behavior. Also, several transgenetic manipulations can be conducted in animal models, such as the engineering of OTRKO (oxytocin receptor knockout) mice or OTKO mice (oxytocin knockout mice), to test the role of the OTR gene or OT system in behavior relevant to social dysfunctions. Instead of knocking out the OT or OTR gene completely, it is also possible to manipulate the density of receptors through viral vectors via genetic technology by manipulating the expression of a gene. Vectors that contain a copy of a gene can cause an ectopic expression in cells leading to up-regulation of density of OTR. Researchers can use the vector to also down-regulate the expression of OTR or to reduce the endogenous expression of OTR using RNA interference mechanisms. We can also use optogenetics technology that uses the light to control neurons that have been genetically modified to express light-sensitivity. This technique can allow us to manipulate in real time individual neurons in living tissues. Today we can use even more advanced

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engineering technologies such as CRISPR, a new genome-editing tool that can target specific mutations in animal models and eventually may prevent genetic diseases in humans. The use of these sophisticated tools in animal research is crucial to study mechanisms, pathophysiology, and the development of targeted drugs for social cognition. The fundamental goal of this preclinical work is to translate these discoveries into clinical studies in humans to understand human brain mechanisms, human behaviors and to alleviate suffering from psychiatric disorders and other pathologies.

In terms of the study of OT's role in human social functioning, there are common tools for investigating OT mechanisms, its endogenous system or exogenous and modulatory effects. Genomic analysis and evaluation of postmortem brain samples are possible. Some researchers measure baseline concentrations of oxytocin (plasma or saliva or urinary) to compare OT levels between individuals with a high degree of sociability and introverted individuals, or between healthy subjects and others with psychiatric disorders (Andari et al. 2010, 2014; Jacobson et al. 2014; Jansen et al. 2006). This can also serve to correlate baseline OT concentrations with other social behaviors such as parent–infant synchrony (Feldman et al. 2007). There is also increasing interest in measuring evoked oxytocin release following socio-emotional manipulations (such as trust and socially interactive games, touch, massages, stress, and others). Currently, there are several controversies regarding the validity of OT peripheral measurements. There is a debate surrounding the use of immunoassay methods such as enzyme immunoassay or radioimmunoassay with or without extraction of OT, which leads to controversial results in some cases. There is a need for the development of more robust tools to measure and detect OT, such as the use of mass spectrometry to detect OT molecules. Also, more research is needed to better understand the degree of correlation between peripheral measurements and central actions of OT. However, despite these above challenges, there is an increasing body of evidence showing that OT can be used as a biomarker of social functioning (Andari et al. 2014; Parker et al. 2014). Genetic variants or plasma oxytocin are associated with the variance in social cognition.

In humans, when administered systemically, OT can have side effects by acting on peripheral organs and it does not cross the BBB to yield neurobehavioral effects. Therefore, researchers tested the idea of administering the molecule intranasally as it can avoid the BBB and cross the brain through the intercellular clefts in the olfactory epithelium and diffuse into the subarachnoid space (Illum 2000, 2012).

In the last two decades, much interest has been given to the exploitation of nasal route for delivery of drugs to the brain via the olfactory region (Bahadur and Pathak 2012; Balin et al. 1986; Quintana et al. 2016; Veening and Olivier 2013).

In humans, a number of studies showed that IN-OT or intranasal administration of AVP (IN-AVP) affects brain activity and enhances OT or AVP levels in the cerebrospinal fluid (CSF), respectively. Recordings of evoked brain potentials (event-related potentials or ERPs) following IN-AVP provided functional evidence for a facilitated access of neuropeptides to the brain after nasal delivery (Fehm et al. 2000). IN-AVP increased the amplitude of several components of the late ERPs, in particular the amplitude of P3, which reflects a higher level of cognitive and attention processing (Born et al. 1986; Fehm-Wolfsdorf et al. 1988;

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Naumann et al. 1991; Pietrowsky et al. 1989). More importantly, intravenous administration of AVP enhanced plasma AVP but did not affect the brain activity (measured by ERP) (Pietrowsky et al. 1989), showing that the effects after IN-AVP are not dependent on the AVP plasma concentration. On the contrary, it indicates that there is likely a pathway from the nasal mucosa to the brain, independent of BBB penetration of AVP. In addition to the effects of IN-AVP on brain activity, researchers showed that it enhances significantly AVP concentration in the CSF in a dose-dependent manner (fivefold increase with 40 IU and tenfold with 80 IU) (Born et al. 1986). Mean CSF concentrations began to rise within 10 min of intranasal administration and stayed above those in placebo groups 100–120 min after intake. Not only does IN-AVP increase AVP CSF levels, IN-OT (24 IU) also enhances OT concentration in the CSF (60% increase) 75 min after intake (Striepens et al. 2013). There are several neuroimaging studies showing that IN-OT affects the BOLD (Blood Oxygen-Level Dependent) activity of brain regions and the cerebral blood flow of key regions that are supposed to have high levels of OTR. A recent elegant study using arterial spin labeling showed that IN-OT increases the levels of cerebral blood flow of key regions of the SBN such as ventral striatum, amygdala, hippocampus, caudate nucleus, anterior and middle cingulate cortices, anterior insula, ventral tegmental area (VTA), inferior frontal gyrus, inferior parietal cortex, and superior temporal gyrus (Paloyelis et al. 2016). These regions are shown in the animal literature to have high levels of OTR (Boccia et al. 2013). It is possible that IN-OT affects the activity of these brain regions by acting on OTR.

In addition to the accumulated evidence in human subjects, there are several reports of a significant increase of OT levels in the brain following IN-OT in rodent species and in nonhuman primates. In mice and rats, IN-OT increased OT content within the dorsal hippocampus and amygdala (Neumann et al. 2013), with peak activity between 30 and 60 min after spray intake, very similar to human findings. Also, in monkeys, IN-OT or OT intake via a nebulizer (25 or 48 IU) increased OT CSF concentration compared to placebo (Chang et al. 2012; Dal Monte et al. 2014; Modi et al. 2014). A more recent study provided evidence for dose-dependent penetration of OT into the CSF in monkeys. Authors reported that while a small dose of IN-OT (between 0.58 and 5.5 IU) did not increase CSF OT, a bigger dose that is frequently used in human trials (between 29 and 36.5 IU) increases CSF OT 15–30 min following spray intake (Freeman et al. 2016). This enhancement in oxytocin levels in the CSF could be interpreted as an endogenous release of OT following peripheral increase of OT levels, and not as directly related to IN-OT. This critique was recently addressed in a breakthrough study using specific mass spectrometry assay that distinguishes labeled OT from endogenous OT. Authors found that a significant CSF increase in labeled OT that is solely related to the exogenous IN-OT delivery (Lee et al. 2017).

These numerous replications of the effects of IN-OT on brain OT concentration are in line with several other findings in the medical field showing that proteins (such as insulin, nerve growth factor, and tracer molecules) and large biological particles (such as viruses and stem cells) accumulate in the brain tissue after intranasal administration. Therefore, intranasal mode of delivery can be used as a noninvasive method for studying the exogenous hormonal effects of OT on the alteration of behavior and brain function in humans. More research is needed to better evaluate IN-OT effects on behavior, to better characterize objective outcome

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measures, and to continue investigating its therapeutic avenues in social and anxiety disorders.

4 Neurobehavioral Functions of OT

OT's role in social behavior and emotional processes has become well defined in the literature. A search of PubMed with the term "oxytocin and social" yields 1970 hits. Strikingly, a PubMed search between the years 1996 and December 2016 with the terms "oxytocin and social" revealed 1,892 papers, showing that the majority of research done on the role of oxytocin in social behavior has been performed within the past 20 years.

OT was known first for its role in reproduction and breastfeeding, acting through its release in the periphery via the posterior pituitary. Around the onset of labor, there is an up-regulation of OT receptor messenger-RNA levels and a 200-fold increase in the density of OT receptors in the myometrium (Gimpl and Fahrenholz 2001). During lactation, the secretion of the mammary glands is triggered when the infant begins to suck on the nipple, sensory impulses that are transmitted to the spinal cord and then to the secretory oxytocinergic neurons in the hypothalamus. These neurons display a synchronized high-frequency brief bursting activity that consists of action potentials. Each burst leads to a massive release of OT in the blood stream and to lactating breasts. It causes a contraction of the myoepithelial cells and the ejection of milk following the tactile stimulation. Also, sexual activities such as vaginocervical stimulation, copulation, or orgasm stimulate a burst of OT release.

In addition to the known peripheral effects of OT, this molecule plays a key role in orchestrating complex social behaviors, such as maternal attachment, pair bond formation, prosociality, reduction of stress and anxiety, and social cognition, through its release in the brain and its actions as a neuromodulator.

4.1 Maternal Behavior

Giving birth elicits a cascade of hormonal, physiological, and neurochemical changes that affect brain systems and connectivity between key socio-emotional brain regions and ultimately lead to a significant shift in maternal behavior (Rilling and Young 2014). This neurobehavioral shift can be dramatic in some species (such as in mice and rats) from a complete aversion or avoidance (in virgin rodent species) to a significantly increased interest in pups. Other species (such as prairie voles and humans) display more subtle shifts that consist of changes from a voluntary general care for offspring (alloparental behavior before pregnancy) to a more selective and a stronger mother–infant bond. There are several forms of maternal care across species. In some species, dams display promiscuous maternal motivation and care toward offspring following birth and in other species mothers display selective mother–infant bonds. Several lines of research have also shown that there are natural variations in the expression of these neurobehavioral changes within species that can vary from one individual to another in terms of reception of parental care early in development, depending on genetic predispositions and early-life environment.

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Numerous hormones play a role in evoking maternal nurturing behaviors, such as estrogen, progesterone, OT, prolactin, dopamine, and noradrenaline. Throughout the pregnancy, there is a significant increase in estrogen and progesterone, which are secreted by the ovaries followed by a sudden drop in progesterone at the end of pregnancy and an increase of OT and prolactin, especially during delivery. These hormonal changes are mainly orchestrated by the medial preoptic area (MPOA) within the hypothalamus, a region that is very rich in steroid receptors and that plays an important role in maternal nurturing behavior. MPOA is involved in the maternal behavioral switch through its effects on the brain activity of other regions, such as reducing amygdala activity and increasing the activity of the mesolimbic dopaminergic system (Rilling and Young 2014). The effects of MPOA on the reward system is through direct effects on the VTA and indirect effects via increased OT projections from the PVN to the VTA, all of which lead to a significant release of dopamine in the NAcc (mainly activating D1 receptors). The first evidence for the role of OT in the onset of maternal behavior comes from a study in rats showing that a central injection of an OT antagonist blocks the onset of maternal behavior in parturient dams. Also, a central injection of OT to virgin rats, which usually show aversive or avoidance behaviors toward pups, induces the onset of maternal responsiveness (Pedersen and Prange 1979). In addition to the generalized maternal responsiveness that is observed in rats and mice, OT initiates selective maternal bonds in sheep. While mice and rats can display promiscuous maternal behavior for all offspring, including their own, it's necessary for ungulates such as sheep to have selective care for their own young given that they live in herds and deliver offspring at the same time and in large numbers. Intracerebro-ventricular injection of OT can evoke maternal behavior in estrogen-primed nonpregnant ewes (Kendrick et al. 1987). In addition to initiating maternal behavior, OT reinforces the memory formation of olfactory cues through the interaction with noradrenaline. Also, prairie voles display parental care even in the absence of parturition (Ross and Young 2009). This alloparental behavior or spontaneous maternal behavior is very similar to human behavior. There is a significant correlation between OTR density in the nucleus accumbens and the display of alloparental behavior in juvenile and adult virgin females (Olazabal and Young 2006). Administration of an OT antagonist into the NAcc blocks maternal behavior toward pups in adult females, but enhancing OTR density in the NAcc of adult female voles does not enhance alloparental behavior (Ross and Young 2009). This suggests that the existence of these OTR in the NAcc is relevant during development and the early phase of mother–infant interaction, which can later shape the nurturing behavior in adulthood. OT also regulates maternal aggression toward intruders in rodents as part of maternal care (Bosch and Neumann 2012). There is genetic evidence for the role of OT in the onset of maternal behavior. For instance, OTRKO dams are still able to give birth but display robust impairments in maternal care and longer latencies to retrieve the pups (Takayanagi et al. 2005). Also, CD38 knockout mice display impairments in maternal behavior, similar to OTRKO mice, which is found to be restored by injection of oxytocin.

Natural variation in maternal nurturing received by pups alters OTR brain expression in these pups, which can in turn affect the quality of maternal behavior that they provide to their own offspring during adulthood. Researchers have shown that rats reared by high-licking and grooming mothers displayed high-licking and grooming when they become

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mothers, regardless of the maternal behavior of their biological mothers. Also, mothers with high maternal care showed increased OTR density in the MPOA, PVN, lateral septum, amygdala, and BNST, regions highly involved in producing maternal affiliative behavior (Champagne and Meaney 2001). Therefore, it appears that the transgenerational transmission of maternal behavior is orchestrated in part by the expression of OTR.

In humans, the neural circuitry of parental care is much more sophisticated than in rodent species and involves several levels of socio-cognitive and emotional processes (Feldman 2015; Swain et al. 2014). Similar to rodent species, the motivational and emotional aspects of human parenting involve the reward and subcortical brain networks that include amygdala, hypothalamus, NAcc, VTA, striatum, and substantia nigra (Swain et al. 2014). The socio-cognitive processes of parenting incorporate perception and understanding of infants' verbal and non-verbal cues, empathizing with their distress and regulating their emotions. Detecting infants' social cues activates a perceptual brain network that includes the amygdala, inferior parietal, and supplementary motor area (Rizzolatti and Craighero 2004). Understanding infants' subtle and nonverbal cues requires the activity of a mentalizing network, including the superior temporal sulcus, the posterior cingulate gyrus, temporal parietal junction, and vmPFC (Kanat et al. 2014; Yang et al. 2015). Parents also show activation in empathy-based circuitry, including anterior insula and anterior cingulate gyrus, when responding to infants' cries or pain (Yang et al. 2015). Emotion regulation involves the activity of dorsolateral prefrontal gyrus and middle frontal cortex. A synchrony and balance between all these social brain networks are necessary to ensure optimal emotional responsiveness and emotion regulation (Feldman 2015).

There is also growing evidence for OT's role in human parenting. OT peripheral levels are associated with the quality of mother–infant or father–infant interaction, affectionate contact, engagement, and affect synchrony (Feldman et al. 2010). Administration of intranasal oxytocin to parents results in a rise in the infant's oxytocin levels (Weisman et al. 2012). There are also genetic associations between several polymorphisms of OTR gene and CD38 gene and human parenting behavior (Feldman 2012; Riem et al. 2011, 2012). Hence, OT, along with other neurotransmitters, plays an important role in triggering parental responsiveness toward offspring. The quality of early-life interactions between children and their parents is crucial and can be transferred across generations, leading to a more healthy mental and psychological state.

4.2 Pair Bond Formation

Given OT's role in triggering affiliative maternal responses toward offspring following delivery, researchers hypothesized that this molecule may play also an important role in the formation of bonds between pairs following mating. Researchers studied the neurobiological system of prairie voles (*Microtus ochrogaster*) and meadow voles (*Microtus pennsylvancius*) or montane voles (*Microtus montanus*), closely related rodent species that differ dramatically in their social relationships. While prairie voles are socially monogamous, form life-long bonds with their mated partners, show bi-parental care, and display selective aggression toward unfamiliar conspecifics after bonding, meadow voles and montane voles are not socially monogamous and do not form affiliative attachments with their partners.

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These species-specific behaviors are generated by a brain hardwired for affiliation and attachment. Researchers found that these differences in behavioral phenotypes are associated with species-specific differences in OTR density in key reward and social brain areas, such as the NAcc and PFC, between the prairie vole and the meadow vole.

In order to test behaviorally the formation of pair bonds in these rodent species, researchers have come up with a laboratory assay, the “partner preference test” (PPT). Prior to the PPT, adult subjects cohabitate with an opposite-sex mate either under conditions that are insufficient to form a bond (6 h or less without mating), or under conditions that are suitable for long-term bond formation (24 h or more with mating). Subjects are then challenged with the PPT, which is conducted in a three-chamber apparatus where one chamber contains the familiar mate and another contains a novel stranger. The subject is allowed to freely room the apparatus for 3 h. The primary measure is the amount of time the subject spends huddling next to either animal. The majority of prairie voles will spend their time in social contact with either animal, whereas the meadow voles spend most of the time in the empty chamber. Mating during cohabitation can facilitate partner preference formation, but partner preference can form in the absence of mating with prolonged periods of co-habitation. Central injection of OT into the brain facilitates pair bonding after a short period of cohabitation in the absence of mating. Conversely, blocking central oxytocin signaling using oxytocin antagonists prevents prairie voles from forming pair bonds following mating (Johnson et al. 2016a, b). More specifically, injection of an OTR antagonist in the NAcc or the PFC prevents mating-induced partner preference formation. It seems that both OT and dopamine are essential for the formation of mating-induced partner preference. Dopamine is released in the NAcc during mating and an intra-NAcc shell injection of dopamine 2 receptor antagonist inhibit mating-induced partner preference or partner preference induced by OT treatment (Aragona et al. 2003; Liu and Wang 2003; Wang et al. 1999). In addition to the role of OT in NAcc and PFC in the formation of bonds, our lab recently showed that OT plays an important role in coordinating the brain activity of several regions relevant to reward and perceptual circuitry (such as NAcc, PFC, PVN, amygdala, and olfactory bulb) in prairie voles after mating (Johnson et al. 2016a). This is in line with the increasing evidence in humans showing that intranasal oxytocin is affecting the functional connectivity of a social brain network.

In addition to rodents, several lines of research in rhesus macaques and bird species show the association between social diversity and OTR distribution in the brain. Primate species that are not monogamous, such as rhesus macaques, did not express OTR and AVRP1A in the nucleus accumbens or ventral pallidum, respectively. However, monogamous species, such as the common marmosets, express OTR and AVRP1A in the nucleus accumbens or ventral pallidum, respectively. Also, more gregarious species of birds, such as the zebra finch, exhibit higher OTR in the lateral septum (LS) relative to isolated species, which lack OTR in the dorsal part of LS. This variation in the distribution of OTR in these birds is functional, and an injection of an OTR antagonist into the LS can reduce social preference (Goodson 2013). OTR seems to shape social functioning across several species.

Pair bonds or social bonds in general are essential for a better healthy life. Indeed, social loss or a loss of a close person can cause emotional distress and loneliness and, in some

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situations, can lead to psychiatric problems such as depression. In animal models, the loss of a female partner (and not a sibling) is a stressful event that leads to increased levels of cortisol and increased passive stress coping reminiscent of depression or bereavement (Bosch et al. 2009). Interestingly, chronic stress can increase CRF signaling and lead to depression-like symptoms by suppressing OT signaling in the NAcc shell. OT could be an essential factor for social buffering and reduction of stress. The presence of social support or a new partner following a social loss can prevent depression-like symptoms by reducing stress and increasing OT levels. Indeed, researchers found recently that the loss of partner in monogamous species prairie voles suppresses OTR signaling and that infusion of OT in the NAcc reverses the adverse emotional response to the loss of a partner (Bosch et al. 2016).

Despite the importance of love and attachment in human daily lives, we still have a great deal to learn about the neurobiological correlates of pair bond formation in humans, in part because of limitations in feasibility. Neuroimaging studies showed that brain regions implicated in feelings of reward, such as the VTA, NAcc, and caudate that were previously documented in pair bond formation in animal species, are activated during the perception of romantic partner's face (Acevedo et al. 2012; Aron et al. 2005; Bartels and Zeki 2000; Scheele et al. 2013). IN-OT increases the rating of attractiveness of partners' faces (Scheele et al. 2013), reduces conflict between couples (Ditzen et al. 2009), and enhances the distance between pair bonded men and unfamiliar attractive individuals (Scheele et al. 2012). In the latter study, authors measured the distance that single and pair bonded men kept from an unfamiliar attractive woman who either maintained or avoided eye contact with them during a first encounter and also assessed their willingness to approach or avoid pictures of attractive women. IN-OT promoted a greater distance (10–15 cm) between men in a monogamous relationship and attractive female strangers. It is possible that OT helps maintain monogamous relationships by making men avoid signaling romantic interest to others through approach behaviors, for instance. SNPs in the oxytocin receptor gene are found to be associated with complex human prosocial behaviors such as trait empathy and pair bonding (Luo et al. 2015; McQuaid et al. 2015). We believe that the neurobehavioral functions of OT observed in animal species are also conserved in humans, and that healthy bonds with partners are essential to reduce the risk of mental disorders and health-related issues.

4.3 Prosociality

In addition to the well-documented role of OT in socio-sexual behaviors and maternal attachment, OT is also involved in other forms of attachment not only towards kin but also towards familiar individuals. OT plays a crucial role in empathy and modulates empathy-based behaviors. Prosociality and cooperation between individuals evolved among humans because of psychological phenomena such as reciprocal altruism, indirect reciprocity (gaining a social reputation), and group competition. Displaying empathetic responses requires the individual to detect relevant social cues (such as distress of a partner) and to display an emotional response (such as console the partner with the intention to reduce the stress or the pain of a partner). Naturally occurring consolation has been observed among humans and some other animals with high cognitive abilities, such as great apes. Recently, we have demonstrated that rodents are also able to display instinctive consoling responses

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toward a stressed cagemate or a partner. Burkett et al. (2016) developed a novel behavioral assay to test consolation in prairie voles (Burkett et al. 2016). In this assay, co-housed pairs of prairie voles are separated and one member of the pair received foot shocks in a separate room. Upon reunion, the naïve observer increased partner-directed grooming toward the stressed cagemate. More grooming was observed in response to familiar conspecifics compared to strangers, resulting in a familiarity bias. We have demonstrated that this consoling response is an empathy-based behavior given the presence of a state-matching response (positive correlation between the self-grooming in the stressed and the non-stressed animal), emotional contagion (increased freezing behavior in the stressed animal during the observation of the other partner freezing and correlated corticosterone levels in stressed and non-stressed animals), and helping behavior (the anxiety level of the stressed partner decreases with the presence of the partner compared to the alone condition). Importantly, we found that consolation can be abolished in prairie voles with the administration of a selective OT antagonist in the ACC, a region involved in empathy and salience in humans (Singer et al. 2004). This demonstration shows that OT is essential for consolation behavior and emotional empathy in rodents. In keeping with these findings, authors found that IN-OT intake enhanced emotional empathy in response to emotional stimuli (Hurlemann et al. 2010). In another study, authors showed that IN-OT improved empathic accuracy only for those who are less socially proficient (as measured by Autism Spectrum Quotient) (Bartz et al. 2010). The empathy test consisted of videos of individuals discussing emotional events and participants were asked to rate how positive or negative they thought the target individual felt at each moment during the narrative. IN-OT enhances interpersonal distance for those who have high empathetic scores (Perry et al. 2015). Hence, the prosocial effect of IN-OT can depend on several individuals' characteristics (social aptitudes, empathetic tendencies, gender, etc.). IN-OT can also enhance empathy in Israeli Jewish participants toward the pain of Palestinians, reducing the effect of in-group empathy bias observed in the placebo (Shamay-Tsoory et al. 2013). Moreover, there is increasing evidence for genetic associations between common OTR polymorphisms and empathy (Huetter et al. 2016; Laursen et al. 2014; Luo et al. 2015; Tost et al. 2010; Wu et al. 2012). Amygdala activity during the processing of emotional cues was significantly affected by the common variant (rs53576) in the OTR. It is possible that IN-OT enhances empathy-based behaviors by affecting the BOLD activity of brain regions as well as the functional connectivity between the regions involved in perception, theory of mind, cognition, and emotional processes. Empathy-based behaviors encompass both cognitive-based components and emotional components. It is also plausible that individuals have genetic predispositions to display prosocial feelings toward other's pain or the cognitive capacity to understand other's hidden intentions. Understanding the neurobiological foundations of these behaviors can help researchers find new-targeted treatments for patients who lack empathy, such as psychopathy and autism.

4.4 Anxiety and Social Cognition

In addition to the crucial role of OT in several forms of attachment, this molecule is also involved in more generalized social behaviors related to social cognition and social recognition. First evidence for OT's role in social recognition came from animal models relevant to autism. Social recognition or social memory in mice is depicted by a significant

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reduction of the duration of olfactory investigation of the familiar stimulus animal. Early studies showed that OTKO mice fail to recognize familiar conspecifics (Ferguson et al. 2000) and do not reduce their olfactory investigation even following several encounters. However, these OTKO mice are able to recognize nonsocial olfactory scents, which make their deficit selectively a social recognition deficit. A central infusion of oxytocin before and not after the first encounter rescues their capacities to recognize a familiar conspecific. In a subsequent study (Ferguson et al. 2001), we found that OT acts in the medial amygdala during initial exposure to other conspecifics to facilitate social recognition. Using c-Fos immunoreactivity as a marker of neural activation, we showed that while both wild-type and OTKO mice show an induction of Fos activity in the olfactory bulb, piriform, cortical amygdala, and lateral septum, they do not exhibit an induction in the medial amygdala following social recognition. These studies provided relevant perspectives on the neural mechanisms of social deficits. In addition, mice with a genetically altered OT system, such as CD38 knockout mice (cluster of differentiation 38, which is a transmembrane receptor involved in releasing OT by mobilizing Ca^{2+} from intracellular stores), show social deficits that are restored with OT intake. OT administration improves sociability of mice that have lower levels of sociability naturally (Teng et al. 2013). These findings provide more support for construct validity and predictability for mouse models related to OT or OTR genes in terms of animal models for social disorders such as Autism Spectrum Disorder.

Social encounters are more rewarding than isolation for social animal species and this is likely to be orchestrated by OTR. In an elegant study, authors showed that mice form a preference for social bedding compared to the isolated bedding (Dolen et al. 2013). Moreover, mice treated with an OT antagonist within the NAcc did not form this preference. Serotonin in the NAcc is additionally important for social reward, and it could be that by releasing serotonin from dorsal raphe terminals, OT triggers social preference. These findings are in congruence with the recent neuroimaging results in humans showing that IN-OT modulates brain serotonin activity at rest (Mottolese et al. 2014).

More recently, researchers showed that chronic exogenous OT administration to Cntnap2 knockout mice, a mouse model of autism, rescues their social deficits (Penagarikano et al. 2015). These mice display social deficits in addition to epilepsy and cortical dysplasia and show a reduction in neurons expressing OT in the PVN. Authors have shown that similar effects or slightly larger effects are found with acute intranasal administration of OT. Also, daily chronic intranasal administration of OT early in life (between P7 and P21) in Cntnap2 knockout mice rescues their social interest and social approach. This effect was sustained 1 week after the cessation of the treatment. This is in line with recent studies in newborn macaques showing that inhaled oxytocin increases affiliative behaviors such as lip smacking and visual attention and close proximity to the caregiver (Simpson et al. 2014). There is accumulated research on the role of IN-OT in promoting social exploration, enhancing social motivation and attenuating social vigilance in nonhuman primate models (Chang et al. 2012; Chang and Platt 2014; Ebitz and Platt 2013; Parr et al. 2013; Putnam et al. 2016).

These findings in animal models are very promising and translational in terms of OT's potential for therapeutic efficacy in ASD. Oxytocin is thought to modulate neural activity by affecting the excitatory/inhibitory balance and also seems to improve the signal-to-noise

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ration by stimulating fast spiking parvalbumin inter-neuron activity (Owen et al. 2013). OT enhances responses to pup calls by balancing the magnitude and the timing of inhibition with excitation within the left auditory cortex (Marlin et al. 2015). It also appears that OT plays an important role in shifting neuronal GABA excitatory activity in immature neurons into inhibitory function (Leonzino et al. 2016). Tyzio et al. (2014) showed that oxytocin treatment in the embryonic period suppresses GABA-mediated excitation in mice and that these effects were blocked by the infusion of an OTR antagonist (Tyzio et al. 2014). OT seems to have a neuro-protectant role in the developing brain and early treatments with OT could be essential to prevent the associated deficits that arise from a deficit in OT function. OT's effects on GABAergic neurons have been also documented with relation to its anxiolytic functions and its role in reducing central amygdala activity.

OT release in central amygdala is known to attenuate fear responses in rats (Knobloch et al. 2012). OT injection in the lateral part of central amygdala stimulates GABAergic interneurons, leading to an increase in the rate of inhibitory postsynaptic activity in the central medial amygdala (Huber et al. 2005). Optogenetic activation of OT terminals in the central amygdala reduces freezing in fear-conditioned animals and injection of an OTR antagonist restores the freezing behavior. These results highlight OT's role in modulating emotional behavioral responses and attention to social cues by altering the activity of reward neural circuitry, perceptual network, and the fear-stress circuitry (Knobloch et al. 2012; Knobloch and Grinevich 2014; Viviani et al. 2011).

In humans, there is accumulating evidence for the role of OT in social cognition. In early studies, researchers documented the anxiolytic effect of IN-OT (24 IU) and showed that subjects who received both OT and social support exhibited the lowest cortisol concentrations and displayed decreased anxiety during the Trier Social Stress Test (Heinrichs et al. 2003). This reduction in anxiety and fear is in line with an increasing body of evidence showing that IN-OT reduces the BOLD activity of the amygdala region in response to faces (Domes et al. 2007a; Kanat et al. 2015a, b; Kirsch et al. 2005). Importantly, IN-OT attenuates heightened amygdala reactivity to fearful faces in patients with generalized social anxiety disorder (GSAD) (Labuschagne et al. 2010). This is a promising line of research that can lead to potential treatments for social anxiety disorders with OT.

Researchers found that IN-OT increases cooperation and social trust in others (Kosfeld et al. 2005), increases envy and schadenfreude in situations of loss (Shamay-Tsoory et al. 2009), enhances mind-reading capacities (Domes et al. 2007b), increases memory for faces (Rimmele et al. 2009), and improves emotion recognition (Schulze et al. 2011). IN-OT increases trust by reducing the BOLD activity of amygdala and midbrain regions, neural systems that mediate fear processing (Baumgartner et al. 2008). During cooperative interactions, Rilling et al. (2014) found that OT increased the BOLD activity in men in reward regions such as the striatum (Rilling et al. 2014). Interestingly, the effects of IN-OT on brain activity are moderated by genetic polymorphisms of the OTR gene (Feng et al. 2015).

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There is increasing evidence for OT's role in enhancing attention to social cues and reward sensitivity to these cues. IN-OT increases gaze time or visual fixation toward the eye region and the face (Auyeung et al. 2015; Domes et al. 2013; Guastella et al. 2008). Hurlemann et al. (2010) showed that IN-OT enhances socially reinforced learning and emotional empathy (Hurlemann et al. 2010). IN-OT increases the functional coupling between amygdala, anterior insula, and inferior frontal gyrus in response to remembered emotional items (Striepens et al. 2012). Scheele et al. (2013) showed that IN-OT increases the activity of VTA and NAcc in response to a partner compared to unfamiliar individuals (Scheele et al. 2013). While hearing infant's laughter, IN-OT reduces the activation of the amygdala and enhances the functional connectivity between the amygdala and the OFC, ACC, hippocampus, and precuneus (Riem et al. 2012). During resting state fMRI, IN-OT enhances the functional connectivity between amygdala and rostral medial frontal areas, regions that are crucial for social cognition and emotion regulation (Sripada et al. 2013). IN-OT seems to impact attention to social cues and reward sensitivity to these cues by enhancing the functional connectivity between perceptual networks and reward brain circuitry such as amygdala, striatal regions with frontal areas, and insula, a network that is necessary for social cognition. These findings are very promising in terms of the role of OT in alleviating social dysfunctions and reducing fear and stress-related responses in neuropsychiatric disorders such as ASD.

5 Promising Role of Oxytocin in Psychiatry

With the increasing evidence for the role of OT in social behavior and emotional processes, researchers became interested in investigating the link between OT function and neurodevelopmental disorders such as ASD. Deficits in social communication and social reciprocity are the hallmark of ASD symptomatology. These individuals show less interest in social cues and display less attention to them (such as by looking less at faces and making less eye contact with others during conversations). They have difficulty with initiating social conversations, understanding and communicating nonverbal cues, and in maintaining long-term relationships. These core social symptoms are often accompanied by much comorbidity, such as anxiety, depression, obsessive compulsive disorder (OCD), hyperactivity, irritability, conduct and behavioral problems, epilepsy, and intellectual disabilities. The presence of these comorbid disorders explains in part the enormous heterogeneity of ASD that has challenged the study of the underlying pathophysiology, and therefore the development of targeted pharmacotherapies. The FDA has approved risperidone and aripiprazole for treating irritability in individuals with ASD and other medicines are used off-label, such as the SSRIs (selective serotonin reuptake inhibitors) to regulate anxiety, depression, and OCD symptoms in ASD. Despite the importance of the current medication in controlling comorbid disorders in ASD, they do not treat core social deficits of ASD.

In the past decade, evidence has accumulated for the presence of some dysfunctions in the OT system in individuals with ASD and for the promising role of exogenous administration of OT in alleviating social deficits in ASD. Studies in our lab and others have found that OT plasma concentration is significantly lower in patients with ASD than in healthy subjects (Andari et al. 2010; Modahl et al. 1998). We also showed that OT concentration correlates

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with sociability scores in healthy subjects (Andari et al. 2014). By using the NEO Pi-R personality test, we showed that there is a positive correlation between extraversion scores (gregariousness and sensation seeking facets) and OT plasma levels. Baseline OT levels and extraversion scores correlate with the volume of grey matter in amygdala and hippocampus regions. Recently, Parker et al. (2014) reported that plasma oxytocin concentration and OTR polymorphisms correlate with social aptitudes in children with and without autism (Parker et al. 2014). Thus, low baseline OT levels are not necessarily a biomarker of social dysfunctions in ASD, but instead a general biomarker of sociability.

A recent meta-analysis reported significant genetic associations between ASD and the OTR SNPs (single-nucleotide polymorphism) rs7632287, rs237887, rs2268491, and rs2254298 (LoParo and Waldman 2015). Importantly, one of these SNPs (rs237887) was found to be strongly associated with recognition memory in individuals with ASD, their parents, and their siblings (Skuse et al. 2014), suggesting a critical role of the OT system in social recognition.

In terms of exogenous effects of OT, we showed that intranasal administration (24 IU) of OT to adults with ASD (men between 18 and 45 years old) enhanced their attention to faces and improved the social recognition of implicit cues within an interactive social game in a within subject placebo-controlled study (Andari et al. 2010). During the first experiment, we recorded participants' eye movements (via an eye tracker) while they performed simple tasks on the computer screen (gender identification and detection of the direction of eye gaze of facial stimuli). IN-OT significantly enhanced the gaze duration on the face, and the eye region in particular, in ASD. In a second experiment, we developed a socially interactive computerized ball-game during which participants played with three other fictitious players. We manipulated the degree of cooperation between players and between each of the players and the participant in order to create three different social profiles based on players' degree of reciprocity (good, bad, and neutral). While healthy subjects sent significantly more ball throws to the good player compared to other players, adults with ASD sent the same amount of ball throws to all three players in the placebo condition. We found that IN-OT significantly enhanced the number of ball throws toward the good player compared to other players in individuals with ASD. This was accompanied by a significant increase of feelings of trust and preference toward the good player. Hence, when treated with IN-OT, participants with ASD were able to recognize implicit social cues during the social game, display appropriate emotional responses toward players, and respond appropriately based on the different social profiles of the different players. More recently, in an fMRI study, individuals with ASD playing the social ball-toss game showed enhanced BOLD activity of visual areas (inferior occipital lobe) during the perception of players' faces following IN-OT intake (Andari et al. 2016), a finding that is in line with the OT-dependent attention increase to social cues. IN-OT reduced amygdala and hippocampal activity during the social ball-game in a context-dependent fashion and increases the activity of orbitofrontal and insula regions during the interaction with the fair and the unfair player. It is possible that IN-OT enhances attention and emotional sensitivity to these cues and increases social recognition in ASD by modulating the neural systems involved in perception and socio-emotional processes.

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In line with the above findings, several lines of research have shown improvements in socio-emotional skills in ASD following IN-OT. IN-OT enhances emotion recognition and theory of mind in ASD (Aoki et al. 2014; Guastella et al. 2010), and gaze to the eyes in ASD and in healthy subjects (Auyeung et al. 2015). At the neural level, IN-OT enhances anterior insula activity during inference of others' emotions (Aoki et al. 2014).

Researchers also investigated the effects of chronic intake of IN-OT in young males with ASD and found that it is safe and showed some improvements in clinical scores (Tachibana et al. 2013), but not in other measures such as the child behavioral checklist. Other reports showed no direct benefit of chronic IN-OT intake following 8 weeks of treatment to young children with ASD on Social Responsiveness Scale (SRS) or social cognition measures, but instead showed placebo effects on caregiver's perception of their children (Guastella et al. 2015). In another subsequent study from the same group, researchers found significant improvements on SRS outcome following chronic administration of IN-OT in children with ASD using a cross-over clinical trial design (Yatawara et al. 2016). These promising findings are supported by numerous studies performed in Japan showing positive outcomes at the behavioral and neural level with IN-OT in ASD. For instance, Watanabe et al. (2015) showed that IN-OT significantly reduced autism core symptoms in social reciprocity following a 6-week intranasal oxytocin regimen (Watanabe et al. 2015). The improvement was accompanied by increased resting state functional connectivity between ACC and dmPFC in addition to an increased eye gaze during a social-judgment task. More recently, researchers showed a dose-dependent effect of IN-OT in behavioral improvements in ASD. A larger dose of IN-OT (>21 IU) per day was more effective than a smaller dose (<21 IU) per day in terms of Clinical Global Impression-Improvement scores in ASD. They also found that a genetic SNP in the OTR gene (rs6791619) predicted IN-OT effects on CGI-scores (but only <21 IU). Promising results have been shown with IN-OT, but more research studies with target engagement are needed to optimize its therapeutic effects in ASD.

In addition to the promising avenues for OT in ASD, there are increasing evidence for the role of OT in reducing anxiety, fear, and stress, in part by dampening amygdala activity (Bethlehem et al. 2013; Domes et al. 2007a; Labuschagne et al. 2010; Meyer-Lindenberg et al. 2011; Petrovic et al. 2008). Researchers have investigated the role of IN-OT in enhancing or facilitating the extinction process of learned fear (Acheson et al. 2013; Eckstein et al. 2015) and in reducing anxiety in patients with anxiety disorders (Dodhia et al. 2014; Gorka et al. 2015; Labuschagne et al. 2010). IN-OT restores functional connectivity between subcortical regions such as amygdala and frontal areas, including the ACC and mPFC, and reduces the heightened amygdala reactivity to fearful faces in patients with generalized anxiety disorders (Labuschagne et al. 2010). These results are in line with preclinical studies in rodents showing that administration of OT before fear conditioning decreased fear expression and facilitated fear extinction, and that blockage of OT neurotransmission before conditioning impaired fear extinction (Toth et al. 2012). However, the authors also showed that the infusion of OT after fear conditioning and before extinction instead impaired fear extinction in mice and rats. These results can provide more insights on the future OT-based therapeutic strategies that can be used for treating patients with posttraumatic stress disorder.

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6 Precision Medicine Perspective for OT

Despite the promising avenues of the OT system in alleviating social dysfunctions and anxiety disorders, there is a substantial need for additional translational preclinical and clinical investigations of the mechanisms of action of OT in order to better evaluate its targeted effects on behavior. There is a recent movement in the literature to study the different factors that underlie the individual variation in OT's effects on social behavior and brain function, including childhood experiences, personality, attachment style, and OTR polymorphisms, and evaluating the efficacy of OT in neuropsychiatry is very complex. There are several opportunities with IN-OT and other drugs that stimulate endogenous release of OT in the brain to promote social functions. However, there is a substantial need for a precision medicine approach in studying its effects in both human and animal studies. Preclinical work should rely more on targeted behavioral outcome measures that better model the complexity and the heterogeneity of social disorders such as autism. For instance, currently, in order to determine that a particular rodent model with a particular gene manipulation is an animal model of autism, the animal needs to fail the simple social interaction or social discrimination task and display less social approach. These tests do not necessarily take into account the complexity of the social deficits and the heterogeneity of behavioral phenotypes of individuals on the autism spectrum. More sophisticated assays are needed to better understand the neurobiological underpinnings and genetic mechanisms of social behaviors that are more relevant to autism and other disorders. Also, in clinical and human-based studies with relation to OT, there is a need for additional hypothesis-driven studies that rely on mechanisms of action of this neuropeptide and its function. Lastly, there is a need for more theoretical frameworks that define the complexity of social functioning, more objective outcome measures that can delineate genuine behavioral and emotional responses, and more replications in order to avoid false positive outcomes.

Anxiety symptoms (including traits of anxiety, generalized anxiety disorder, social anxiety disorder, and posttraumatic stress disorder) as well as social disorders (including lack of emotional and cognitive empathy, lack of intuitive understanding of others' hidden intentions, and social reciprocity) are highly complex and vary from one individual to another, even within the same disorder. There is a need for a more objective and specific classification of the different symptoms of a disorder. The development of objective outcomes measures that capture genuine intentions and responses is essential. This will provide essential data for phenotype specificity, which can lead to a better classification of behavioral phenotypes. Only after understanding the phenotype of a particular deficit and measuring it with the appropriate outcome measure we can continue to explore neural mechanisms and biological underpinnings of a disorder. There is an increasing body of evidence showing that drugs and bio-behavioral treatments should be personalized and that they should account for basic individual characteristics, genetic and epigenetic factors, neurobiology, early life environment, and different dosage and forms of drugs. Adoption of such a precision medicine approach would ensure significant progress in neuropsychiatry. Therefore, with careful psychological and behavioral screening, genetic testing, brain imaging, and screening for immune factors, we could design therapeutic interventions that are optimal for a group of patients. Heterogeneity may be precisely the reason that the

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outcome of the majority of drug-based clinical trials represents small-to-moderate effect sizes or to negative results and lack of replications. Instead of avoiding heterogeneity within social disorders, we should better understand it and use targeted therapies that can help alleviate some of the main symptoms and lead to a better future for these patients and their families.

We encourage more translational work and fruitful liaisons between clinical and preclinical fundamental research, behavioral science and neuropharmacology, neuroimaging, biochemistry, and molecular genetics in order to harness these complex brain disorders and provide help for patients and families.

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