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Interplay between Oxytocin and Sensory Systems in the Orchestration of Socio-Emotional Behaviors.

Running title: Oxytocin: Sensations and Sensibility

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• This work is dedicated to the memory of Prof. Dr. Peter H. Seeburg (1944-2016), a founding father of molecular neuroendocrinology and molecular neuroscience, who enthusiastically advised and supported our initial studies on the axonal oxytocin release in the brain.

Summary

The neuropeptide oxytocin (OT) attracts the interest of neuroscientists, psychologists, and psychiatrists due to its capacity to modulate emotional and social behavior. Although much has been published on the effects of OT on brain regions and mechanisms at the origin of these processes, its role in sensory processing, so important for detecting social context with sufficient accuracy and sensitivity, has been much less studied. In the present review, we summarize evidence for OT modulation of sensory processing and, conversely, effects of sensory input on endogenous OT signaling. We start with invertebrates and work our way up the phylogenetic tree to mammals describing the reciprocal regulation between sensory and OT systems. With this review we aim to provide a systematic analysis of the current knowledge on this reciprocal regulation and the role it may play in social and emotional behaviors.

Organization of the Central Oxytocin System: Peptides and Their Production Sites

The nine amino-acid neuropeptides oxytocin (OT) and arginine-vasopressin (AVP) and their homologues have been found in representatives of five *phyla* of invertebrates (echinoderms, mollusks, annelids, arthropodes, and nematodes), indicating that the basis for this hormonal neuropeptide system has been laid in evolution more than 700 million years ago (Beets et al., 2013). Although the presence of OT/AVP-like systems has been reported in numerous invertebrates (Gruber, 2014; Gruber and Muttenthaler, 2012), sequences encoding OT/AVP-like genes are surprisingly missing in the genomes of “social” insects, such as honey bees, termites and ants (Stafflinger et al., 2008). For these species, which already display complex communicative/social behavior, it has been hypothesized that competing hormonal systems (such as biogenic amines) have taken over the function of OT/AVP signaling in the course of evolution (Stafflinger et al., 2008).

While lacking in insects, the organization and physiology of the OT/AVP-like system has been characterized in other invertebrates such as nematodes. Neurons expressing nematocin, the homolog of OT/AVP in *C. elegans*, include several types of sensory, inter- and motor neurons located in the head, ventral cord and tail of the worm. Altogether, these neurons correspond to ~5% of all neurons, which is far more than the relative number of OT/VP neurons in vertebrates and especially in mammals. This phenomenon can be explained by more compact and multifunctional organization of the nervous system in *C. elegans* compared to the CNS of vertebrates, which evolved in the direction of expansion of the brain size and an anatomical and functional specialization of neuronal types (Markram et al., 2015). In contrast to mammalian OT/AVP neurons, nematocin neurons often exhibit multimodal features. For example, some of nematocin neurons have sensory (ciliated) endings and processes that could release nematocin-containing granules into the *pseudo-coelomic* fluid, suggesting that these ancient "OT/AVP neurons" may have both sensory and neuroendocrine capacities. The recent findings from the Garrison laboratory indicate that some neurons can release nematocin systemically into the *pseudo-coelome*, while other neurons are

capable of releasing this neuropeptide synaptically or peri-synaptically (Jennifer Garrison, personal communication). These distinct systemic or synaptic releasing types of nematocin-expressing cells may have evolutionarily developed in vertebrates into neuroendocrine (magnocellular) cells and non-neuroendocrine (parvocellular) cells (Wircer et al., 2017). The parvocellular OT neurons in mammals have also been named "pre-autonomic" neurons (Swanson and Sawchenko, 1980), but in this review, we will not use this term, because the function of parvocellular neurons is not limited by the modulation of autonomic nervous system activity (Althammer and Grinevich 2017).

Similar as in worms, neurosecretory neurons of basal vertebrates are closely associated with the ventricular system, protruding ciliated dendrites into the ventricular lumen. Cilia are known sites of active exocytosis and clathrin-dependent endocytosis (Pedersen et al., 2016). In neuroendocrine cells, they may mediate release or uptake of neurohormones/peptides to/from the periphery/blood and cerebro-spinal fluid (CSF). The membranes of cilia contain distinct classes of G protein-coupled receptors, including those sensitive for neuropeptides that may be found in the CSF or intercellular space. For example, it has been shown that Kissr1 is localized on cilia of GnRH neurons, enhancing kisspeptin-mediated GnRH neuron activation (Koemeter-Cox et al., 2014). OT neurons of basal and advanced vertebrates also carry cilia (Lafarga et al., 1980), but their function has not been precisely elaborated yet.

During evolution the OT system seems to have transformed from a few scattered OT-like neurons in invertebrates to clearly segregated nuclei – the preoptic nucleus in basal vertebrates and the supraoptic (SON), paraventricular (PVN) and accessory nuclei – in advanced vertebrates (Knobloch and Grinevich, 2014). In the mammalian hypothalamus, as in worms, two types of OT neurons have been identified. These are referred to as magnocellular OT neurons (~ 8.000 cells in rats, and ~ 50.000 cells in humans) and parvocellular neurons, the latter representing less than 3% of OT cells (Althammer and Grinevich, 2017). It should be noted that in mole rats

(*Fukomys anseli)* OT neurons have also been found in the posterior mammillary nuclei of the hypothalamus. However, in this species the projection sites of these neurons remain to be determined (Valesky et al., 2012).

Magnocellular OT neurons project to the posterior pituitary to release OT for systemic circulation (Burbach et al., 2001). At the same time, these neurons (or a fraction of them) send out collaterals to more than 50 different forebrain structures (Knobloch et al., 2012). Their local release of OT (Chini et al., 2017) can modulate brain region-associated behaviors, such as contextual fear responses (via action at the central amygdala; (Knobloch et al., 2012), social fear responses (via action in the lateral septum, (Menon et al., 2018)), and social recognition (via anterior olfactory nucleus, AON; (Oettl et al., 2016). Conversely, parvocellular OT neurons mostly project to the spinal cord and hindbrain structures, affecting processing of somatosensory information (Eliava et al., 2016) and modulating social reward (Hung et al., 2017). Intriguingly, this clear-cut difference in projection targets has become less obvious in light of recent findings that parvocellular OT neurons also project within the forebrain (Eliava et al., 2016) and that magnocellular OT neurons give rise to projections terminating in the midbrain (Hung et al., 2017).

While OT neurons in the mammalian brain are exclusively located in the PVN, SON, and accessory nuclei of the hypothalamus, AVP neurons are also found in various extra-hypothalamic forebrain nuclei, including the bed nucleus of *stria terminalis* (BNST) and the medial nucleus of the amygdala (De Vries et al., 1984). In a transgenic rat line, expressing AVP-GFP fused protein under the control of the AVP promoter (Ueta et al., 2005), GFP signal was also found in neurons of the olfactory bulb, where it modulates the processing of olfactory social signals (Tobin et al., 2010). Very recently, the same group led by Ludwig also showed that a small fraction of ganglionic cells in the retina expresses AVP and, through its projections to the suprachiasmatic nucleus, modulates circadian rhythmicity (Tsuji et al., 2017). This finding is in line with previous reports that AVP-like neurons in the annelids and fish co-express

opsins suggesting the direct coupling of peptide secretion to the light cycle (Tessmar-Raible et al., 2007).

Oxytocin and Vasopressin Receptors

In most vertebrates, there are four receptors with specific sensitivities to OT and AVP homologues. These receptors are thought to have emerged by two rounds of early vertebrate genome duplication of their shared genomic region (Lagman et al., 2013). In mammals, they are known as the OT receptor (OTR) and the AVP - V1a, V1b and V2 receptors. Although OT has highest affinity for the OTR (EC_{50} 1-100 nM) (Busnelli et al., 2012), a significant cross-sensitivity is present for the other receptors. Conversely, vasopressin also displays high affinity for the OTR. Although hormonal actions of AVP and OT in the periphery may thus allow cross-reactivity for different functions, in the brain a higher specificity is probably obtained as a result of their targeted delivery to specific receptors through a wide system of fibers that originate from their respective production sites. Consistently, OTR expression in the brain is typically matched by innervation of fibers targeting OT to its receptor. However, it remains possible that OT is also delivered and active in regions where vasopressin receptors are expressed and *vice versa*.

As with regard to the development of the expression of these receptors with age, relatively little is known. A recent study in mice showed a transient expression of OTRs throughout the neo-cortex peaking at postnatal day 14 and decreasing gradually to much lower levels at day 60 (Hammock and Levitt, 2013). This follows similar transient expression in voles (Wang and Young, 1997) and in rats where this transient cortical expression seems to be limited to the midline cingulate cortex (Shapiro and Insel, 1989; Tribollet et al., 1989). Interestingly, this parallels the major time period of synaptic wiring and pruning in subcortical and cortical structures (Levitt et al., 2003; Li et al., 2010), suggesting a role for OT during the development of these structures. This stands in contrast to the apparent continuous high levels of OTR expression in both rats and mice in the accessory olfactory bulb (AOB), ventral subiculum and central amygdala (CeA) (Hammock and Levitt, 2013;

Shapiro and Insel, 1989; Tribollet et al. 1989). OTR expression is also influenced by the release of sexual hormones, and it is possible that OTR expression and activation partially mediates gender specific adolescent brain development (Miller and Caldwell, 2015; Uhl-Bronner et al., 2005). In the present review, we have focused our attention on the involvement of OT in regulating sensory signaling. For a role of VP in this regard, we refer the reader to a recent review by Bester-Meredith and colleagues (Bester-Meredith et al., 2015).

Evolution of Oxytocin Signaling in Sensory Processing

Neurons producing OT/AVP homologs in annelids (and fish) express common tissue-restricted microRNAs and a cell-type-specific combination of transcription factors homologous to the vertebrate *orthopedia*, *retina homeobox* and *nk2.1* genes (Tessmar-Raible et al., 2007). Expression of these transcription factors together with morphological peculiarities, such as ciliated processes, specify the identity of an ancient OT/AVP neuronal cell type possessing dual sensory-neurosecretory properties. Sensory-neurosecretory cells may thus represent an ancient neuronal architecture for the magnocellular OT/AVP-related signaling system, conveying sensory input to changes in physiology or behavior through neuropeptide secretion (Beets et al., 2013).

In invertebrates, the involvement of OT-like signaling into sensory modulation has been reported in the nematode *C. Elegans*, where the OT/AVP homologue nematocin can affect processing of gustatory cues (salt chemotaxis) (Beets et al., 2012) and can modulate thermal and mechanical cues to promote reproductive behavior (Garrison et al., 2012). However, the precise neural circuits underlying these behavioral effects of nematocin have not been dissected.

In non-mammalian vertebrates, information on the contribution of OT in modulation of sensory processing is very limited. Due to the expression of OT/AVP-receptors in cells of the lateral line system in fish (Hausmann et al.,

1995; Mahlmann et al., 1994) it was proposed that these neuropeptides can modulate mechano-sensory perception of water motion and pressure gradients, and thereby contribute to collective behavior in school of fish. Evidence for the involvement of OT-like peptides in modulation of vocal signals has been obtained in unique, vocally-communicating plainfin midshipman fish by Goodson and colleagues (Goodson and Bass, 2000). The authors showed that centrally infused isotocin modulates social vocalization in a sex- and type-specific manner. More specifically, isotocin applied to the preoptic area of the anterior hypothalamus (the primary regions for endocrine and behavioral integration, e.g. in vocal production) modulates reproduction-unrelated social vocalization in females and type I males, both of which typically do not display parental care. In addition, the authors demonstrated the presence of OT-like (isotocin-ergic) axons in the ventral telencephalon and hypothalamic and brainstem regions that are components of ascending auditory pathways, suggesting a role for OT in modulation of auditory signal processing (Goodson et al., 2003).

In songbirds, the expression of OT-like (VT3) receptors within auditory brainstem nuclei and vocal motor neurons also suggests the contribution of this neuropeptide in processing of auditory signals and possibly in song learning (Klatt and Goodson, 2013). Since OTR expression has also been found in the motor nuclei of cranial nerves of rodents and marmosets, it is possible that OT directly and rapidly influences various motor and autonomic responses to social stimuli. Rodents, which primarily use olfactory inputs for social recognition and social memory, present as a common feature a high level of OTR expression in the olfactory system. In primates, OTRs are found in the nucleus basalis of Meynert and the superior colliculus, which modulate visual attention. This supports the hypothesis that OT acts in a *plethora* of different species at the most relevant sensory systems to regulate social behavior (Freeman et al., 2014).

In the sections below, we will treat the modulation of different sensory systems by OT with a primary focus on mammals. We will describe its modulatory effects starting for each system from the sensory organs up to the

different brain regions that are involved in further processing of sensory information. OTRs are often found in connected brain regions suggesting they may affect sensory processing by simultaneously acting at consecutive levels of each pathway. Furthermore, besides the direct effects of OT on connected regions, we have also found, in diverse sensory systems, projections from different regions of processing onto the hypothalamic regions that produce OT.

Oxytocin and Olfactory System

Modulation by OT has been found both in the main olfactory system, which processes odor signals, and the accessory olfactory system, which is important for detecting pheromones. Here we will discuss modulation of both types of olfactory processing in parallel.

Detection of ordinary odors not affecting reproduction starts with their binding to highly specific receptors expressed by olfactory sensory neurons, which, together with sustentacular cells, compose the olfactory epithelium (Figure 1A). Pheromones, on the other hand, bind to specialized receptors in the adjacent vomeronasal organ.

Expression of OTRs receptors has been found in the nasal cavity of mice at embryonic day 18.5 (Hammock and Levitt 2013). In primary cultures of the rat olfactory epithelium, intracellular calcium increases were induced by vasopressin through V1a receptors expressed at the apical side although a small effect may have been mediated through the OTR (Levasseur et al., 2004). Primary olfactory neurons of the nasal epithelia project to the main and accessory olfactory bulbs where modulation by OT has been described on different cell types that are part of intricate local circuitries: Inputs from the olfactory glomeruli arrive on the mitral and tufted cells (MCs) which are the main relay neurons to the olfactory cortex. MC dendrites make excitatory contacts with dendrites of inhibitory granule cells (GCs) whose dendrites, in turn, make further inhibitory synapses onto MC dendrites. This process it thought to lead to a lateral inhibition of surrounding MCs and thus to increase

the “signal-to-noise” ratio of incoming odors (Brennan and Kendrick, 2006; Yokoi et al., 1995). OTR mRNA has been found in both GC and M/TC layers (Vaccari et al., 1998; Yoshimura et al., 1993). Local stimulation of PVN neurons, similar to micro-ionophoretic injection of OT in the main olfactory bulb, leads to an increased spiking of GCs (Yu et al., 1996b). Spontaneous inhibitory currents in MCs (presumably originating from the dendritic contacts of the GCs) are decreased by local OTR activation (Osako et al., 2000). Conversely, spontaneous excitatory currents in GCs (presumably originating from the dendrites of MCs) are increased upon local OTR activation (Osako et al., 2001). These effects, in combination with a possibly underlying mechanism of synaptic depletion (see below, figure 4), may explain why OT in the olfactory bulb positively affects maternal behavior (Yu et al., 1996a).

Granule cells, furthermore, receive top-down glutamatergic inputs from the AON. It was recently demonstrated that OTR-mediated excitation of these projection neurons increases signal-to-noise ratio of odorant-evoked responses in the main olfactory bulb (MOB, increasing peak odorant responses of MCs while lowering background noise) (Oettl et al., 2016). Interestingly, although Oettl et al. (2016) reported expression of the OTR on these AON neurons, consistent with a direct effect of OT on excitability of these neurons, they also reported an indirect excitatory effect. Thus, OT also appeared to increase the frequency of postsynaptic excitatory currents in AON neurons suggesting, in addition, a presynaptic effect. The AON is known to project also to periglomerular cells, which can inhibit odor responses. OT effects on the AON neurons, although decreasing baseline activity in the M/T cells, increased odor responses, leading effectively to an increase in signal noise ratio. It is thought that OT, by exciting a subgroup of AON neurons that only projects to granule cells, can promote specifically transmission of socially-relevant odor signals (Oettl et al., 2016).

Further processing of socially relevant olfactory signals occurs in the medial amygdala (MeA), onto which projections from MOB and AOB converge and which relays these further to the BNST and septal nuclei (Pro-Sistiaga et al., 2007). The MeA forms, together with the BNST and nucleus *accumbens,* the

so-called "extended amygdala" throughout which OT and VP receptors are found in juxtacellular apposition (Pro-Sistiaga et al., 2007; Veinante and Freund-Mercier, 1997). In the MeA, OTR activation appears necessary for social memory formation (Lukas et al., 2013; Samuelsen and Meredith, 2011). Gur and colleagues found, in the rat, that stimulation of the AOB with theta bursts induced long-term depression in the MeA that appears to underlie the formation of social memory (Gur et al., 2014). Thus, the induction of this long-term depression occluded further formation of social memory and was absent in rats impaired in long-term social recognition memory as a result of social isolation. Furthermore, exogenous application of OT augmented its induction whereas an OTR antagonist prevented it.

In the BNST of female Syrian hamsters, male odors increase c-fos expression and lead to concomitant increases in vaginal markings, used to attract the males to the nest (Martinez and Petrulis, 2011). Central injection of OTR antagonists prevented increases both in c-fos and in the vaginal marking (Martinez et al., 2013). It is possible that these effects are mediated by OT projections from the PVN as recently identified by Dabrowska and colleagues (Dabrowska et al., 2011). Taken together, these findings provide interesting mechanisms through which neuromodulation by OT can affect social interaction and memory formation by its modulatory effects on olfactory signal processing.

In the rat, direct inputs from the MOB (as opposed to indirect pathways) have initially been reported onto neurons in the SON ((Smithson et al., 1989), Figure 2) and subsequently electrophysiological experiments even showed monosynaptic inputs. The identity of the postsynaptic target cells, however, remained unknown. More recently, inputs from the main olfactory bulb into the hypothalamus has been further characterized in mice and been found to terminate onto AVP producing neurons in both the PVN and in the SON, but not onto OT producing neurons (Bader et al., 2012). Projections from the olfactory system onto OT neurons in the PVN have, however, been reported from subsequent levels of processing in the olfactory system. Thus, corticotropin releasing hormone (CRH)-expressing neurons in the BNST have

been shown to project onto OT neurons in the PVN which project, in return, back to GABAergic neurons in the BNST that can inhibit these very same CRH neurons (Dabrowska et al., 2011). Other possible intermediary areas that may project to hypothalamic OT neurons are the anterior olfactory nucleus, piriform cortex and olfactory tubercle (Price et al., 1991).

Oxytocin and Gustatory System

In mammals, taste buds on the tongue allow for precise discrimination between taste modalities: Salt, sweet, bitter, sour and umami. Except for sour and umami, the other taste modalities appear to be modulated by OT. OTRs can already be found at the earliest stage of taste signaling, namely in the taste buds of the tongue papillae (Figure 1B). In these taste buds three types of cells are important for detection of tastants. Type I cells appear to serve glia-like functions, such as clearance of glutamate and ATP (Bartel et al., 2006; Lawton et al., 2000), and redistribution of K^+ (Dvoryanchikov et al., 2009) and have been suggested to play a role in salt taste. Type II cells can detect bitter, sweet, and umami and type III cells detect sour taste (Roper and Chaudhari, 2017). By immunostaining tissues from OXTR-YFP knock-in mice and single cell RT-PCR, the group of Chaudhari (Sinclair et al., 2015; Sinclair et al., 2010) found that OTRs are expressed in type I cells, where their activation can mobilize calcium, as well as in cells on the periphery of taste buds. Either directly or indirectly OT could thus affect different taste sensing. Recent findings in human taste cells isolated from fungiform papillae (basically the experimenter rips off a taste bud from his/her own tongue or that of a volunteer) have shown that human bitter taste cells may also be sensitive to OT (Hochheimer et al., 2014), suggesting OTR expression in type II cells. Although type II cells can also detect umami and sweet taste, there seems to be no evidence that OT could also be involved modulating the perception of these tastants (but see below). On the other hand, bitter taste receptors have, interestingly, also been detected in OTR expressing uterine smooth muscle cells (Zheng et al., 2017).

In principle, the source of OT for OTR-mediated modulation of gustatory stimuli can be both blood or saliva as local synthesis of OT in the tongue has not been reported. However, the possibility that systemic OT reaches sensory cells in the tongue (and other peripheral sensory receptors) remains in need of further investigation requiring the employment of radioactive- or fluorescent marker-tagged OTR ligands infused into the blood.

Besides the expression of OTRs in the tongue, OTRs can also be found further down in the gastrointestinal tract, namely in mucosal epithelial cells of the gut (Welch et al., 2009): OTR mRNA was detected in the developing rat epithelium between P0 and P15, and OTR-immunoreactivity appeared in the enterocytes lining growing villi (although the specificity of used antibodies against OTR is doubtful). Nevertheless, these and above findings raise the question regarding the origin of the OT that reaches these receptors. In this regard, the finding that OT has also been detected in mother milk (Takeda et al., 1986) opens an interesting role for OT-mediated functions of breast feeding. Alternatively, local endogenous sources of OT may exist. Though apparently absent in the tongue (Sinclair et al., 2010), in the gut, Welch et al. (2009) have identified OT-immunoreactive neurons.

Functionally, Chaudhari's group reported that i.p. administration of OT in mice can specifically decrease sweet intake (Sinclair et al., 2015). Mice lacking OT (via global knockout) do consume specifically more sweet, but also non-sweet carbohydrate solutions without affecting intake of palatable lipid emulsion (Sclafani et al., 2007). These effects did not seem to be caused by changes in appetitive drive, but it is possible that they are related to post-ingestive satiety (Sclafani et al., 2007). On the other hand, Sinclair et al. (2015) found that i.p. OT did decrease the licking rate of sucrose solutions suggesting rather a direct orosensory detection effect. Whether the OTRs on the taste buds themselves play a role in this (i.e. whether the detection of the taste molecules is affected) or whether OT signaling in higher brain centers is able to selectively affect this intake is not yet clear.

It seems that OT is also involved in regulating intake of salt-rich nutrition. In fact, OTR blockade causes water depleted rats to consume increased amounts of water containing salt at a concentration not consumed when they are not water-deprived (0.5 M NaCl) (Blackburn et al., 1992a; Blackburn et al., 1992b). Similarly, OT KO mice deprived overnight from water or maintained in metabolic cages consumed more water with high salt concentrations (0.35-0.5 M) than wild type mice (Amico et al., 2003; Amico et al., 2001; Puryear et al., 2001). These differences were not found when KO mice were longer maintained on such diets (Vollmer et al., 2006).

While the above-mentioned effects of OT on intake of sweet and salt receptor ligands may result from modulation at the taste receptor level, it is also possible that they are caused by motivational (hedonic) component of food intake as a result of OT modulation in higher order brain centers, such as the ventral tegmental area and nucleus accumbens (Herisson et al., 2016; Mullis et al., 2013). In respect to effects on homeostasis, it has been shown that OT decreases food intake by affecting complex signaling pathways in the brainstem, which control satiety (Atasoy et al., 2012). More specifically, parvocellular OT neurons modulate the activity of the nucleus *tractus sollitarius*, which receive vagal input from cholecystokinin-sensitive fibers ascending from the intestine (Sabatier et al., 2013). On the other hand, a wide range of molecules, including neuropeptides, GABA, and glutamate originate from neurons of the arcuate nucleus, intestinal peptides and peripheral hormones, is capable to modulate the activity of OT neurons. Since this rapidly growing (and at times controversial) field does not match the focus of our review, we address the readers to the following recent works (Fenselau et al., 2017; Garfield et al., 2015; Ho et al., 2014; Motojima et al., 2016; Ong et al., 2017; Shah et al., 2014).

OT also seems to play a role in memory formation for food intake, in particular in conditioned taste aversion (CTA). CTA can already be found in worms which, normally attracted to salt, will start avoiding salt if it is paired with the absence of food. In *C. elegans* this CTA is lost when nematocin - the worm equivalent of OT - or its receptor NTR-1, is lacking in the chemosensory ASH

neurons (Beets et al. 2012). These neurons seem to promote avoidance behavior at high salt concentrations and one model proposes that CTA leads to a sensitization of these avoidance neurons to lower salt concentrations (Hukema et al., 2006) which may be mediated by nematocin signaling (Beets et al., 2013). Interestingly, this nematocin signaling interacts with serotonergic and dopaminergic neurotransmission, two signaling pathways that are also affected by AVP and OT in vertebrates. In rodents, CTA has been linked to synaptic plasticity in the amygdala and in mice OT has indeed been found to affect acquisition of CTA (Olszewski et al., 2013). To what extent this involves effects of OT in the amygdala, however, remains still unclear, since in particular the basolateral part of the amygdala is important for CTA (Molero-Chamizo and Rivera-Urbina, 2017), whereas OTRs have mostly been found in the central amygdala (Huber et al., 2005).

Oxytocin and Somatosensory System

The effects of OT on somatosensory processing are among the most extensively studied due to the very profound analgesic effects of the neuropeptide. However, OT modulates neuronal activity of structures involved in processing of both nociceptive and non-nociceptive pathways, which largely overlap at peripheral and central levels (Boll et al., 2017). Therefore, it is difficult to discriminate OT effects on non-painful vs. painful stimuli.

The somatosensory system is composed by two components: trigeminal (head) and body compartments. The trigeminal nerve with its three branches, the ophthalmic, maxillary and mandibular nerves, represents the largest of the cranial nerves and is involved in sensory perception (temperature, touch) and motor functions (biting, chewing, facial expression) of the face. Its three branches converge on the trigeminal ganglion, enter the brainstem via a single sensory root and convey information to the trigeminal motor nucleus and the three sensory trigeminal nuclei (the mesencephalic, principal, and spinal) residing in resp. the midbrain, pons and medulla, respectively (Walker, 1990). While the motor nucleus predominantly innervates facial muscles, essential for mastication (Inagaki et al., 1987), the three sensory nuclei

innervate various targets in the brain stem and spinal cord (Cechetto et al., 1985; Ruggiero et al., 1981; Zeng et al., 2011), some of which directly modulate the hypothalamic OT system via noradrenergic inputs (Brown et al., 1998; Raby and Renaud, 1989; Shioda and Nakai, 1992). OTR expression has been detected in the trigeminal ganglion of rats (Tzabazis et al., 2016) and the spinal trigeminal nucleus of rats (Murata et al., 2011), primates (Freeman et al., 2017; Schorscher-Petcu et al., 2009) and humans (Loup et al., 1991). This suggests in mammals a modulatory role of OT at various levels of the trigeminal sensory processing pathway (Figure 2, upper panel). In line, it was recently shown that the PVN provides prominent innervation to the spinal trigeminal nucleus (Abdallah et al., 2013). Although the authors provided no further specification of the cellular nature of those neuronal projections, it seems plausible that some of them represent parvocellular OT neurons, which have been described to innervate various brain stem regions (Swanson and Kuypers, 1980; Swanson and Sawchenko, 1980) as well as the spinal cord (Eliava et al., 2016). Studies on isolated skull preparation that includes the dura mater and trigeminal ganglion showed that ex vivo application of OT inhibits the release of calcitonin gene-related peptide (CGRP), typically released from neurons of the trigeminal ganglion and a major component of migraine attack, thereby decreasing responses of neurons to noxious stimuli (Tzabazis et al. 2016). These results suggest that OT may decrease responses of neurons of trigeminal ganglion in vivo and potentially attenuate migraine". Similarly, orofacial mechanical hypersensitivity, as a result of partial ligation of the maxillary infraorbital nerve, has been shown to be alleviated by OT via actions on the V1a receptor in rat trigeminal ganglia (Kubo et al., 2017), following a V1a receptor upregulation (OTRs showed no such upregulation) .. An interesting study of Dubois-Dauphin and colleagues (1985) revealed that lesions of the mesencephalic lateral tegmentum disrupt the OT-dependent milk ejection reflex in rats, while retrograde labeling with horseradish peroxidase revealed that the spinal trigeminal nucleus provides innervation to this structure (Dubois-Dauphin et al., 1985). These findings suggest how the modulatory effects of OT in the trigeminal nucleus may also play a role in the milk reflex.

In newborn rats, i.p. injections of OT decreased pain sensitivity, while injections of an OTR antagonist enhanced pain sensitivity in newborn, but not in two-days old pups. OT reduced GABA-evoked calcium responses in isolated neonatal trigeminal neurons, which suggested to the authors a depolarizing action of GABA resulting from an elevated intracellular chloride concentration that was reduced by OT (Mazzuca et al., 2011). These results suggest that OT influences pain and sensory processing during early development (Fuchs et al., 1992), potentially already at late embryonic stages via interaction with maternal OT through the placenta. In fact, the development of the trigeminal system is completed before birth: Vibrissae follicles in the rat embryo resemble the ones in adult already at E18 (Erzurumlu and Killackey, 1983), papillae formation of the tongue is completed around E19-E21 (Mbiene and Mistretta, 1997; Mistretta et al., 2005), and respective trigeminal gustatory pathways are functional around E20 (Mistretta et al. 2005). Given that OT is present in breast milk (Higashida et al., 2017; Takeda et al., 1986), it is tempting to speculate that the oral supply with maternal OT is involved in the priming of sensory trigeminal pathways, which enables pups to develop adequate responses to pain, temperature, and gustatory processing.

In periphery, OT is capable of activating C-fibers in the skin, exerting long-lasting inhibition of sensory (wide dynamic range, WDR) neurons in the spinal cord (Gonzalez-Hernandez et al., 2017) (Figure 2, lower panel). A similar action has been proposed for OT in neurons of the dorsal root ganglia (DRG), which express OTRs (Moreno-Lopez et al., 2013; Wrobel et al., 2011). Peripheral OT from the blood may directly act through OTRs on C-fibers in skin or on cell bodies of primary somatosensory neurons in DRG. This may underlie analgesic effects of OT, but also opens questions on touch-induced OT action during social interactions (Grinevich and Charlet, 2017).

In the spinal cord, OT axons innervate cells expressing OTRs in superficial layers preferentially in thoracic and lumbar segments in rats, monkeys and humans (Juif and Poisbeau, 2013; Schoenen et al., 1985; Swanson and McKellar, 1979). In rats, OTR activation in lamina II reduced the firing of

neurons with burst firing patterns, but had no effect on cells with single spike firings. The OT in the spinal cord appeared to stem from descending projections of PVN neurons as their stimulation reduced both Aδ and C evoked discharges in lamina II neurons (Miranda-Cardenas et al., 2006). *In vivo* studies by DeLaTorre and colleagues further showed that exogenous as well as endogenous OT - released through PVN stimulation - could reduce or prevent long-term potentiation in spinal wide dynamic range neurons (DeLaTorre et al., 2009). The analgesic role of endogenous release of OT in the spinal cord was further demonstrated and extended to lamina X, imc and ima: a few specialized (so called “parvocellular”) OT neurons can both control release of OT in blood from magnocellular neurons and directly target deep layers WDR neurons to ensure a coordinated and complementary effect of peripheral and central release of OT on nociception (Eliava et al., 2016). The role of this pathway for non-nociceptive stimuli is under current investigation by our groups.

In the midbrain, the periaqueductal grey (PAG) seems to be primary target of parvocellular PVN OT neurons (Campbell et al., 2009; Figueira et al., 2008). Two studies by Yang and his colleagues, have shown that painful stimulations are able to elevate the OT content in the PAG and that intra-PAG injection of OT can decrease pain (Yang et al., 2011a; Yang et al., 2011b). Furthermore, it was found that the rostral ventrolateral medulla (RVLM), as part of the PAG-RVLM–spinal cord nociceptive pathway, is highly innervated by PVN OTergic neurons (Lee et al., 2013; Mack et al., 2002) and the specific “pain-off” cells in the RVlM can be directly activated by OT (Wager and Atlas, 2015), although this hypothesis requires further investigation.

As a part of the forebrain, the amygdala is involved in the circuitry that assigns emotional significance to salient sensory information (Sah and Lopez De Armentia, 2003) and seems to represent a key structure in the emotional regulation of pain and associated mood disorders (Neugebauer et al., 2009). In human neuroimaging, painful stimulation has also been shown to change BOLD responses in the amygdala (Tracey, 2008), without dissociation into subregions. Studies in rats have revealed that the lateral part of the central

amygdala (CeL) contains many OTR-expressing interneurons whose exogenous as well as endogenous activation by OT attenuates threat responses (Huber et al., 2005; Knobloch et al., 2012). Intriguingly, the CeL also receives projections from CGRP neurons of the parabrachial nucleus and silencing these cells blocks pain perception and fear memory extinction (Han et al., 2015). This opens the possibility for an interaction between OT and CGRP on perception and anticipation of pain at the level of the amygdala.

In the cortex, OT neurons project axons to the somatosensory barrel cortex (Grinevich et al., 2016), which expresses moderate levels of OTRs (Campbell et al., 2009; Vargas-Martinez et al., 2014). Interestingly, whisker trimming in newborns decreased the number of OT-immunoreactive neurons in adult animals, whereas *in vivo* OT injection elevated excitatory synaptic transmission in multiple sensory cortices and rescued the effects of sensory deprivation. This suggests a function for OT in promoting experience-dependent cortical development ((Zheng et al., 2014) (see also outlook section of this review).

Despite accumulating evidence for targets and mechanisms underlying effects of OT on somatosensory processing, the origin of somatosensory input onto OT neurons remains unresolved. Anterograde tracing from the dorsal horn (Gauriau and Bernard, 2004) revealed only minor direct projections to the rat PVN, which targeted indiscriminatively OT-ergic and other cell types (Swanson and Sawchenko, 1983). On the other hand, polysynaptic retrograde tracing employing rabies virus injected into various peripheral organs, including the lip and nipple, demonstrated viral labeling of many brain structures and resulted in appearance of non-characterized back-labeled cells preferentially allocated in the parvocellular subdivision of the PVN (Gerendai et al., 2001). Although further studies are required to identify the main peripheral afferents to OT neurons in somatosensory processing, these findings clearly demonstrate that the neural basis for an interaction between hypothalamic OT neurons and somatosensory inputs from the periphery exists. However, extra-hypothalamic structures labeled with wild type rabies virus injected into the PVN rather represent ascending noradrenergic and dopamine-ergic pathways (via nucleus of *tractus solitarii*, ventral medulla,

zona inserta; (Onaka et al., 2015) and refs therein) than sensory pathways. In line with this, direct projections from PAG, sensory thalamic nuclei or somatosensory cortex to OT neurons have not been reported, and will require further investigation with the use of advanced cell type-specific viral techniques.

Oxytocin and Visual System

In rodents and primates (including humans) the expression of OTR has been documented in the retinal pigment epithelium (RPE) cells (Halbach et al., 2015; Mitre et al., 2016), where it depolarizes cells by blocking a potassium Kir 7.1 channel (York et al., 2017). Although the precise effects on vision remain to be determined, the RPE is thought to function as a facilitator of photo-transduction in the photoreceptors (Strauss, 2005). The source of OT for these receptors is not completely clear, although a recent study in rhesus monkeys suggests that it may be produced by cone photoreceptors (Halbach et al., 2015).

In the primary visual cortex, the presence of OTRs (but not OT axons) has been documented in rodents (Mitre et al., 2016). In this area, Xiang Yu's group demonstrated that the dark rearing from birth effectively reduced the frequency of miniature excitatory postsynaptic currents (mEPSCs) and spontaneous firing rates in layer II/III pyramidal neurons in adult mice. Importantly, in vivo, OT application significantly increased excitatory synaptic transmission and rescued the effects of dark rearing (Zheng et al., 2014). In primates, OTR expression and OT binding have been demonstrated in the superior colliculus, pulvinar and primary visual cortex, indicating that the visual system is a major target of OT in these mammals ((Freeman and Young, 2016). It is interesting that prominent OT binding in primates, but much more modest in rodents, has been found in the *nucleus basalis* of Meynert, which is providing dominant cholinergic input to the visual cortex. This discrepancy highlights the necessity of intensifying studies directed at unraveling the communication between the cholinergic and OT system (Boccia and Baratti, 2000; Gimpl et al., 2000) and their possible co-modulation of neuronal activity in the visual cortex. OT has been

demonstrated to increase a2-adrenoreceptor responsiveness in the *locus coeruleus*, a structure, which has been implicated in the facilitation of visual attention shifts (Petersson et al., 1998). In addition, recent work from Pajkossy and colleagues revealed that noradrenergic activity modulates explorative behavior and attentional set shifting (Pajkossy et al., 2017). Moreover, OT has been shown to be involved in mother-to-Infant gaze, as OT levels positively correlate with the duration of visual attention (Kim et al., 2014).

It should be noted that the modulation of visual processing by OT can also occur as a result of social contact between different species of animals, such as illustrated by human-animal bonds (Herbeck et al., 2018). In humans and domestic animals, 'domestication syndrome' (e.g. increased tolerance and pro-sociality, cooperative communication) coincides with increased peripheral OT release, as eye-contact between dogs and humans induced an elevation of OT in the urine of both species (Nagasawa et al., 2015). In humans, numerous publications have already shown that the intranasal administration of OT can stimulate eye contact, increase face recognition and potentiate communicative behaviors (Bartz et al., 2011). Similarly, intranasal OT application to dogs increases the time spent in mutual gazing (Nagasawa et al., 2015) and improves interpretation of directions to find hidden food (Oliva et al., 2015). Taken together, these results indicate that at least in primates and carnivores OT may predominantly modulate visual signal processing and visual attention shifts.

Looking back at evolution, the magnocellular preoptic area in fish, where isotocin is produced and which is considered as an equivalent to the mammalian PVN, receives direct retinal projections (Mangiamele et al., 2017; Springer and Gaffney, 1981; Vanegas and Ito, 1983; Wullimann and Northcutt, 1988). In mammals, a number of reports in different species, including humans, have demonstrated direct retinal projections to both PVN and SON and areas adjacent to these nuclei (Reuss and Fuchs, 2000; Sadun et al., 1984; Saeb-Parsy et al., 2000; Youngstrom et al., 1991). However, anatomical evidence for the termination of retinal axons on identified OT neurons appears, thus far, to be lacking.

In the suprachiasmatic nucleus (SCN), a hypothalamic region that directly receives projections from the retina, OT cells have not been reported for any mammalian species, except dromedary camel, in which a small population of OT cells of unknown function was found in this nucleus (El Allali et al., 2017). The termination of SCN axons on OT neurons of the PVN has been reported and the origin of OT innervation are VP cells (Caba et al., 1996; Egli et al., 2004), which are usually considered as a part of the intra-SCN circuit. Interestingly, the expression of circadian clock gene 1 is synchronized in VP and OT cells of the SCN and PVN respectively (Dzirbikova et al., 2011). In line with these observations, it was reported that OT mediates circadian regulation of birth time: global deletion of OT resulted in delivery of pups at random times of the day, while wild type mice delivered pups regardless shift in onset of the light (Roizen et al., 2007). These results suggest that OT plays a critical role in minimizing labor disruption due to circadian clock resetting (Roizen et al., 2007).

Oxytocin and Auditory System

Although modulation of auditory processing by the OT homologue isotocin has been reported in vocal fish, our knowledge about OT effects in the auditory system of mammals is rather limited. Among structures of the rodent auditory system, OTR expression has been reported only in the inner ear (cell types have not been identified: (Kitano et al., 1997), inferior olives (Vaccari et al., 1998) and auditory cortex (Marlin et al., 2015) (Figure 3B) although our findings failed to show OT projections to the latter e two regions (Knobloch et al., 2012). Functionally, a group led by Robert Froemke demonstrated a lateralization of OTR expression within the primary auditory cortex with an OT-mediated activation of left, but not right hemisphere, required for initiating pup retrieval (Marlin et al., 2015). Further, the pairing of pup calls with optogenetic stimulation of OT neurons in the PVN enhanced cortical responses by balancing the magnitude and timing of inhibition and excitation and led to an overall improvement of maternal pup retrieval (Marlin et al., 2015). The same group recently observed that OT neurons in mouse dams

are activated by pup calls (Robert Froemke, personal communication), opening a promising direction to further study auditory inputs to OT neurons.

Oxytocin and Interoception

Interoception, the sensory perception of the internal organs, has all prerequisites for modulation by OT and appears indeed sensitive to OT modulation. OTRs are present on a number of visceral organs such as the heart, the stomach and the intestines (Gimpl and Fahrenholz, 2001; Jankowski et al., 2004; Welch et al., 2009). These organs project in organotopic manner onto the posterior part of the insula, which is specifically involved in the primary sensory detection of interoceptive signals. They also project to the dorsal anterior cingulate cortex (Chang et al., 2012; Critchley, 2004; Kurth et al., 2010; Pollatos et al., 2007; Uddin et al., 2014; Zaki et al., 2012), where, in rodents, OTR expression has been detected (Shapiro and Insel, 1989; Tribollet et al., 1989). OT has indeed been hypothesized to facilitate integration between interoceptive and external cues (Quattrocki and Friston, 2014), although recent tests in humans do not seem to support this: After intranasal OT administration interoceptive accuracy decreased in favor of a switch towards attention to salient social cues (Yao et al., 2017).

Developmental Aspects of Sensory Perception Modulated by Oxytocin

Accumulating reports indicate that the OT system is also involved in the modulation of sensory functions in newborn mammals (Hammock, 2015). For instance, newborn mice lacking OT or OTR genes exhibited low rates of ultrasound vocalization induced by separation from their mothers (Takayanagi et al., 2005; Winslow et al., 2000). A similar observation has been made in mice lacking CD38, a transmembrane protein which regulates OT release, and which were characterized by decreased activity of the OT system and suppressed OT release (Liu et al., 2008). In contrast, the delivery of OT to the brain of isolated rat pups decreases ultrasound vocalization, induced by separation stress (Insel and Winslow, 1991).

Beside vocal signals, somatosensory stimuli seem to be crucial for the activation of the OT system during postnatal development. In line, Kojima and colleagues (2012) showed that the duration of skin-to-skin contacts of newborn rats with surrogate mothers after a period of separation was positively correlated with the concentration of OT in the hypothalamus (Kojima et al., 2012). Similarly, anogenital stimulation (mimicking mother's licking behavior) of newborn rats and rabbits induced immediate early gene c-fos expression in a subset of OT neurons (Caba et al., 2003; Lenz and Sengelaub, 2010). It is plausible that c-fos expressing cells are parvOT neurons, which can be activated by somatosensory stimuli and project to the spinal cord in adult rats (Eliava et al., 2016). Furthermore, in newborn rats it was shown (Lenz and Sengelaub, 2010) that anogenital stimulation also induced an increase in OT concentration in the spinal cord, suggesting that maternal licking may affect the maturation of sensory and autonomic spinal cord centers such as the sexually dimorphic spinal nucleus of the *bulbocavernosus*.

Sensory experience during the early postnatal period is also critical for the development and plasticity of various brain regions, especially of the somatosensory cortex (Broser et al., 2008; Feldman and Brecht, 2005). However, very little is known about the contribution of OT in cortical plasticity. In fact, only one report by Zheng and colleagues (Zheng et al., 2014) demonstrated that a microinjection of OT into the somatosensory (as well as into the visual) cortex rescued the excitatory synaptic transmission abolished by whisker trimming (or dark rearing) in newborn mice. In congruency, the authors found that the sensory deprivation reduced endogenous OT expression as well as OT concentrations in the PVN and cerebrospinal fluid. On the other hand, postnatal environmental enrichment increased OT synthesis and local OT concentrations in the cortices of sensory deprived mice and rescued the excitatory transmission. Altogether, the results of Zheng and colleagues (Zheng et al., 2014) suggest that sensory experience can regulate the activity of the central OT system and modulate synaptic transmission in the cortex during development. This might open new perspectives for studying the developmental role of OT in multiple circuit

components of all sensory systems, including the gustatory system, which displays OTR expression in the taste buds in newborn mice. Furthermore, the exploration of early life effects of OT might be essential for understanding the mechanisms of alterations of sensory processing and multi-modal integration occurring in humans afflicted with neurodevelopmental disorders (Marco et al., 2011). In this context, it is also important to mention that perinatally, OT already appears to play an important role, namely in increasing inhibition in the brain. GABA, the main inhibitory transmitter of the forebrain, can exert fast neurotransmitter actions by opening of ion channels that are permeable to chloride ions. Its inhibitory action stems from the entering of these negative ions into the cell, along a decreasing chloride concentration gradient, thereby hyperpolarizing the cell membrane. Before birth, however, the intracellular chloride concentration is so much higher, that it forces chloride ions to move out of the cell instead, thereby depolarizing the membrane and causing GABA to exert an excitatory effect (Tyzio et al., 2006; Tyzio et al., 2014). Interestingly, OT can decrease this prenatally-high intracellular chloride concentration. Thus, it was shown that during delivery, a surge of OT from the mother's circulatory system can temporarily decrease intracellular chloride in the foetus, leading to a transient perinatal inhibitory action of GABA. This is thought to reduce neuronal activity and metabolic demand, thus helping to protect fetal neurons from hypoxic insults during delivery (Tyzio et al., 2006). Interestingly, in several rodent models for autism spectrum disorder, this decrease in intracellular chloride fails to develop after birth, thereby leading to postnatal over-excitation and the appearance of an autistic phenotype (Tyzio et al., 2014).

As may follow from our review, the information about sensory input to OT neurons as well as OT modulation of sensory processing are rather limited except for a number of studies focused on effects of OT on somatosensory perception largely driving by the cure of pain. Below we list several emerging questions, which are essential not only for understanding the role of OT in sensory modulation, but also for sculpting the functional organization of the central OT system.

How Does Oxytocin Reach Its Targets in the Brain?

This seemingly naive question has been a source of dispute among OT researchers throughout the last decades. A leading theory assumes that after release in the hypothalamus, OT diffuses in the extracellular space to activate OT-receptors in other brain areas or throughout the brain (Landgraf and Neumann, 2004; Ludwig and Leng, 2006). However, we recently uncovered that OT neurons send long-range axonal projections to various forebrain regions, which provide local OT delivery (Eliava et al., 2016; Knobloch et al., 2012). This led us to an alternative hypothesis that OT released from single axons activates micro-ensembles of OT-sensitive neurons and modulates brain-region specific behaviors (Chini et al., 2017). Such a pathway should be more efficient than passive diffusion, as targeted release of OT allows for a rapid initiation of physiological and behavioral changes. On the other hand, the intranasal application of OT, which is used in many different studies nowadays, could reach its targets in the brain via at least two possible routes: 1) OT could pass through the nasal epithelium and transported by olfactory or trigeminal nerves into the brain or 2) OT could enter the blood circulation, act on peripheral OTR and stimulate endogenous release of OT in the brain via activation of ascending axons of autonomic and sensory neurons. Although many current studies testify in favor of the latter, the issue is still not entirely clear (Leng and Ludwig, 2016; Veening and Olivier, 2013).

Why is There an Anatomical Mismatch Between Reported Functions and Oxytocin Axons in Sensory Processing?

Up to now, there are no demonstrations of precise synaptic contacts from sensory pathways to OT neurons, except for SCN-OT neurons of PVN circuit. This may be due to technical limitations with retrograde tracing of synaptic input to OT neurons or with detection of synapses on OT neurons, employing immuno-electron microscopy. On the other hand, keeping in mind the long history of studying of magnocellular OT neurons (Gainer, 2012) in different aspects, especially anatomically, it is possible to speculate that these neurons naturally have rather modest direct or indirect input from sensory and other

systems. Indeed, the number of synaptic sites (reflected by number of spines) on dendrites of magnocellular OT neurons is ~ 500-600 per OT neuron (William Armstrong, personal communication), compared to ~ 10.000 synapses on a single pyramidal neuron of the hippocampus (Hosseini-Sharifabad and Nyengaard, 2007; Megias et al., 2001). On top of this, magnocellular OT neurons are dominantly suppressed by GABA (Decavel and Van den Pol, 1990) and therefore only very strong input may challenge their activity to trigger the release even of one single dense core granule ((Chini et al., 2017) and references therein). Therefore, it is tempting to speculate about the existence of “master” cells in the hypothalamus, which powerfully drive the activity of OT neurons. Potential candidates for such “master cells” are parvocellular OT neurons.

There are two lines of evidence for the role of parvocellular neurons in synchronizing OT neuron activity, at least in respect to somatosensory input. First, during suckling OT neurons of lactating dams exhibit specific pattern of activation – bursting – coinciding with the time of suckling. Anatomical data have shown that the injection of wild type rabies virus into the nipple of lactating rats results in the back-labelling of presumably parvocellular OT neurons in the PVN (Gerendai et al., 2001; Koves et al., 2012). Second, acute pain (nociceptive stimulus) induces the activation of parvocellular OT neurons, which via OT and/or glutamate drive magnocellular OT neuron activity and hence trigger massive OT release into the blood (Eliava et al., 2016). Despite their low number, these cells are equipped with elaborate dendritic trees, suggesting they may receive multiple synaptic inputs. Collaterals of axons synapsing on magnocellular OT neurons may sufficiently regulate their activity and release of OT in the sensory-related brain regions. Both lines of evidence should be further confirmed by additional experiments, applying different sensory stimuli and monitoring connectivity between parvo- and magnocellular OT neurons.

What Mechanisms Underlie the Oxytocin Modulation of Neurons of Sensory Systems?

Recent findings in neuronal circuits suggest an important role for OT in signal filtering and increasing signal to noise ratio in neuronal circuits (Figure 4, right panel). For instance, in the hippocampal region inhibitory interneurons that are excited by collaterals from glutamatergic projections between CA3 and CA1, express high levels of OTRs. While their activation in general serves feedforward inhibition of excitatory input from CA3 to CA1, they can also be long-term excited by exposure to OT (Owen et al., 2013). This results in a high frequency spontaneous release of GABA, eventually leading to a depletion of the synaptic GABA content and a loss of feedforward inhibition, as action potentials can no longer trigger GABA release. This loss of inhibition increases excitatory transmission between CA3 and CA1 (Owen et al., 2013). It is possible that such a mechanism (Figure 4B) applies to other systems in which OTRs are expressed on GABAergic neurons. For example, in the olfactory system (Figure 4A, left panel), OT, by depleting GABAergic inhibition in granule cells, may similarly change its filtering of socially relevant odors. To what extent this mechanism of depletion may indeed be found in other systems outside the hippocampal CA3-CA1 subregions remains to be assessed.

The above-mentioned effects of OT may also have consequences for the opening and closing of critical developmental periods. For example, in the development of ocular dominance plasticity in primary visual cortex, it has been proposed that there is a switch in the predominant learning cues from internally driven spontaneous activity to externally driven evoked activity without changes in plasticity rules (Toyoizumi et al., 2013).. In this model, the suppression of spontaneous-to-visual activity ratio induced by the maturation of inhibition is sufficient to explain the transition from pre-critical period to critical period plasticity. Considering the above-mentioned model in which OT may deplete inhibitory activity in favor of externally driven evoked activity, OT may directly affect the opening of a critical period. In this manner, OT could be an important factor contributing to the development and fine-tuning of sensory systems in the brain.

Conclusions

Over the last decade, numerous studies have demonstrated “pro-social” effects of OT on a wide range types of social behaviors, including sexual behavior, pair bonding, parental care, play behavior, and social communication between adult mammals (Lee et al., 2009; Neumann and Slattery, 2016; Young and Flanagan-Cato, 2012). However, only recently it has been demonstrated that the contribution of the endogenous OT system is crucial in the modulation of many social behaviors that depend on sensory cues (Marlin et al., 2015; Oettl et al., 2016; Wircer et al., 2017). Throughout evolution, it appears that OT homologs modulate very basic sensory signals, such as olfactory and gustatory signals, which are essential for reproduction (Beets et al., 2012; Beets et al., 2013; Oettl et al., 2016). Although effects of OT-like peptides on somatosensory system in invertebrates and non-mammalian vertebrates have not been explored, it is tempting to hypothesize that OT-based tactile sensory systems, such as mechano-sensation and pain also emerged very early in evolution (Smith and Lewin, 2009; Sneddon, 2004). In contrast, visual and auditory systems are among the last ones to have emerged during evolution (Hodos and Butler, 1997; Kaas, 1989, 2008; Niven and Laughlin, 2008) and a number of recent break-through studies reported modulatory effects of OT visual and auditory signals in different orders of mammals (Domes et al., 2013; Freeman and Young, 2016; Kirsch et al., 2005; Marlin et al., 2015; Petrovic et al., 2008; Somppi et al., 2017).

Although it has been recently shown that social behavior in mammals activates OT neurons (Hung et al., 2017), it is still unclear which sensory systems prevalently affect OT neurons during complex social behaviors of adults and during different periods of life. Furthermore, as it becomes evident that the organization of the OT system is rather complex (Althammer and Grinevich 2017), the cellular components mediating the activation of the OT system via distinct sensory-specific inputs should be determined in the future. Human mental disorders are often accompanied by alterations in sensory processing of various sensory stimuli ((Chang et al., 2014; Meyer-Lindenberg et al., 2011; Miller et al., 2009). Therefore, further studies are essential to understand whether a deficient OT signaling caused by altered sensory inputs

to OT neurons contributes to the pathophysiology of diseases that impair normal social behavior. It may turn out possible that pharmacological (Young and Barrett, 2015) or physical sensory stimulation (Uvnas-Moberg et al., 2014) of the endogenous OT system can be an effective treatment of social deficits in human patients (Meyer-Lindenberg et al., 2011). We hope that our overview of the regulation by OT of sensory processing and the potential stimulation by sensory input of OT signaling may provide some new insights into opportunities for treatment and for research in this field.

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FIGURE LEGENDS

Figure 1. Oxytocin, Olfactory and Gustatory Systems

Expression of OTRs (in green; filled or outlined by dashed lines) in peripheral and central components of the olfactory and gustatory systems and extrahypothalamic projections of OT neurons to respective forebrain and hindbrain regions (in red). For illustrative reason, no discrimination between magnocellular and parvocellular OT neurons and their projections has been depicted in this and other Figures. OT release from magnocellular OT neurons into the systemic circulation is depicted by red arrows. Of note: OTR expression has been tentatively depicted in olfactory sensory neurons, although only been demonstrated in the olfactory epithelium.

Abbreviations: AON: anterior olfactory nucleus, GC: granular cells; Ent Ctx: entorhinal cortex; MC: mitral cells; MeA: medial amygdala; NTS: nucleus of *tractus solitarii*; OSN: olfactory sensory neurons; OTub: olfactory tuberculum; Pir Ctx: piriform cortex.

Figure 2. Oxytocin, Trigeminal and Somatosensory Systems

Expression of OTRs and distribution of OT axons within depicted systems. See full description of the schemas in Figure 1 legend.

Abbreviations: Cg Ctx: cingular cortex 1; DRG: dorsal root ganglion; Ins: insular cortex; MTN: mesencephalic nucleus of trigeminal nerve; NTS: nucleus of *tractus solitarii*; PAG: periaqueductal gray; RVM: rostro-ventral medulla; SS Ctx: somatosensory cortex, SpTN: spinal trigeminal nucleus; STN: sensory trigeminal nucleus;

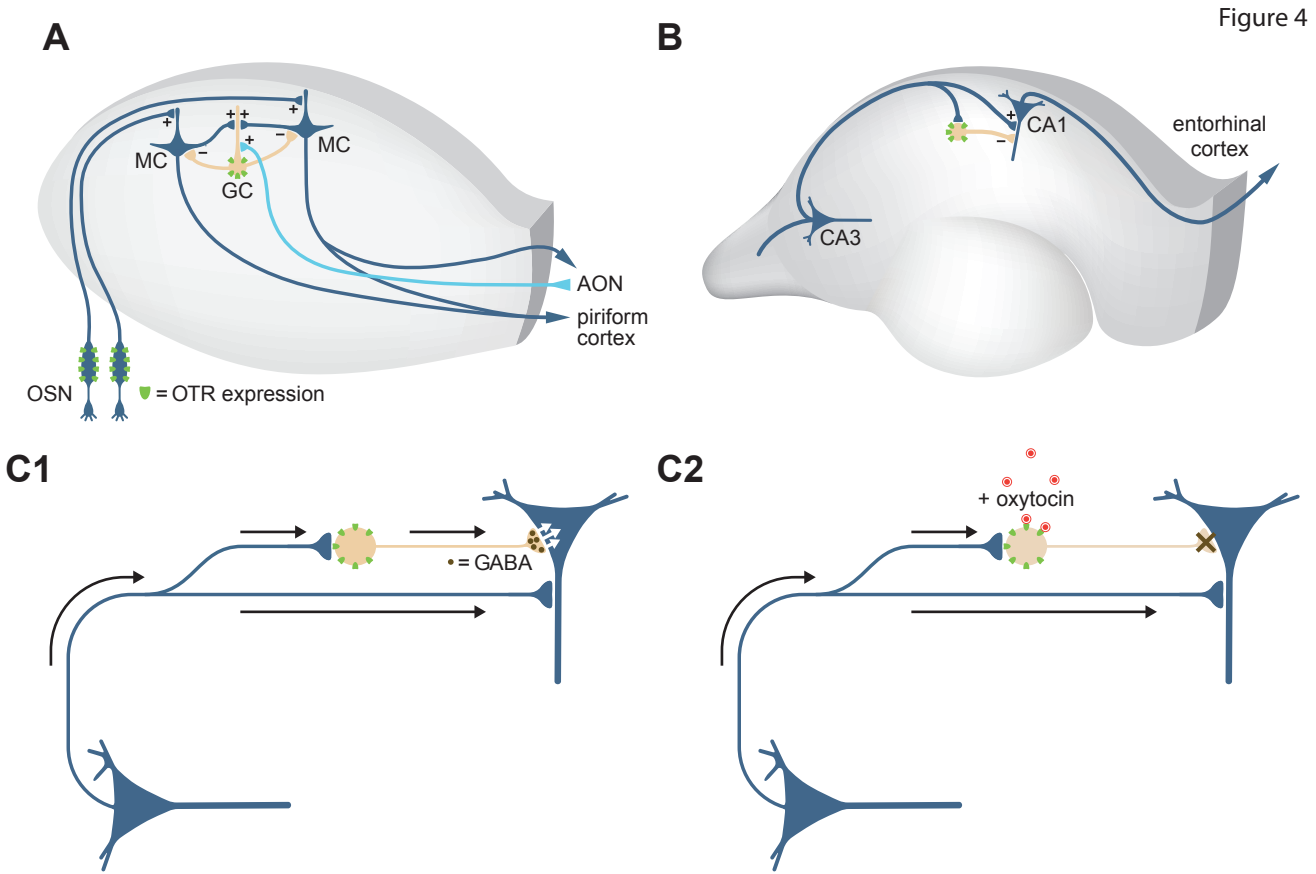
Figure 3. Oxytocin, Visual and Auditory Systems

Expression of OTRs and distribution of OT axons within the visual (A) and auditory (B) systems. See full description of schema in Figure 1 legend. Note, that in primates, but not in rodents, OTR expression has been also found in the SC (Freeman and Young 2016).

Abbreviations: Aud ctx: auditory cortex; DC: dorsal colliculi; IC: inferior colliculi; IO: inferior olive; LG: lateral geniculate nucleus; MG: medial geniculate nucleus; SC: superior colliculi; SOc: superior olivary complex; Tz: trapezoid nucleus.

Figure 4. Filtering Capacity of Oxytocin in the Olfactory Bulb and Dorsal Hippocampus

A. In the olfactory system, OTRs are (transiently) expressed in olfactory epithelium (and presumably in olfactory sensory neurons, OSN) and in cell body of granule cells (GC), which inhibit mitral cells (MCs) via dendro-dentritic synapses. MCs project further to the anterior olfactory nucleus (AON) and piriform cortex. In turn, the principle neurons of the AON send excitatory projections, which activate dendrites of GCs thus creating an inhibitory feedback loop onto MCs. B. In the hippocampus, OTRs are expressed in interneurons that are excited by CA3 neurons and subsequently inhibit CA1 neurons (B). C1. Schematic depicting OT modulation of excitatory signal processing, leading to the increase of signal-to-noise ratio by inhibition of synaptic transmission. C2. Following excitation of inhibitory neuron by OT, GABAergic release is depleted leading to enhanced evoked excitatory transmission to principle neurons. This mechanism can underlie filtering capacity of OT in the olfactory bulb, hippocampus and probably other brain regions.


A
MC
GC
MC
AON
piriform cortex
OSN
= OTR expression
B
CA1
entorhinal cortex
CA3
C1
= GABA
C2
+ oxytocin

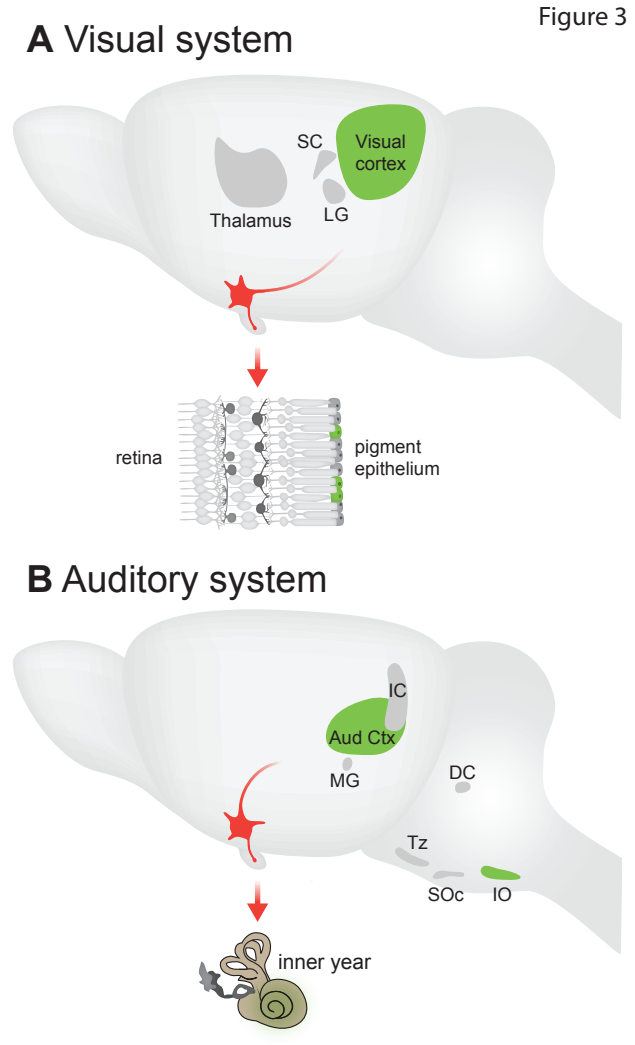
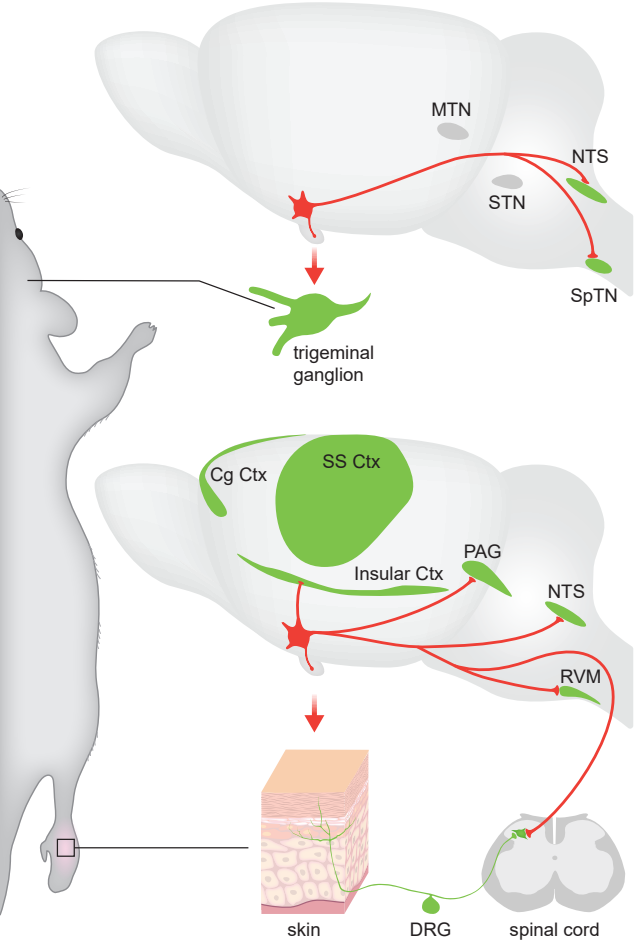
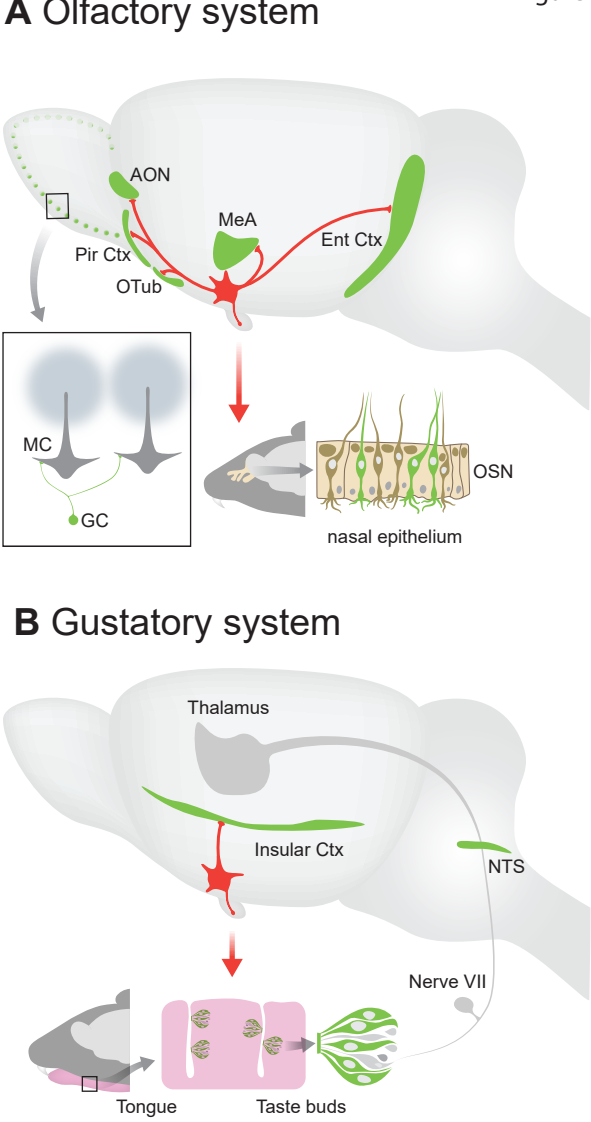

A Visual system
SC
Visual cortex
Thalamus
LG
retina
pigment epithelium
B Auditory system
IC
Aud Ctx
MG
DC
Tz
SOc
IO
inner year

Figure 2

Somatosensory system




A Olfactory system
AON
MeA
Ent Ctx
Pir Ctx
OTub
MC
GC
OSN
nasal epithelium
B Gustatory system
Thalamus
Insular Ctx
NTS
Nerve VII
Tongue
Taste buds