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# Neuromodulation by oxytocin and vasopressin in the central nervous system as a basis for their rapid behavioral effects.

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## ABSTRACT (reduce to 120 words)

The last several years have seen an increasing number of studies that describe effects of oxytocin and vasopressin on the behavior of animals or humans. Studies in humans have reported behavioral changes and, through fMRI, effects on brain function. These studies are paralleled by a large number of reports, mostly in rodents, that have also demonstrated neuromodulatory effects by oxytocin and vasopressin at the circuit level in specific brain regions. It is the scope of this review to give a summary of the most recent neuromodulatory findings in rodents with the aim of providing a potential neurophysiological basis for their behavioral effects. At the same time, these findings may point to promising areas for further translational research towards human applications.

## General principles of action suggested from effects early in evolution.

The evolutionarily oldest neuromodulatory effects of oxytocin (OT) and vasopressin (VP) seem to occur in motor and sensory systems where they affect reproductive behavior. Thus, in leeches, the homologous peptide "conopressin" can induce reproductive behavior by acting on a central pattern generator of oscillating neurons in reproductive ganglia M5&6 (1). Recently *C. elegans* has been added to this list, in which "nematocin" can generate $Ca^{2+}$ transients by binding to the native ntr-1 and ntr-2 receptor on thermo,- and mechanosensory neurons as well sensorimotor neurons which aid in penetration and sperm transfer (2**). In vertebrates, effects of VP and OT have been found at the level of the spinal cord. Thus, in lamina X neurons of the rat spinal cord, OT affects the locomotor central pattern generator (CPG) apparently by enhancing 5-HT release (3), whereas in lamina II VP and OT exert opposite effects on nociception: VP increases the number of action potentials induced by C-type nociceptive fibers and OT inhibits these by increasing neurosteroidogenesis which tonically potentiates GABA(A)R-mediated synaptic transmission (4, Fig 1E). From the findings in these sensorimotor systems, two interesting conclusions may be retained: 1) a simple molecule, through its multiple sites of action, seems capable of organizing different aspects of one type of behavior by increasing the effectiveness through which distributed circuits generate coherent behaviors and 2) since central pattern generators function according to a set of shared general principles, it is possible that similar effects in the spinal cord can also be found on oscillatory activities in higher brain regions (5, 6). Taking this as a starting point I will, after a short background on the receptors and endogenous release, treat the neuromodulatory effects of OT and VP in different systems that are functionally connected.

## Receptors and endogenous release in vertebrates

Although most invertebrates express a single peptide homolog of VP/OT, in vertebrates we can consistently find the two peptides and corresponding, multiple receptors. VP receptors in the brain are of the V1a and V1b type, whereas in the periphery the V2 receptor is also expressed. The same receptor for OT is expressed in the brain and the periphery and exhibits, in fact, equal sensitivity to VP and OT. Unfortunately, it remains difficult to assess the precise cytochemical distribution of these receptors, due to the absence of specific antibodies (7). Intracellular signaling of the receptors, and also affinity to the agonist (8), depends on the coupling to specific G proteins - which can be Gs, Gi or Gq - and the precise intracellular cascades. Coupling to beta-arrestin can lead to rapidly desensitizing responses as a result of receptor internalization (9). It is possible that this plays a role in the recently reported opposite effects by OT following long-term vs short term applications (10**), which would have important consequences for (prolonged) clinical applications.

The large number of reports on central neuromodulatory effects and associated behavioral changes has renewed interest in the endogenous production and function of VP and OT. Although their main production sites are found adjacently in the hypothalamus in the paraventricular (PVN), supraoptic (SON), suprachiasmatic and accessory nuclei, VP is also produced by smaller cell groups in the olfactory bulb, medial amygdala, bed nucleus of stria terminalis and locus coeruleus (7). OT producing neurons in the hypothalamus have recently been shown to send projections to various brain regions where these can functionally release OT (11*). Whereas the effects of endogenous release in the periphery have been well described, the behavioral effects of central endogenous release are currently a topic of increasing interest. This raises the question whether separate cell groups in the hypothalamus regulate peripheral versus central release and, if so, how the centrally releasing cells are affected by internal and external stimuli. In this context, studies that further characterize electrophysiological qualities of these hypothalamic neurons that release VP or OT take a new importance (see e.g. 12).

## Neuromodulation in the olfactory system and extended amygdala.

***Olfactory Bulb***

Neuromodulation by OT and VP plays an important role in social signaling and social recognition for which, in rodents, a major sensory input comes from the olfactory system. Neuromodulatory effects of VP and OT occur on mitral and granular cells in the main (MOB) and accessory olfactory bulb (AOB, 13**). These endogenous effects may be mediated by the recently discovered VP producing neurons in the anterior olfactory nucleus that are specifically activated by social odors from conspecific and heterospecific rats (14). In addition, previous electrophysiological findings revealed monosynaptic afferents from the olfactory system onto the SON (15) and more recently, direct projections from the MOB glomeruli onto VP containing neurons in both PVN and SON. Interestingly, these glomeruli are innervated by a subset of OR-37 receptor expressing olfactory neurons that are implicated in detecting socially relevant chemical signals (16).

***Medial Amygdala (MeA)***

Further processing of socially relevant olfactory signals occurs through the medial amygdala (MeA), onto which projections from MOB and AOB converge and through which they are further relayed to the bed nucleus of the stria terminalis (BNST) and septal nuclei (17, see Fig. 1). 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 (7, 18). In the MeA, OT-R activation is necessary for social memory (19, 20) and female OTKO mice also show impaired lordosis and reduction of oocyte number, but a higher density of dendritic spines (21). Recently, Gur et al. (22**) found that stimulation of the AOB with theta bursts induced LTD in the rat MeA that appears to underlie the formation of social memory. Thus, this LTD induction 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. Taken together, these findings provide an interesting mechanism of synaptic plasticity through which neuromodulation by OT can affect social memory formation (see Fig. 1C).

***Bed Nucleus of Stria Terminalis (BNST)***

A neuromodulatory role for OT in social memory as well as sexual responses has also been suggested in the medial BNST of Syrian hamsters. In female hamsters, male odors increase c-fos expression and lead to concomitant increases in vaginal markings, used to attract males to the nest. Intracerebroventricular injection of OT receptor antagonists prevented increases both in c-fos and in the vaginal marking (23). A role for VP in this area was recently also suggested for the development of aggressive behavior (24*). Following the first reports by the group of Ingram (25), very few electrophysiological studies seem to have further explored neuromodulatory mechanisms of VP or OT in the BNST, although an interesting circuit for neuromodulation by OT in the BSNT was recently proposed based on neuroanatomical evidence (26).

***Nucleus Accumbens***

In addition to effects in the above mentioned parts of the extended amygdala, Dölen et al. (27**) recently showed how OT can affect synaptic transmission in the nucleus accumbens. Activation of OT receptors, presynaptically located on dorsal raphe projections, was found to mediate local serotonin release (Fig. 1B). In this manner, OT induced a serotonin-dependent LTD in medium spiny neurons. The origin of the endogenous OT was located to the PVN, but not the SON. It appears that these coordinated interactions between OT and 5-HT are required for mediating social reward as tested in a social conditioned place preference test (27).

## Neuromodulation in the lateral Septum and cortical areas

***Lateral Septum***

In the lateral septum OT as well as VP signaling has been implicated in social recognition in adult male and female and juvenile male rats (20). In these cases, it is possible that endogenous neuromodulatory effects originate from VP neurons that project from the MeA and BNST to the LS (28, 29, Fig. 1). Progesterone-induced reduction of VP production in these areas indeed decreases social recognition and local VP injections rescues this decrease (30). Guzman et al. (31) recently suggested that

OT signaling in the septal area functions in general as a means to enhance memories for socially relevant stimuli whether they are positive or negative. This may explain previous reports that OT can sometimes enhance fear in rats (32**) and in humans (33, 34**). Enhanced memory of positive social interactions would decrease fear, whereas enhanced memory of negative social interactions would increase it (31).

***Hippocampus***

One can pose the question as to whether the final storage of social memory takes place in the above mentioned structures, or if these rather fulfill a modulatory role. Indeed, connections between septal and hippocampal areas play an important role in memory function and it is possible that the OT/VP modulation of the extended amygdala-septal-hippocampal pathway primarily affects social memory processing but not storage. In this context several new findings on VP/OT neuromodulation of synaptic transmission in the hippocampus are worth mentioning. First of all, OT was recently shown to enhance the fidelity of spike transmission (EPSP-spike coupling) in the CA1 region of the hippocampus (Fig. 1D). This was due to a stimulating effect of OT specifically on feed-forward inhibitory fast-spiking neurons which caused an increase in frequency of spontaneous inhibitory currents and, as a result of synaptic depression, a decrease in amplitude of evoked feed-forward inhibitory currents and concomitant less shunting of (i.e. more efficient) postsynaptic excitatory stimulation of pyramidal neurons. It is possible that such a mechanism also plays a role in other cortical regions such as dentate gyrus or neocortex (35**). Such a filter mechanism may be important for selective detection and storage of specific external stimuli over internal spontaneous activity, which may play an important role in, for example, opening of critical periods (36).

In the dorsal CA2 region, Pagani et al. (37) recently showed neuromodulatory effects that were mediated by V1b receptors and OT receptors. Specific agonists to both caused potentiation of excitatory transmission that developed over 10-20 minutes, depended on basic NMDA receptor activation and required postsynaptic $Ca^{2+}$. They were unaffected by inhibitors of cAMP-activated PKA and did not depend on changes in GABA(A) receptor activation. Thus, by decreasing threshold for potentiation and by rendering neurons more sensitive to external stimulation, OT and VP permit social recognition and concomitant expression of appropriate social aggression (37). Although the endogenous agonist might originate from described projections from the MeA and BNST VP neurons, recent findings indicate projections from the PVN both in mice and rats as an important source (38, 39).

In the CA3 region, Tyzio et al. (40**) recently showed that OT can, transiently during birth and long-lastingly during later development, decrease intracellular $Cl^-$ to regular adult levels. By thus rendering GABAergic transmission inhibitory, OT presumably protects against excessive excitation during birth. Interestingly, these changes are absent in several animal models of autism including the fragile X mouse model as well as rat models based on administration of valproate acid or OT-R antagonists during birth. Although the precise mechanism through which OT mediates this change is still unknown, these findings reveal a new rationale for the treatment of autistic patients based on OT administration (40).

***Medial PreFrontal Cortex (PFC)***

The mPFC also contains OT-sensitive neurons (41), abundantly expresses OT receptors (42, 43) and receives long range axonal projections from OT producing neurons in the hypothalamus (9, 44). In layer V of the infralimbic-mPFC (IL-mPFC), OT suppresses glutamatergic neurotransmission in pyramidal

neurons through a presynaptic activation of CB1 receptors, which can be blocked by the CB1 receptor antagonist AM251 (Fig. 1A). Similar to its effects in the hypothalamus (45), it is possible that OT modulates endocannabinoid release and activates presynaptic CB1 receptors. Interestingly, the application of OT converted LTD induced in mPFC layer V pyramidal neurons by stimulation of layer II/III neurons at 5Hz into LTP by inserting postsynaptically $Ca^{2+}$ permeable AMPA receptors (41). In view of the projections from the IL-mPFC to inhibitory neurons in the CeA, it is possible that these OT effects work in concert with OT's excitatory effects in the CeA on inhibitory neurons (46). Taken together, OT may thus play an important role in fear extinction and concomitantly in the regulation of affective and social behaviors (41).

## Conclusion:

From these recent findings it appears that a large variety of both presynaptic and postsynaptic neurophysiological mechanisms can underlie the neuromodulatory effects of VP and OT. The effects reported here, in particular for OT, occur in regions that are interconnected and that fulfill comparable functions, important for detection, filtering and storage of socially relevant signals and for triggering and rewarding social behaviors. The question arises then how oxytocinergic activation leads to coordinated activation across these regions. It is possible that oscillatory activities between these regions play a synchronizing role. Already well known in the hippocampus and septal area, oscillatory activities were recently also reported in the extended amygdala (47). OT is well known to affect and evoke rhythmic activity starting in the hypothalamus with networks underlying its own release (48), and also affecting the locomotor CPG in the spinal cord (3, see above). Similarly, it is possible that OT affects oscillatory activities in higher brain regions and thereby facilitates or triggers synchronization. Coordinated release of OT from hypothalamic projections towards these different brain regions could be at the basis of the creation of coherent patterns of activation that may rapidly and reversibly affect expression of specific behaviors.

Besides these rapid actions of OT, recent findings also show interesting effects during development (40, 49). Thus, the large release of OT during birth shifts GABAergic excitation into inhibition and it is possible that similarly, a coherent state is created for labor contractions and pain resistance (50). Later in life, OT effects on release sites that are known to be sensitive to synaptic plasticity may also play a role in learning and memory. In the medial amygdala OT appears to underlie plasticity induced by input from the OB leading to LTD. Similarly, it is indirectly affecting synaptic transmission through its interactions with other neurotransmitters such as serotonin (spinal cord, nucleus accumbens, but also amygdala, see 51) and cannabinoids. In view of the recent implications of these neurotransmitters in plasticity and critical periods, this opens the perspective that OT could play a role in opening a window of learning during social interactions.

## Figure1. Neuromodulation by OT and AVP of circuits in the brain

Main (upper) figure: OT-Receptor (in red) and VP-Receptor- (in green) expressing regions in the rodent brain and their connections. Shaded panels indicate levels at which insets were taken below that represent coronal slices from the right hemisphere: A) medial prefrontal cortex, showing the expression of OT receptors (in red) at the synapse of CB1 containing neurons (light purple) that can regulate glutamate release (in blue) through presynaptically expressed CB1 autoreceptors (dark purple). B) nucleus accumbens, receiving serotonergic innervation (in orange) on which OT receptors (in red) are presynaptically expressed. C) MeA, expressing OTRs and OT-R dependent LTD evoked through theta bursts in the olfactory cortex. D) Hippocampus, expressing OT and VP receptors at different levels: in the CA3 region where OT has been shown to affect the Cl equilibrium potential, in the CA2 where both OT and V1b R agonists enhance glutamatergic synaptic transmission and in the CA1 region where OT-R expressed on fast spiking (FS) interneurons affect excitatory transmission onto pyramidal neurons. E) Spinal cord in which OT in Rexed laminae 1 and 2 enhances production of 3alpha5alpha neurosteroids thereby postsynaptically enhancing GABAergic transmission. OT also affects activity of the central pattern generator (CPG) in layer X, presumably by changing release from serotonergic innervation (in orange).

## Conflict of interest statement

Nothing declared.

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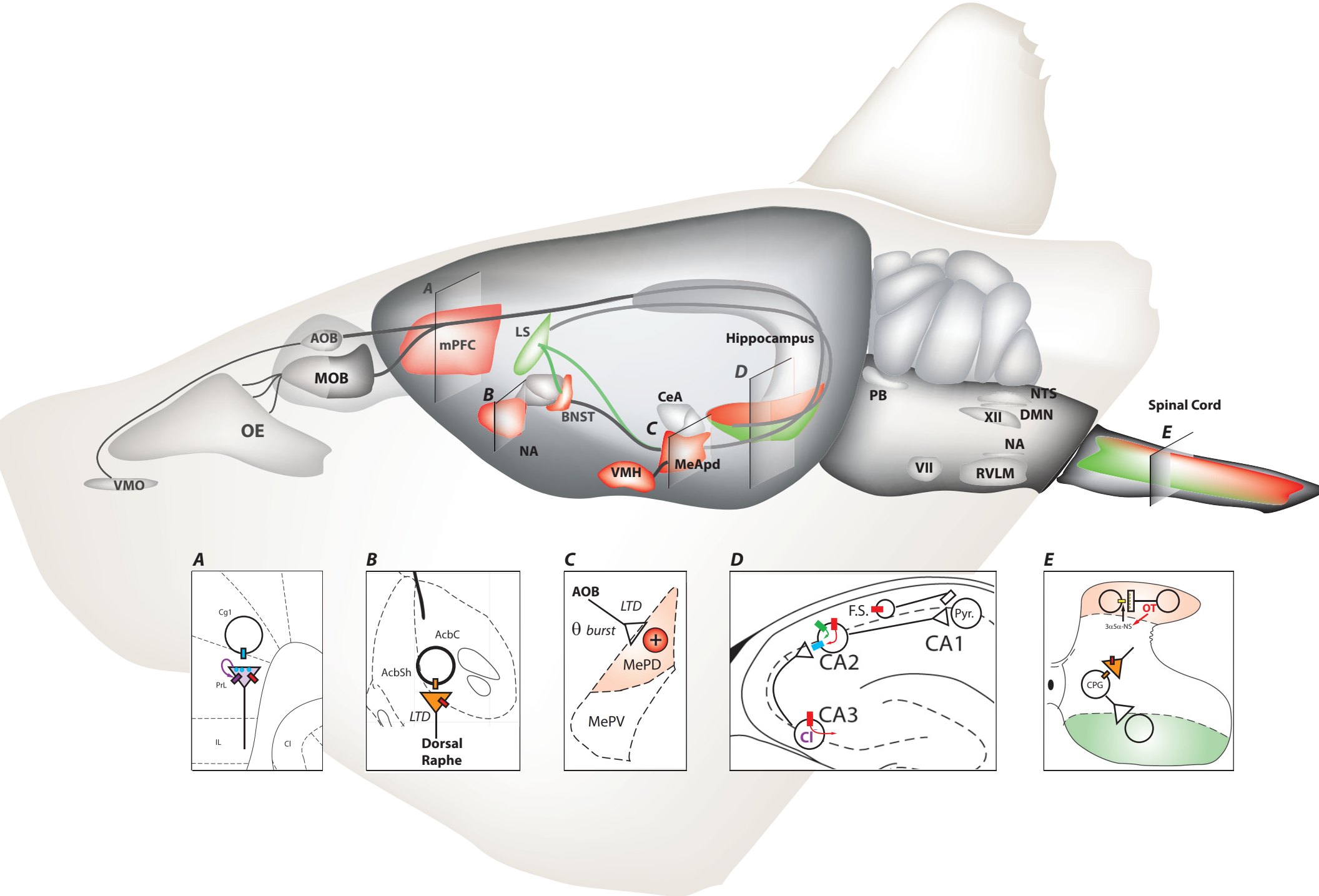
**Highlights**

-Neuromodulation by vasopressin/oxytocin (VP/OT) appears early in evolution
-Pre,- or postsynaptic neuromodulation by VP/OT depends upon vertebrate brain region.
-Neuromodulation of oscillations may synchronize VP/OT effects throughout the brain
-New VP/OT effects on neurodevelopment show treatment promise for psychiatric disease

## Table 1 - List of Abbreviations (both in text and figure)

AcbC – Nucleus Accumbens Core
AcbSh – Nucleus Accumbens Shell
AOB – Accessory Olfactory Bulb
BNST – Bed Nucleus of Stria Terminalis
CB1R – Cannabinoid 1 Receptor
CeA – Central Amygdala
Cg1 – Cingulate Cortex, area 1
CPG – Central Pattern Generator
DMN – DorsoMotor Nucleus
F.S. – Fast Spiking interneuron
IL – InfraLimbic Cortex
LS – Lateral Septum
MeA – Medial Amygdala
MePD – Medial Amygdala  Pars Dorsalis
MePV – Medial Amygdala – Pars Ventralis
MOB – Main Olfactory Bulb
mPFC – medial PreFrontal Cortex
NA – Nucleus Accumbens
NTS – Nucleus Tractus Solitarius
OE – Olfactory Epithelium
OT – Oxytocin
PB- ParaBrachial Nucleus
PrL – PreLimbic Cortex
PVN – ParaVentricular Nucleus
Pyr. – Pyramidal Neuron
SON – SupraOptic Nucleus
VMH – VentroMedial Hypothalamus
VMO – VomeroNasal Organ
VP – Vasopressin
3$\alpha$5$\alpha$–NS – 3$\alpha$5$\alpha$ NeuroSteroid


A
AOB
MOB
OE
VMO
mPFC
LS
B
BNST
NA
C
CeA
MeApd
VMH
D
Hippocampus
PB
NTS
XII
DMN
NA
VII
RVLM
Spinal Cord
E
A
Cg1
PrL
IL
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CA1
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OT
3α5α-NS
CPG

## Table 1 - List of Abbreviations (both in text and figure)

AcbC – Nucleus Accumbens Core
AcbSh – Nucleus Accumbens Shell
AOB – Accessory Olfactory Bulb
BNST – Bed Nucleus of Stria Terminalis
CB1R – Cannabinoid 1 Receptor
CeA – Central Amygdala
Cg1 – Cingulate Cortex, area 1
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