Chemogenetic stimulation of oxytocinergic neurons dynamically modulates fMRI connectivity

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Background and Aims

- Oxytocin (OXT) is a key modulator of complex socio-affective and affiliative behaviours.
- Recent investigations have shed light on the contribution of oxytocin to specific behavioural domains, and the underlying circuit substrates.
- Most of these studies have employed circuit dissection approaches to link restricted oxytocin sub-systems to specific behavioural domains.
- Attempts to complement circuit-specific investigations with large-scale mapping of the network correlates of OXT have been described in humans and in animals using fMRI upon intranasal administration of the peptide[1,2].
- These studies have shown that exogenously administered OXT can robustly modulate cortical and subcotrtical activity
- However, the large-scale networks endogenously modulated by this peptide remain largely undetermined.
- To fill this knowledge gap, here, we combine chemogenetics, fMRI and electrophysiology to map the topography and dynamics of brain networks engaged by endogenously-released OXT at multiple temporal scales.

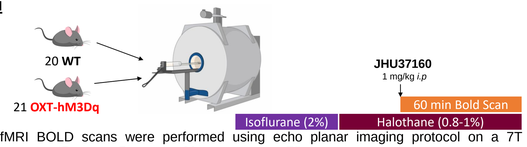
Methods

All experiments were carried out in accordance with Italian regulations governing animal welfare and protection (DL 26/214, EU 63/2010, Ministero della Sanità, Roma). Animal research protocols were reviewed by the Italian Ministry of Health (A.Gozzi; 752/19).

Model Validation

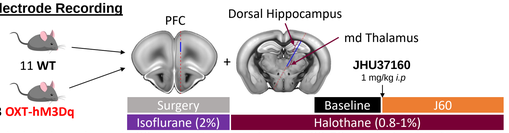
- Mice with double-floxed DREADD activator hM3Dq were crossed with with OXT-specific Cre-recombinase mice.
- Patch Clamp Electrophysiology targetted PVH magnocellular neurons and assessed firing frequency before and after Clozepine-N-Oxide (CNO; 10 µM) administration.
- OXT in blood was quantified by radioimunoassay (RIA) in N=10 (5:5 HT:WT) mice as previously described[2].
- N=46 (23:23 WT:HT) were scored manually for grooming behaviour 60 min after JHU37160 (1 mg/kg; *i.p.*) administration.
- N=10 (5:5 HT:WT) were sacrificed with deep anaesthesia and tissues slices containing the paraventricular nucleus of the hypothalamus (PVH) were taken.
- N=41 (21:20 WT:HT) underwent pharmacological MRI to assess relative CBV (rCBV) after *i.v.* injection of 5 µl/g of a blood-pool contrast agent Molday ION (as in [2]).

fMRI



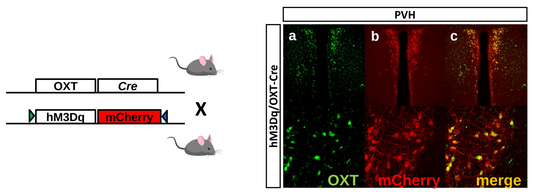
- fMRI BOLD scans were performed using echo planar imaging protocol on a 7T scanner (Bruker Biospin, Milan) using a 72-mm birdcage transmit coil and a 4-channel solenoid coil for signal reception.
- Echo planar imaging (EPI) parameters: TR/TE = 1000/15 ms, flip angle 30°, matrix 100 × 100, field of view 2.3 × 2.3 cm, 18 coronal slices, slice thickness 600 µm for 4620 volumes (total duration 77 minutes, 17 min before JHU37160 i.p. administration and 60 min after).

Multi-electrode Recording

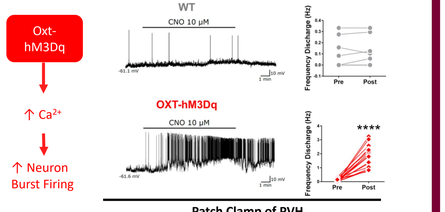


- Analysis is based on min 20 mins before injection and 30-50 mins after injection.
- Analysis was completed in Matlab using methods in Rocchi et al (2022)[3]

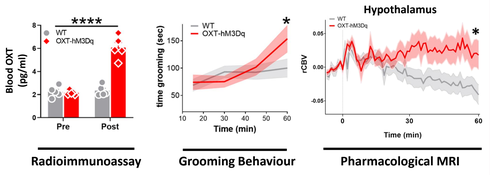
Oxt-Cre allows specific chemogenetic targeting of Oxytocin-producing Neurons



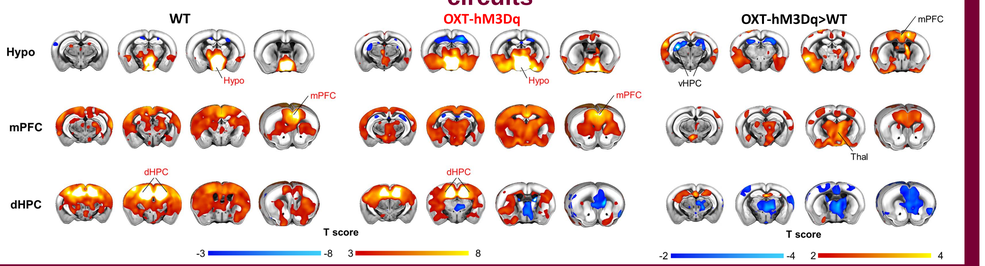
Ex vivo activation of OXT-hM3Dq causes increased activity in PVH



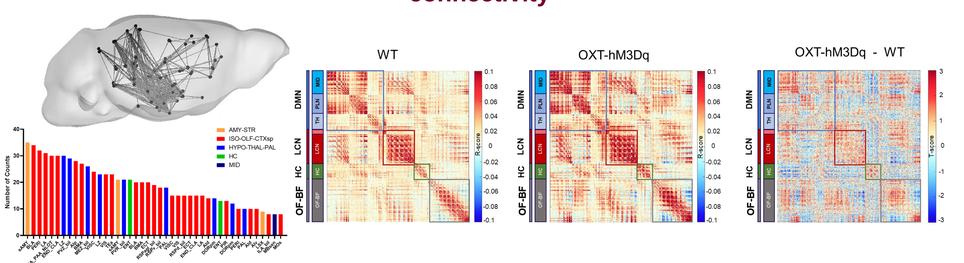
In vivo OXT-hM3Dq activation causes physiologically relevant release of oxytocin and fMRI activation of hypothalamus



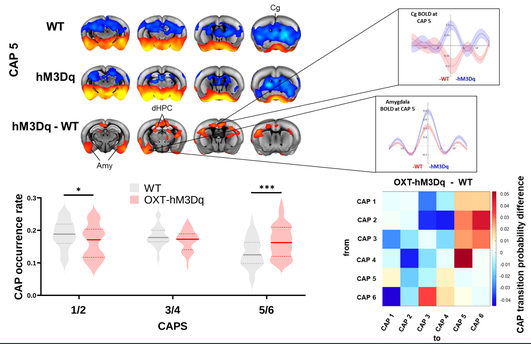
Endogenous OXT differentially modulates socially relevant cortico-limbic circuits



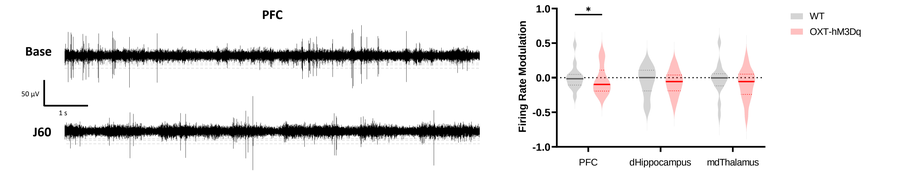
Endogenous OXT release robustly reconfigures brain-wide functional connectivity



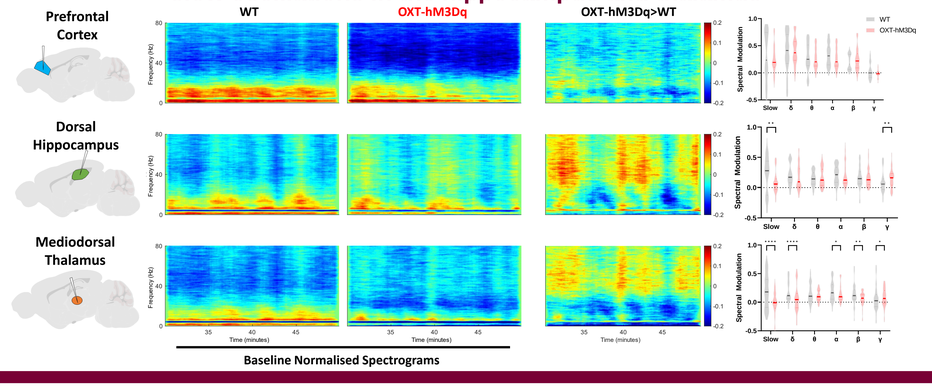
Endogenous OXT release increases occurrence of salience-encoding fMRI states



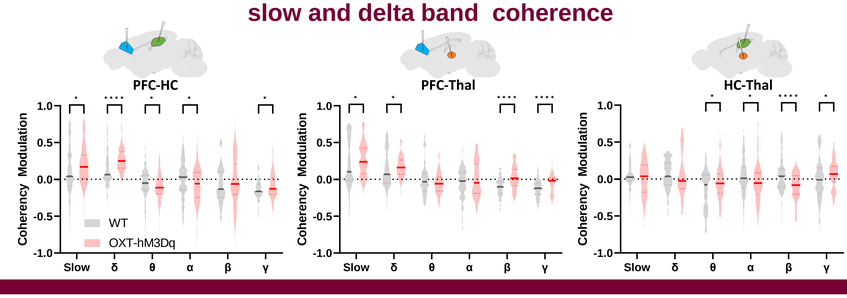
OXT-hM3Dq activation reduces multiunit firing in the PFC



OXT-hM3Dq activation increases hippocampal gamma power while reducing slow oscillations in the hippocampus and thalamus



OXT-hM3Dq activation increases interareal gamma, slow and delta band coherence



Discussion

- Intersectional genetic manipulations to generate OXT-hM3Dq allows targeted activation of the endogenous oxytocin system
- Activity of the endogenous oxytocin system strengthens and reconfigures fMRI connectivity in corticolimbic networks involved in social cognition
- These fMRI changes entail increased occurrence of temporal sub-states encompassing social salience encoding regions
- Endogenous oxytonergic neurons also profoundly reorganize oscillatory activity in hippocampus and mediodorsal thalamus, with increased gamma and reduced slow oscillation power
- Increased interareal coherency in gamma and infraslow frequency bands serve as plausible correlate for some of the fMRI connectivity changes described here
- Further analysis is in progress to investigate this and other links across this data

References

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