From Pair Bond to Partner Loss

Neuropeptides are Indispensable

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Neurobiology Of Grief International Network (NOGIN)
presents
SOCIAL NEUROSCIENCE OF GRIEF: 2020 VISION
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Formation of social bonds

- First & strongest social bond in life
  → infant to its mother
- Evolutionary origin to form adult social bonds
- Broad overlap in brain regions, pathways, neurotransmitters

Numan & Young, 2016 *Horm Behav*

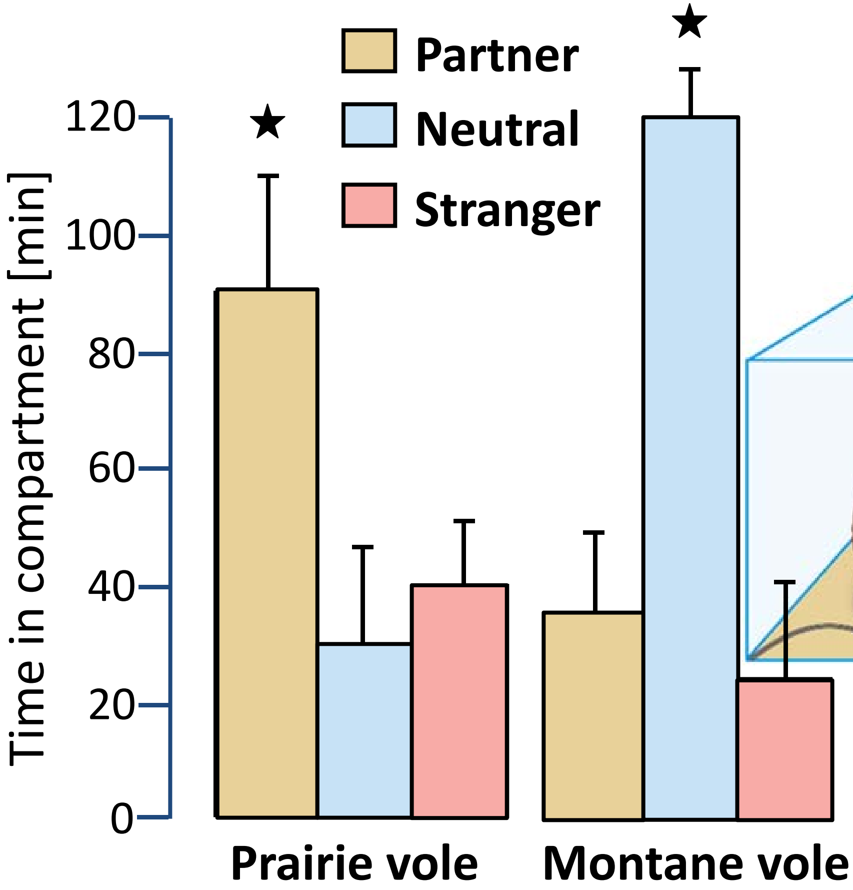
Animal model for social relationships

Prairie vole *(Microtus ochrogaster)*

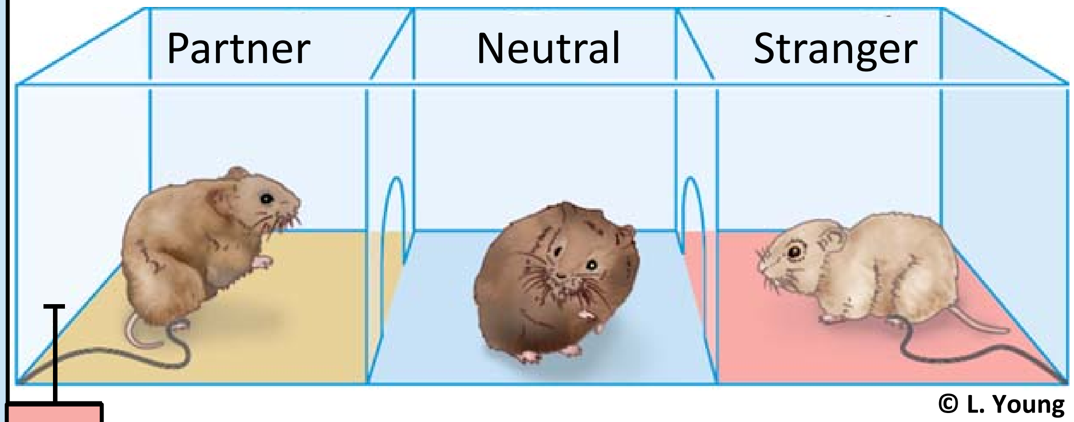
- **biparental species**
- **socially monogamous**
- **form enduring and selective pair bonds**

e.g. Carter & Getz, 1993; Carter et al., 1995; DeVries et al., 2002; Young & Wang, 2004; Lim et al., 2004, 2007; Donaldson et al., 2010; McGraw & Young, 2010; Keebaugh et al., 2015; Johnson & Young, 2015; Walum & Young, 2018

Assessing the pair bond in the laboratory



- **oxytocin (OT)**
- vasopressin
- CRF
- dopamine



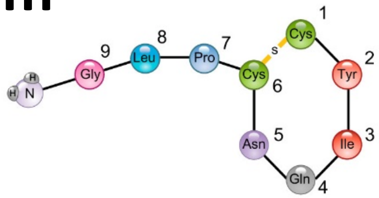
Partner Preference Test

3 hour duration, Score huddling

2X with partner = PP

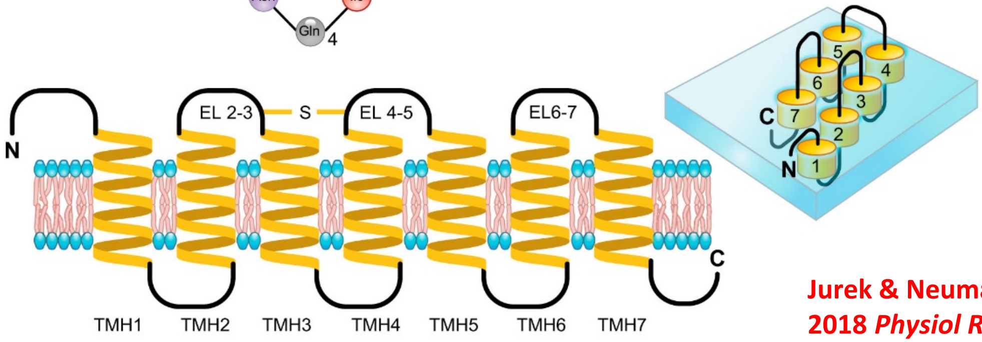
e.g. Carter & Getz, 1993; Carter et al., 1995; DeVries et al., 2002; Young & Wang, 2004; Lim et al., 2004, 2007; Donaldson et al., 2010; McGraw & Young, 2010; Keebaugh et al., 2015; Johnson & Young, 2015; Walum & Young, 2018

The oxytocin system



nonapeptide

synthesized in hypothalamus



Jurek & Neumann, 2018 *Physiol Rev*

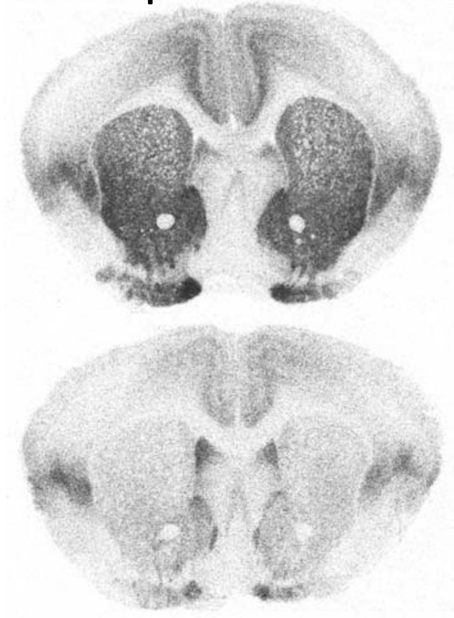
one type of GPCR → OTR

<u>functions</u>

peripherally uterus contraction
milk ejection reflex

centrally neurotransmitter/-modulator
→ positive emotions
→ social behavior
→ buffers against stressors

Oxytocin facilitates the pair bond in both sexes



- ❖ **Higher OTR densities in the NAc of prairie voles than in non-monogamous vole species**
- ❖ **Natural genetic polymorphism in the OTR gene**
  → robustly influences OTR density in the NAc
  → predicts partner preference formation
- ❖ **OT signaling in the NAc required for partner preference formation**
- ❖ **In humans: less evidence**

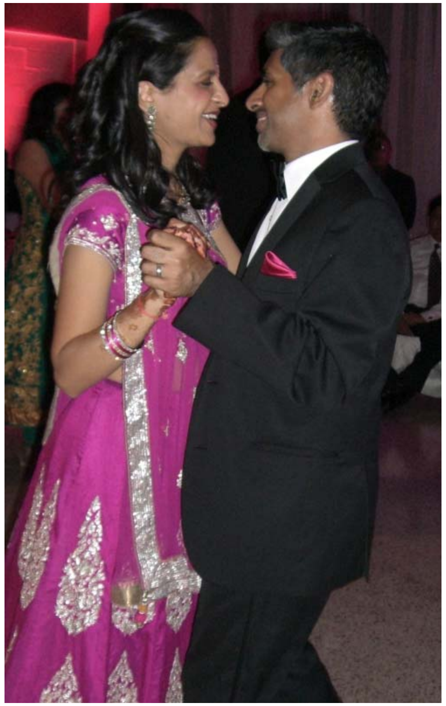
  <u>But</u> intranasal OT
  → men rate attractiveness of their partners higher
  → heightened NAc activation

e.g. Liu & Wang 2003; Ross et al. 2009a,b; Keebaugh & Young 2011; Keebaugh et al., 2015; Johnson et al., 2016; King et al., 2016; Schneiderman et al., 2012; Scheele et al., 2013; Hurlemann & Scheele, 2016

Oxytocin facilitates benefits arising from positive social relationships

- **Positive social relationships**
  → essential for healthy psychological development and well-being

- **For example:**
  - **decreased risk for cardiovascular disease**
  - **decreased risk for infectious disease**
  - **increased stress resilience**
  - **reduced likelihood to develop depression and anxiety disorders**

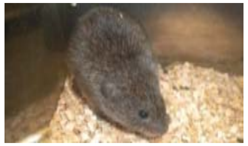


e.g. Clayton & Darvish, 1979; House et al., 1988; Berkman, 1995; Biondi & Picardi, 1996; Uchino et al., 1996; Zisook et al., 1997; Shear & Shair, 2005; Hensley et al., 2009; Resendez & Aragona, 2013

Partner presence acts soothing after stress - role of oxytocin in the PVN

1h stress (immobilization)

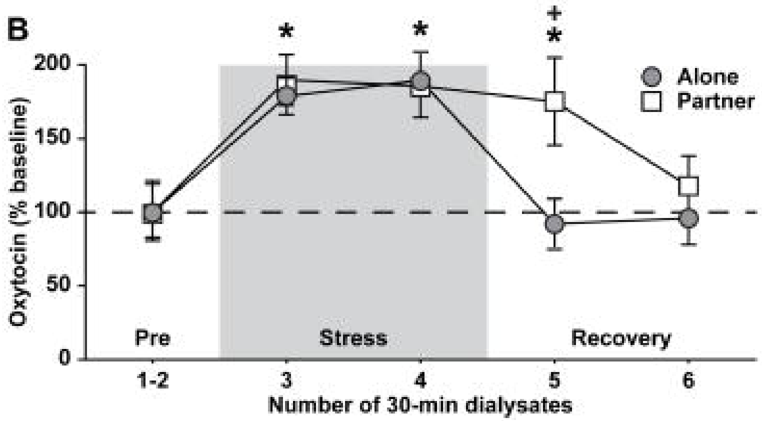
recovery alone



recovery with partner

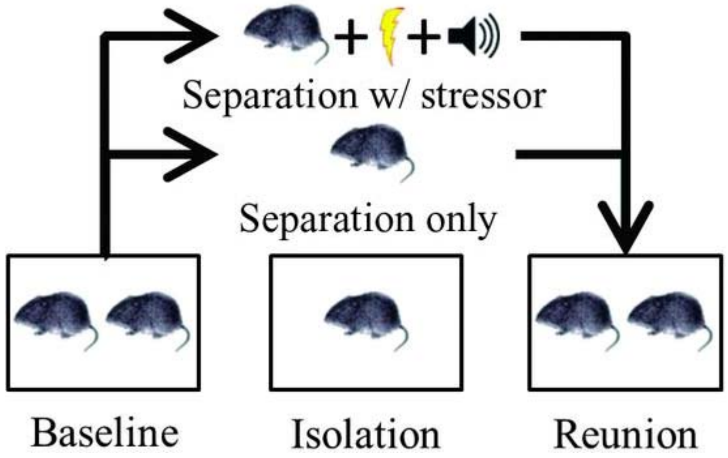
	corticosterone	anxiety
recovery alone	↑	↑
recovery with partner	↔	↔

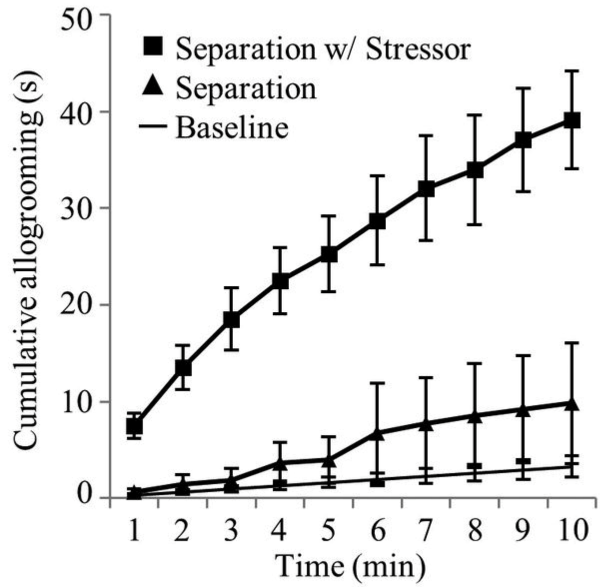
- Recovery in presence of partner
  - → observer increases social behavior
  - → which - in turn - prolonges OT release in the PVN of demonstrator



Smith et al., 2014 *Biol Psychiatry*

I feel for you
- observer shows consoling behavior





- ❖ **Mediated via OT signaling in the anterior cingulate cortex**
  → linked to empathy in humans **Lamm et al., 2011**

Burkett et al., 2016 *Science*

Consequences of partner-loss

- Negative impact on physiological and mental health

- For example, with loss of spouse
  → the odds of physical illness can increase by 40x
  → mortality rates double in first year
  → depressive symptoms develop in appr. 40% of individuals within one month

→ Prairie vole animal model   Bosch & Young, 2018 *CTBN*

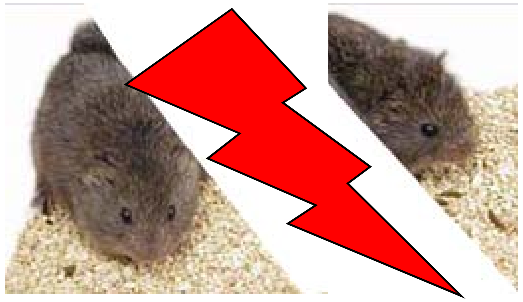
e.g. Clayton & Darvish, 1979; House et al., 1988; Berkman, 1995; Biondi & Picardi, 1996; Uchino et al., 1996; Zisook et al., 1997; Shear & Shair, 2005; Hensley et al., 2009; Resendez & Aragona, 2013; Sun et al., 2014; Chen et al., 1999; Thompson et al., 1984; Boyle et al., 2011; Kaprio et al., 1987; Schaefer et al., 1995

Animal model for pair bond separation

Co-housing for 5 days
- with female partner **fp**
- with male partner **sp**

paired

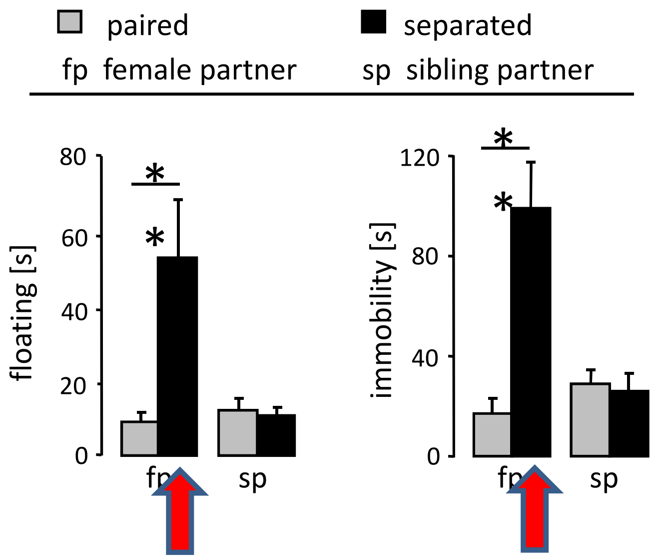
separated



Bosch et al., 2009 *NPP*

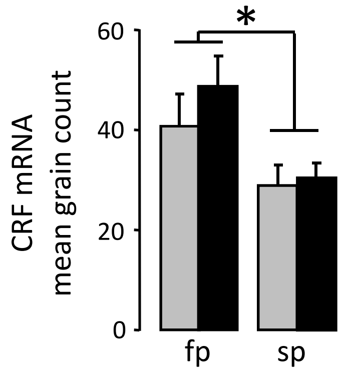
Consequences of separation in males

forced swim test



tail suspension test

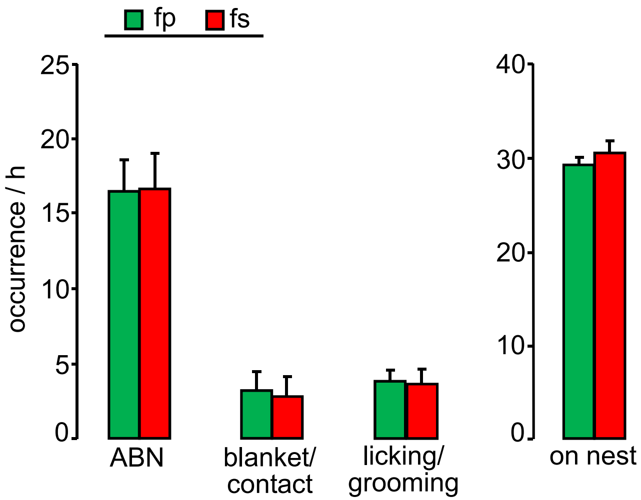
- increased passive stress-coping in fp separated[1,2]
- overall effect of separation on anxiety[1]
- increased heart rate in fp separated[2]
- increased basal cort[1,2] & adrenal weight in fp separated[1]
- increased CRF mRNA in mBNST in fp[1]



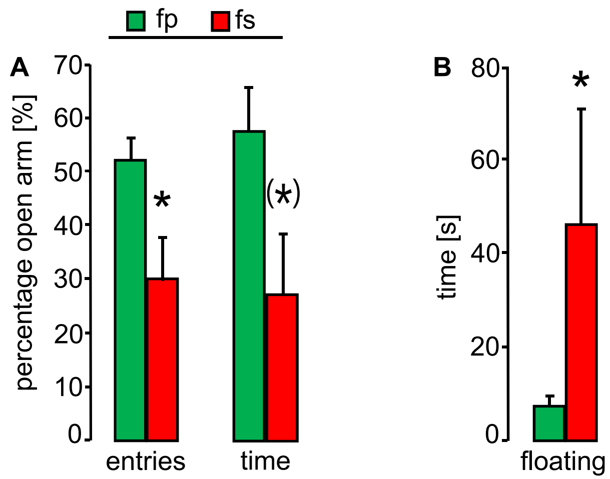
[1]Bosch et al., 2009 *NPP*
[2]McNeal et al., 2013 *Auton Neurosci*

Consequences of short-term separation in lactating mothers

unaltered maternal care…



…but increased emotionality



Bosch et al., 2018 BehavBrainRes

Consequences of long-term separation

Co-housing for 24 hrs
with female partner

testing after 2w and/or 4w

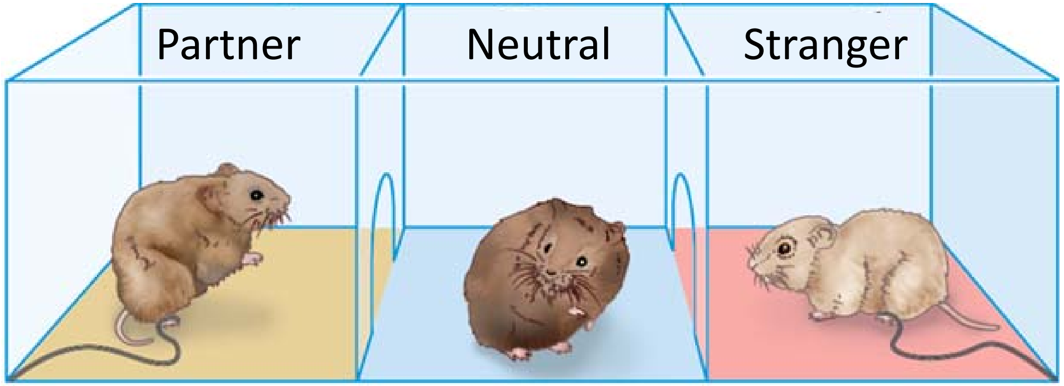
separated

separation	2 weeks	4 weeks	short-term
passive stress-coping	not tested	⇧	⇧
anxiety	not tested	⇧	⇧
partner preference	yes	no	yes
aggression	not tested	⇩	not tested
plasma corticosterone	⇧	⇧	⇧

Sun et al., 2014 Behav Brain Res

Assessing the pair bond in the laboratory

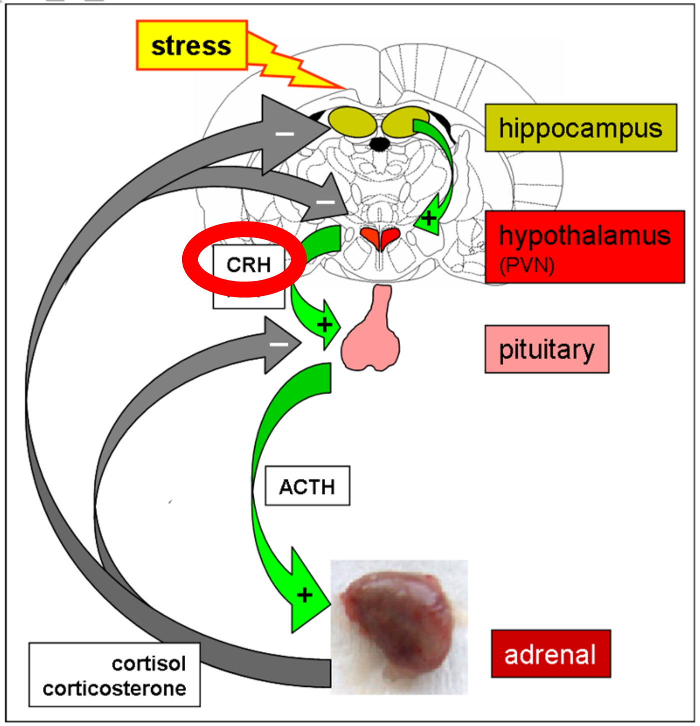
- **oxytocin (OT)**
- **CRF**
- vasopressin
- dopamine



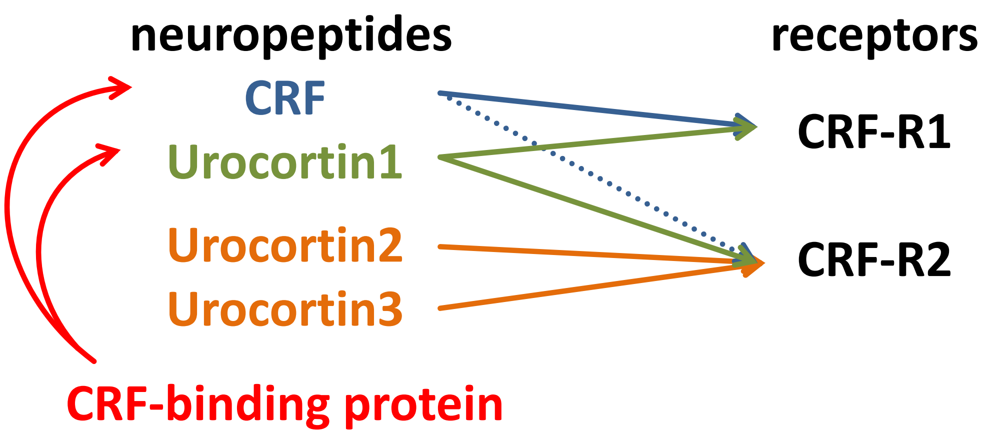
Cohabitation

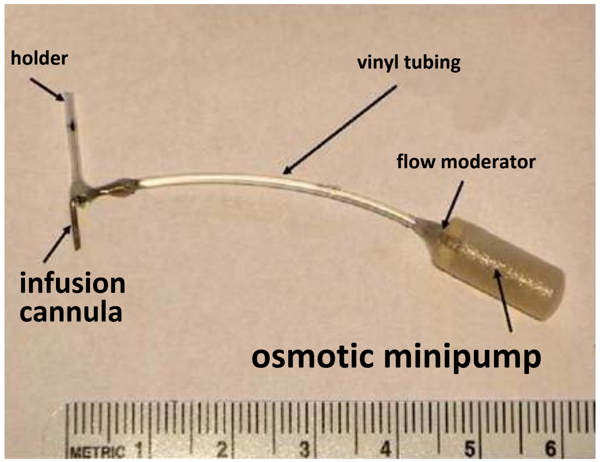
Partner Preference

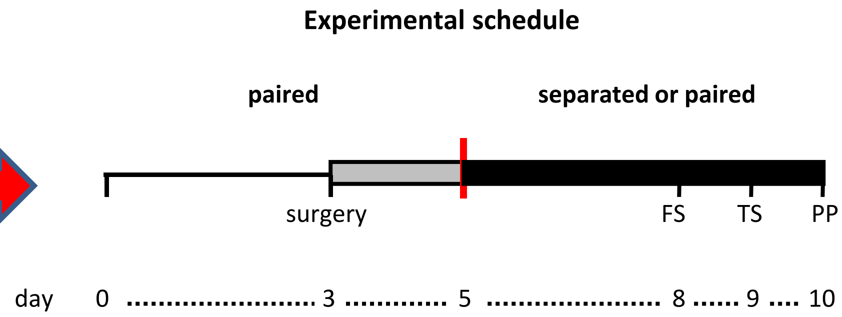
e.g. Carter & Getz, 1993; Carter et al., 1995; DeVries et al., 2002; Young & Wang, 2004; Lim et al., 2004, 2007; Donaldson et al., 2010; McGraw & Young, 2010; Keebaugh et al., 2015; Johnson & Young, 2015



The brain CRF system

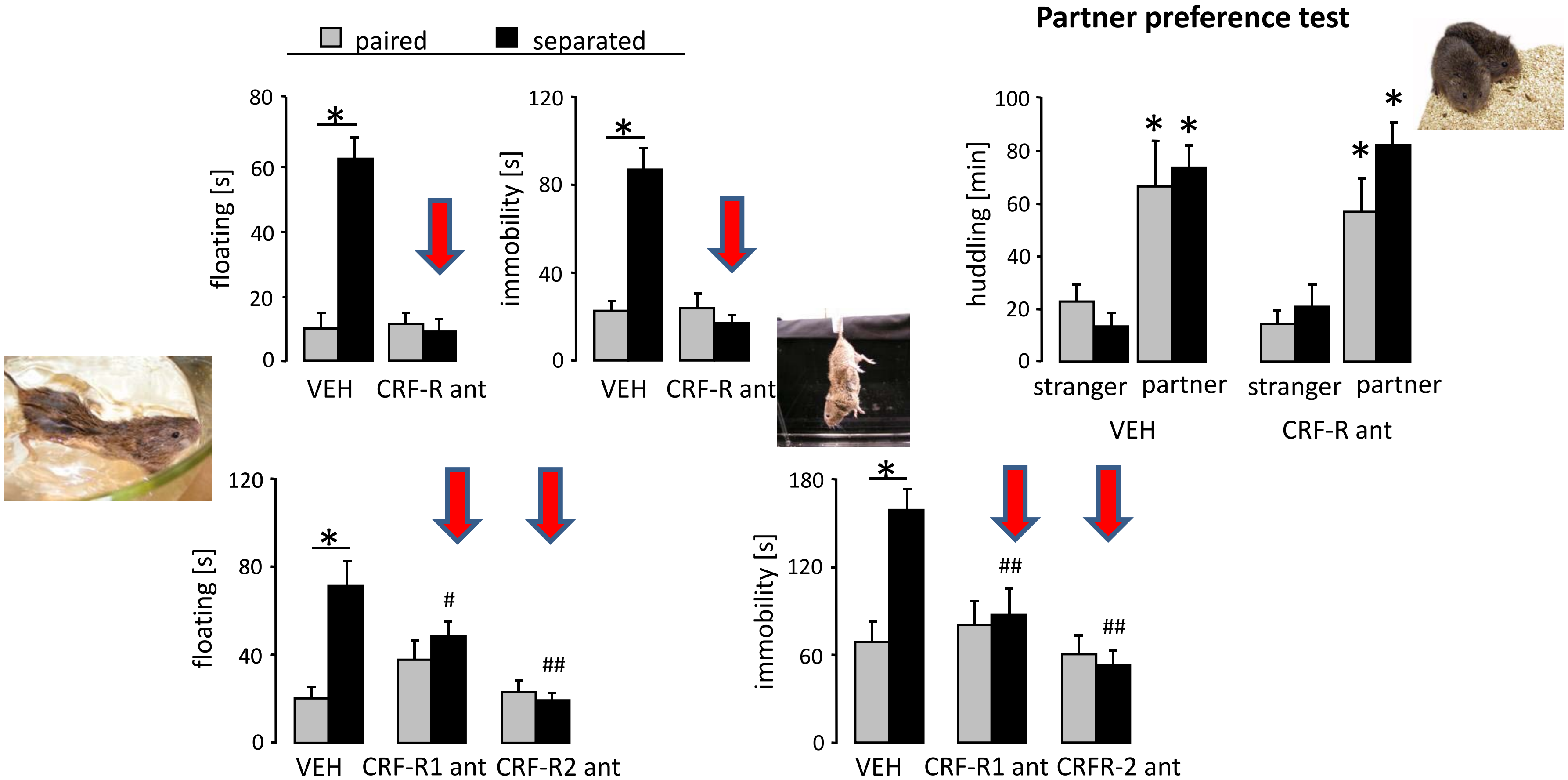






Bosch et al., 2009 *NPP*

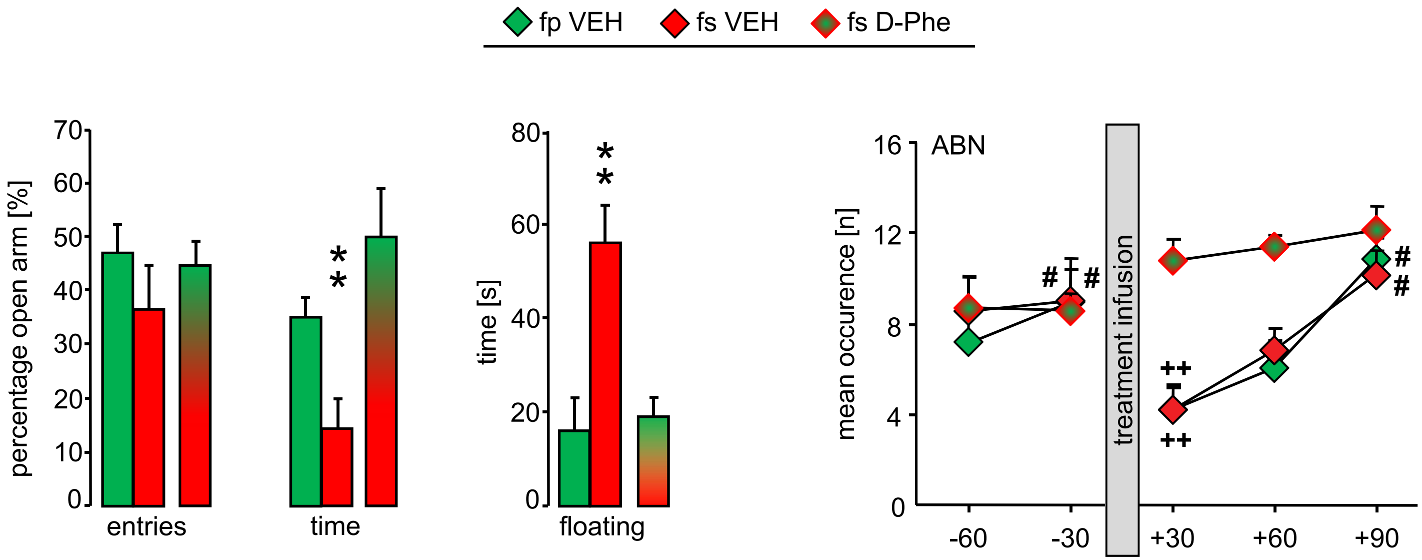
Effects of chronic central CRF-R blockade



CRF-R-blockade prevents passive stress-coping after separation
- without affecting partner preference

Bosch et al., 2009 *NPP*

Effects of acute central CRF-R blockade on single moms



emotionality

maternal care

CRF-R-blockade normalizes maternal care and emotionality following separation-induced stress

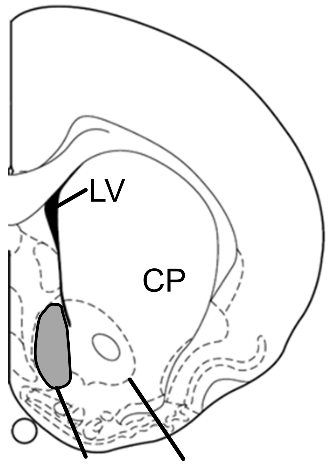
What do we know about the Nacc?

CRF system in prairie voles

- CRF immunoreactive fibres and CRF receptors **Lim et al., 2007**
- CRF-R2 more and CRF-R1 less abundant in monogamous *versus* non-monogamous vole species **Lim et al., 2005**
- pair bond formation is facilitated by acute CRF signalling in the NAcc **DeVries et al., 2002; Lim et al., 2007**

…and in rats

- severe stress switches CRF actions from being appetitive to aversive **Lemos et al., 2012**
- CRF-R activation increases depressive-like behavior **Chen et al., 2012**



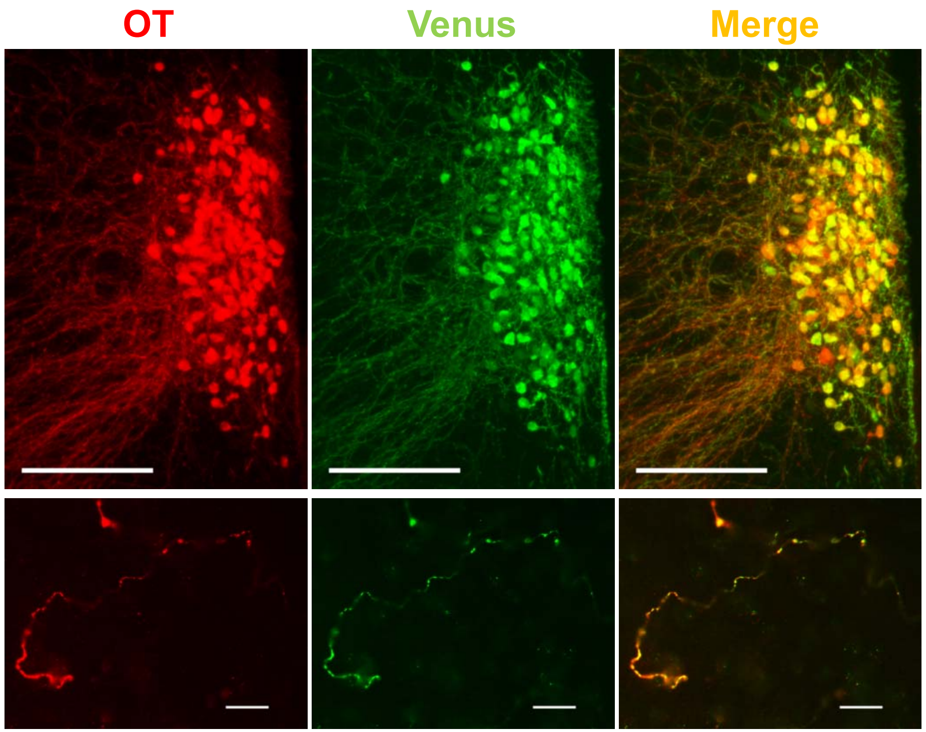
OT system

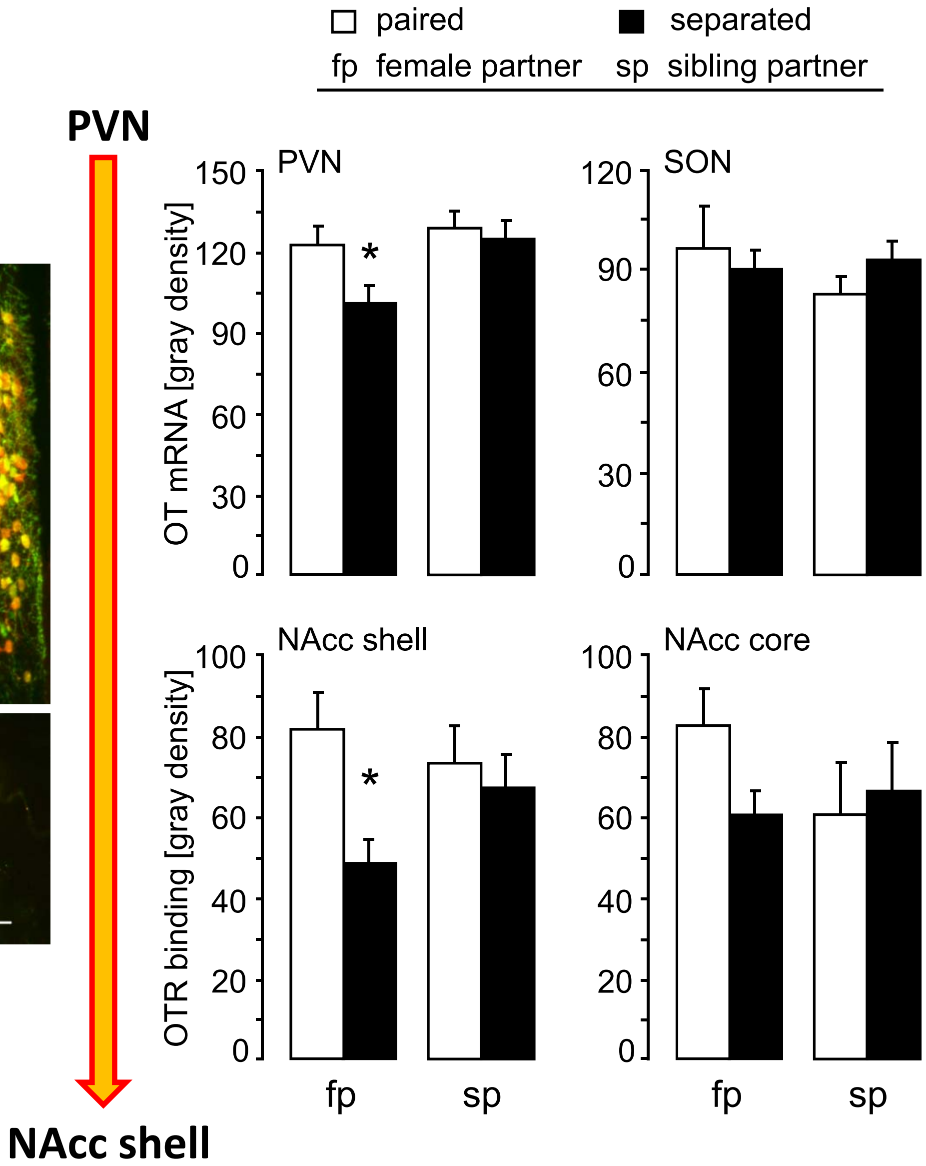
- OT mediates social buffering against stressors in female prairie voles **Smith and Wang, 2014**
- In NAcc shell of rats, OT axons mainly from PVN **Ross et al., 2009**
- In rats, >99% of OT neurons in the hypothalamus co-express CRF-R2 **Dabrowska et al., 2011**

Oxytocin neurons in PVN and NAcc shell

90% of OT fibres innervating NAcc shell originate from PVN

(OT-Venus virus)





Bosch et al., 2016 *PNEC*

Oxytocin neurons in PVN and NAcc shell

90% of OT fibres innervating NAcc shell originate from PVN

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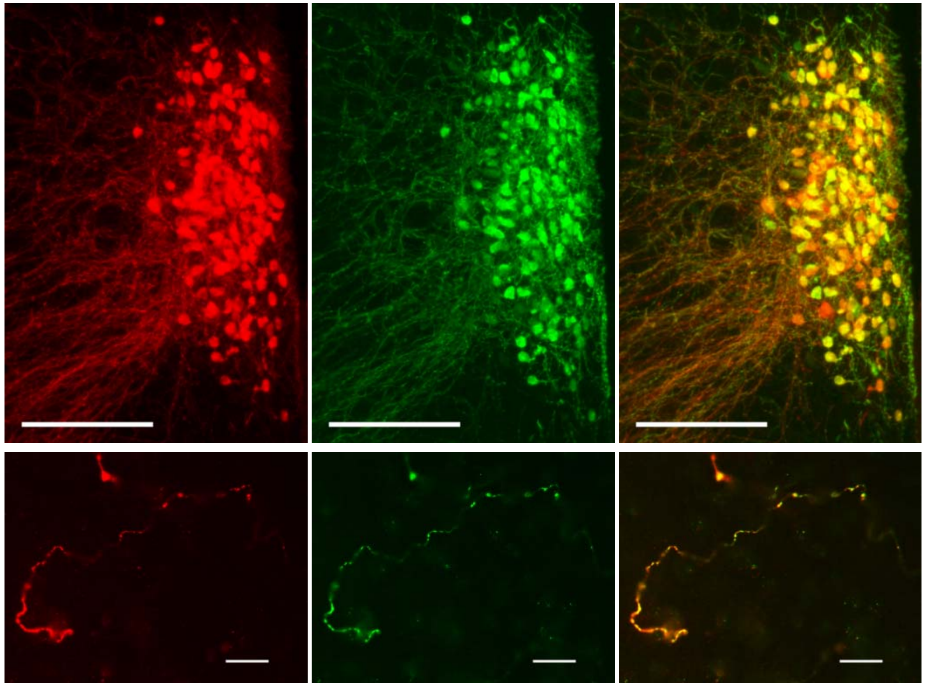
OT Venus Merge

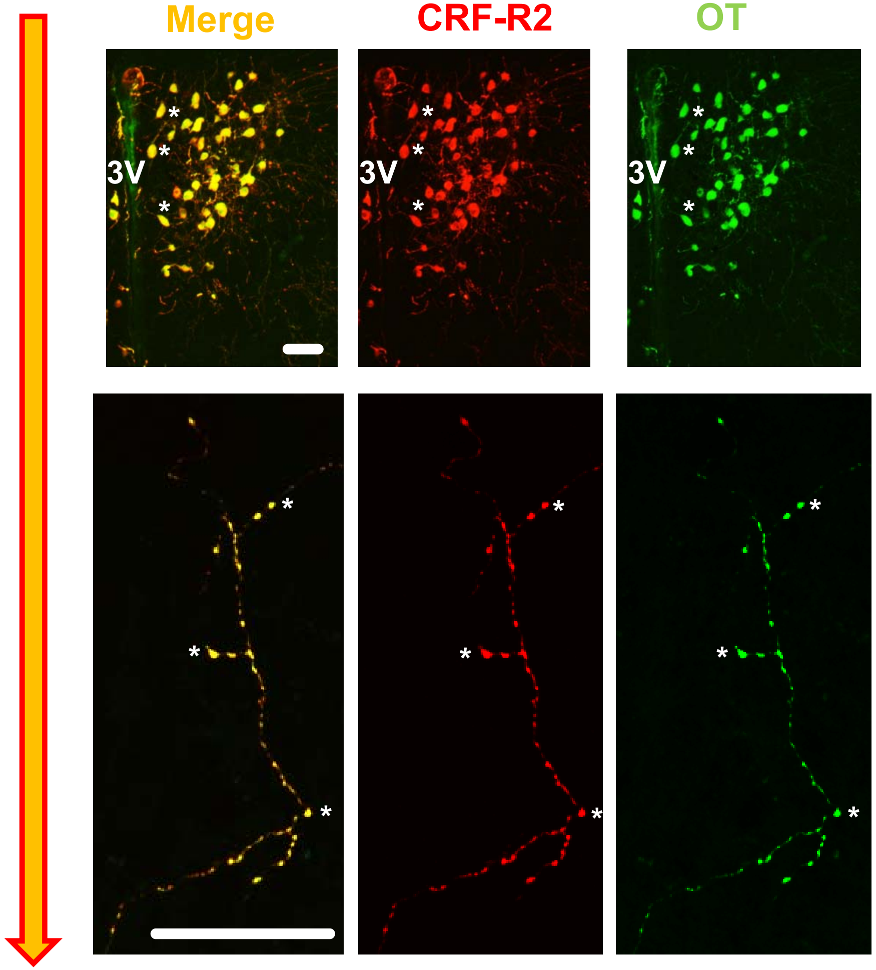


Co-localization of CRF-R2 on OT neurons

(immunohistochemistry)

PVN

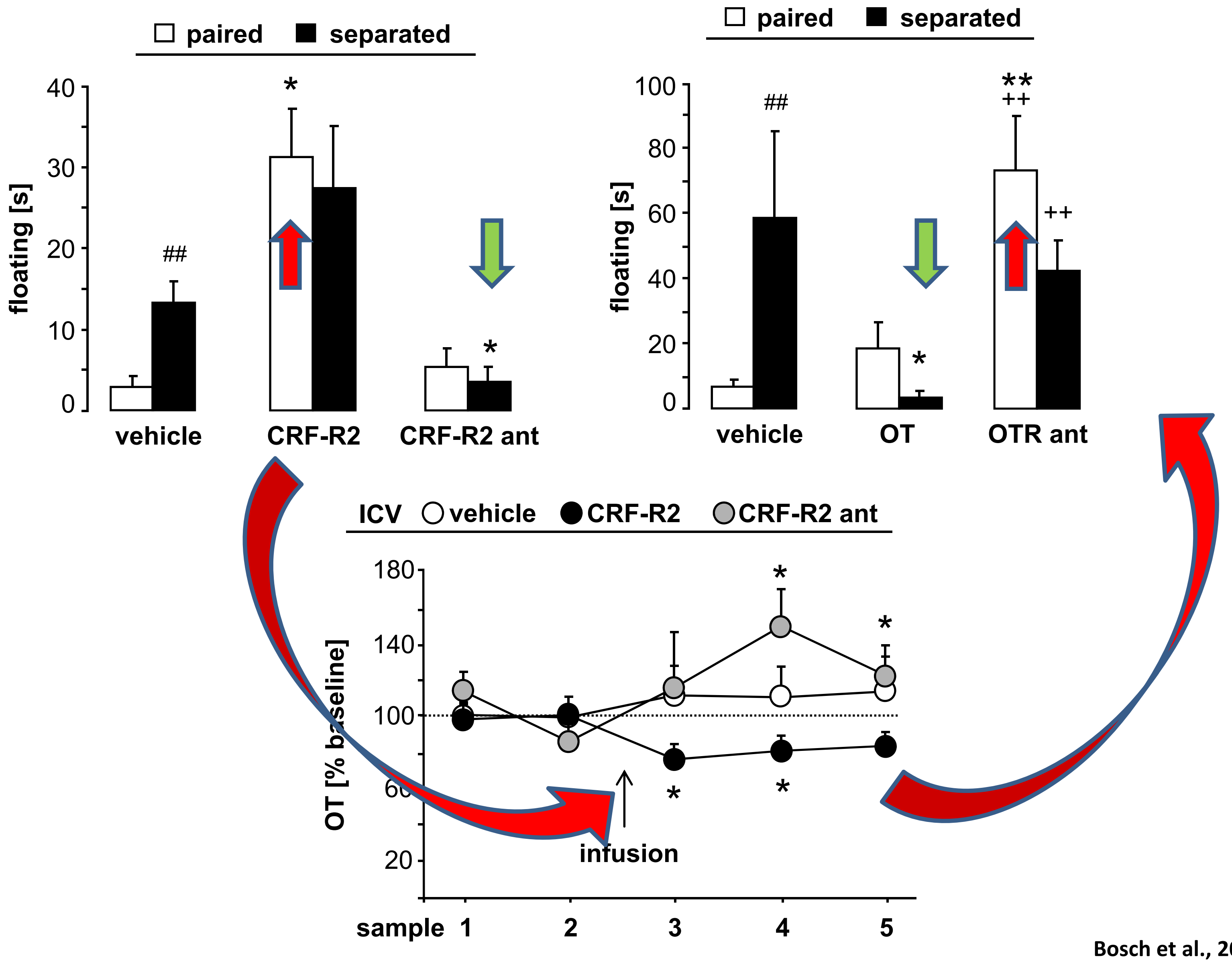
Merge CRF-R2 OT



NAcc shell

Bosch et al., 2016 *PNEC*

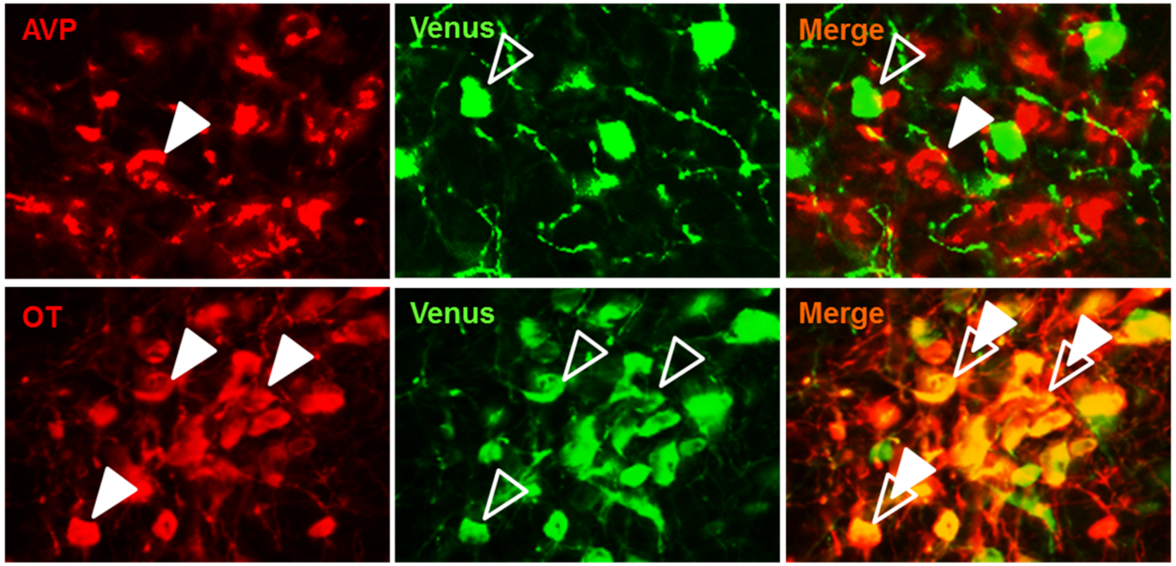
Separation impairs OT signalling via CRF-R2 activation in NAcc



Bosch et al., 2016 *PNEC*

Ephys evidence for CRF-R2 – OT neuron interaction in PVN

recordings from OT axons in the NAcc not feasible → record from PVN neurons



Joanna Dabrowska

Identification via double-labelling OT-Venus

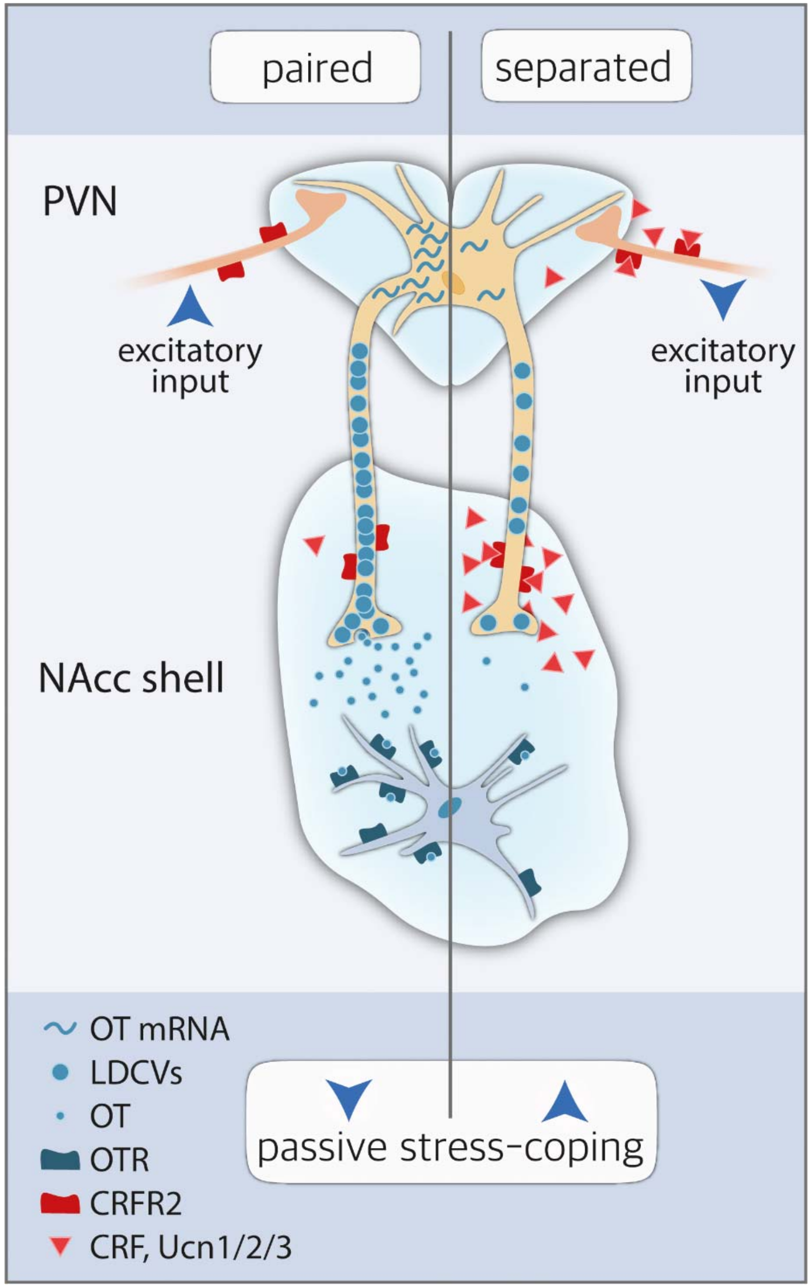
Activation of CRF-R2 by stresscopin

→ acts primarily at pre-synaptic locus to regulate excitatory drive onto OT neurons

→ **CRF-R2 activation decreases glutamate drive and excitability of OT neurons**

Bosch et al., 2016 *PNEC*

well-being ↑



well-being ↓

Tobias Pohl

→ separation acts as chronic stress

→ encourages reunion with the partner

In humans: activated NAcc in complicated grief
O'Connor et al., 2008

Bosch & Young, 2018 *CTBN*
Pohl et al., 2019 *Int J Psychophysiol*

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