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Affiliative Social Interactions Activate Vasopressin-Responsive Neurons in the Mouse Dorsal Raphe

Tirth Patel

Rowan University

Hanna O. Caiola

Rowan University

Olivia Mallari

Rowan University

Benjamin D. Rood

Rowan University

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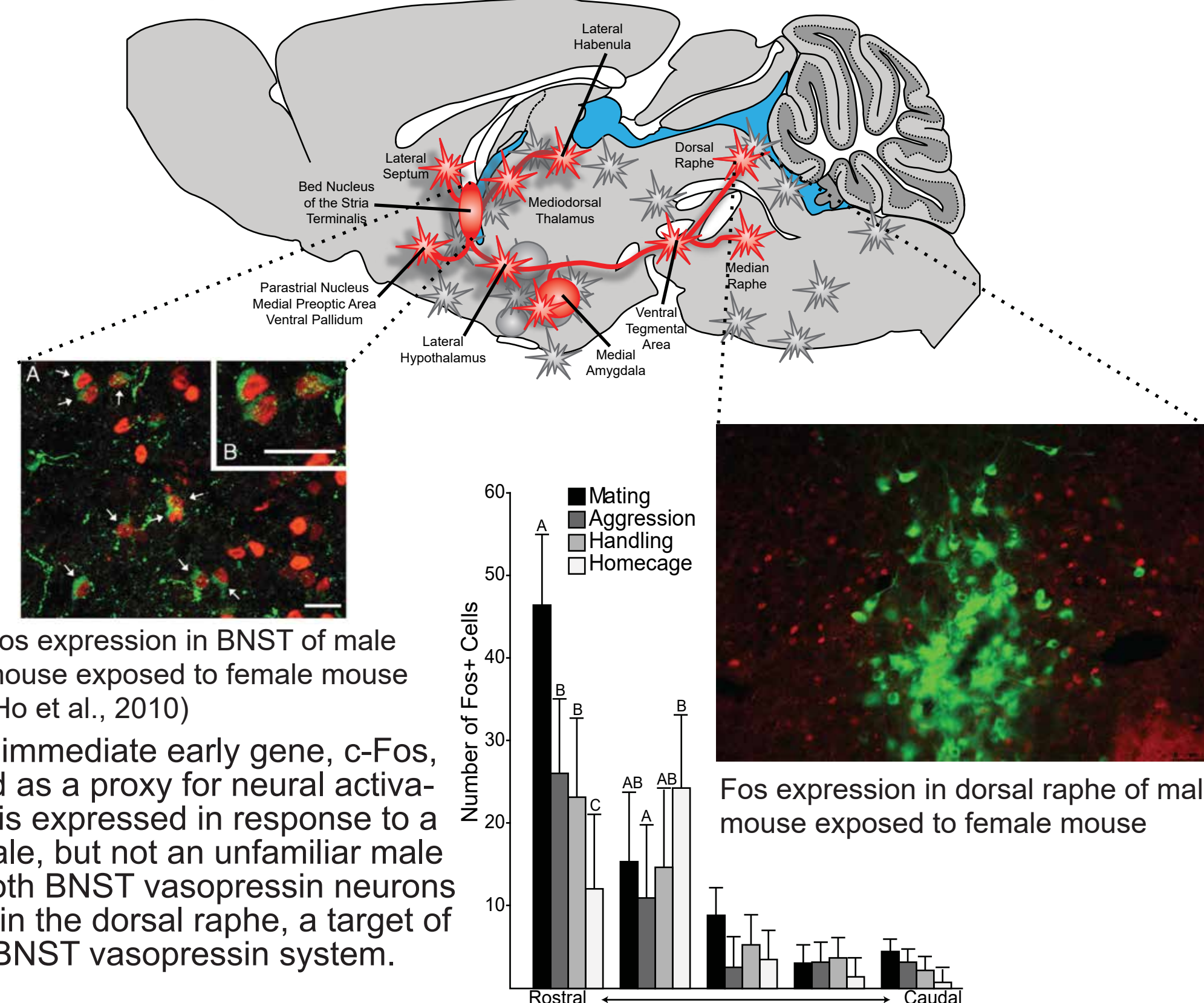
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Introduction

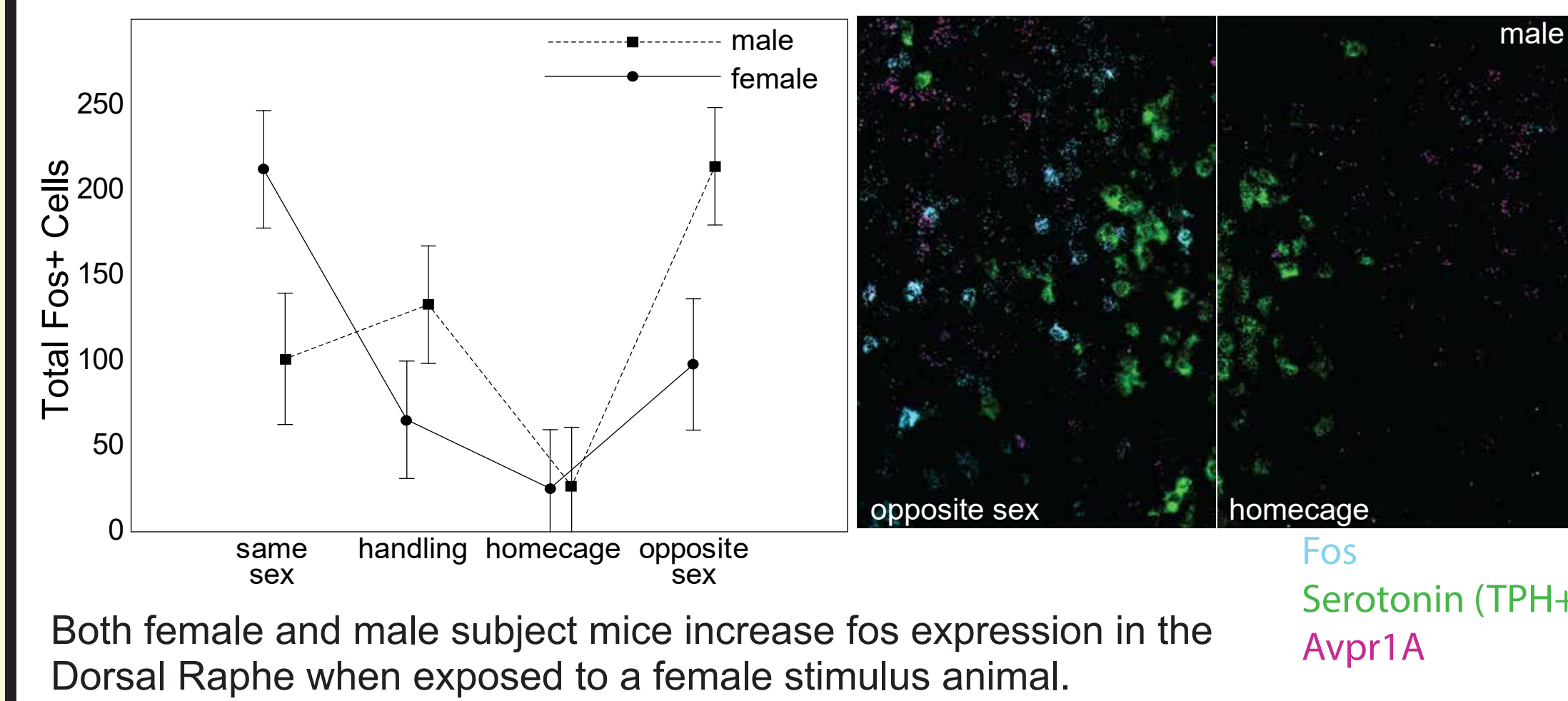
Social behavior is inextricably linked to human health shaping both our susceptibility and resilience to disease and stress. Positive interactions as simple as maternal contact or friendships among children and adults can protect against emotional distress and improve treatment outcomes, whereas negative interactions such as abuse, social isolation, or bullying can increase aggression and precipitate mood disorders. Discovering the structure and function of neural circuits underlying social behavior is critical to understanding the link between social interaction and health.

The neuropeptide vasopressin has been implicated in the regulation of multiple social interactions including social memory, aggression, mating, pair-bonding, and parental care. Vasopressin producing neurons in the bed nucleus of the stria terminalis (BNST) and medial amygdala (MeA), in particular, are predicted to be involved in social behavior. While the innervation targets of BNST and MeA vasopressin neurons and patterns of vasopressin receptor binding have been well-documented in multiple species, the identity and functional characteristics of neurons targeted by vasopressin innervation are less well understood.

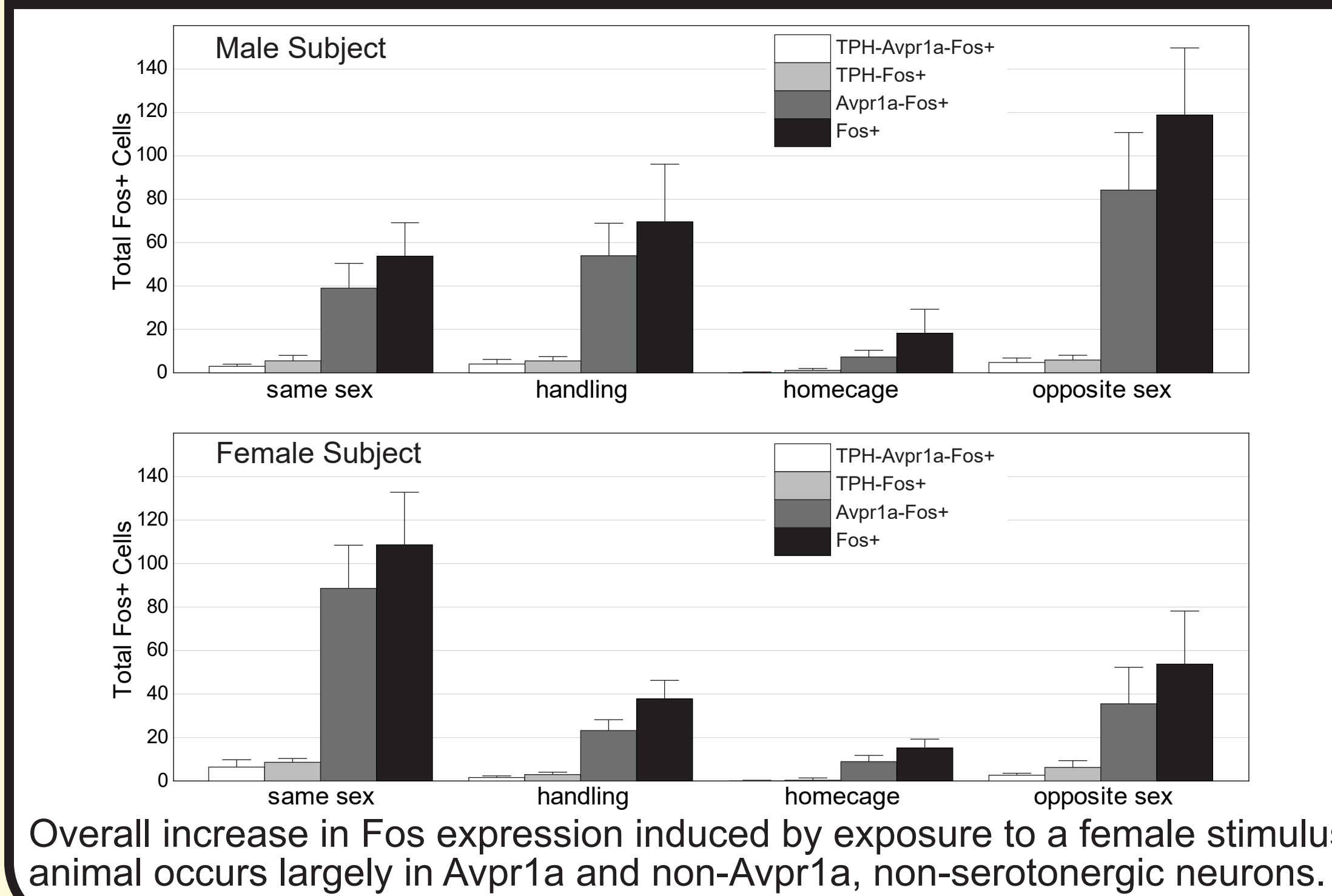
Vasopressin Social Behavior Network



In situ hybridization data suggests that Avpr1a activation in the DR may be stimulus specific

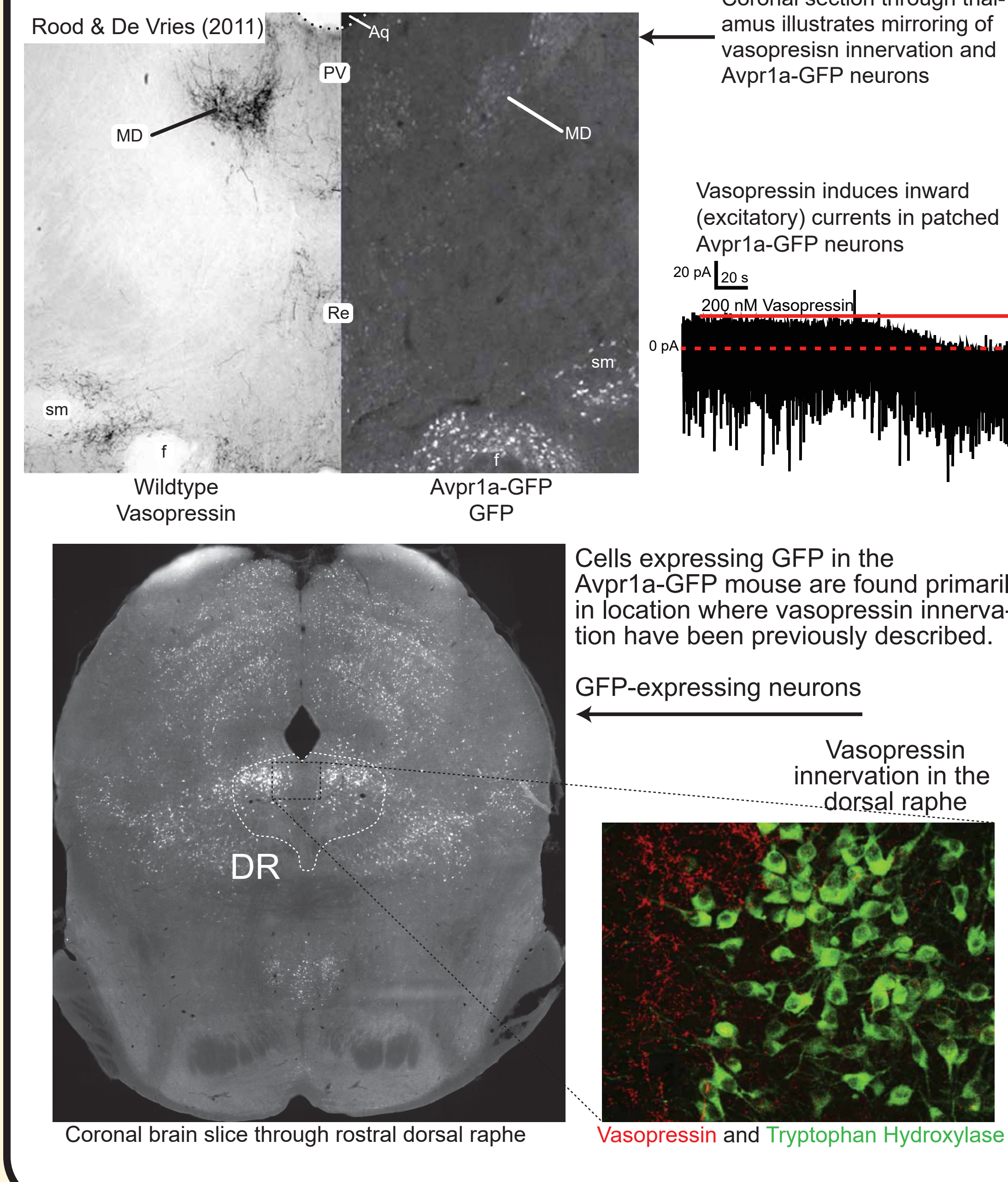


Both female and male subject mice increase fos expression in the Dorsal Raphe when exposed to a female stimulus animal.

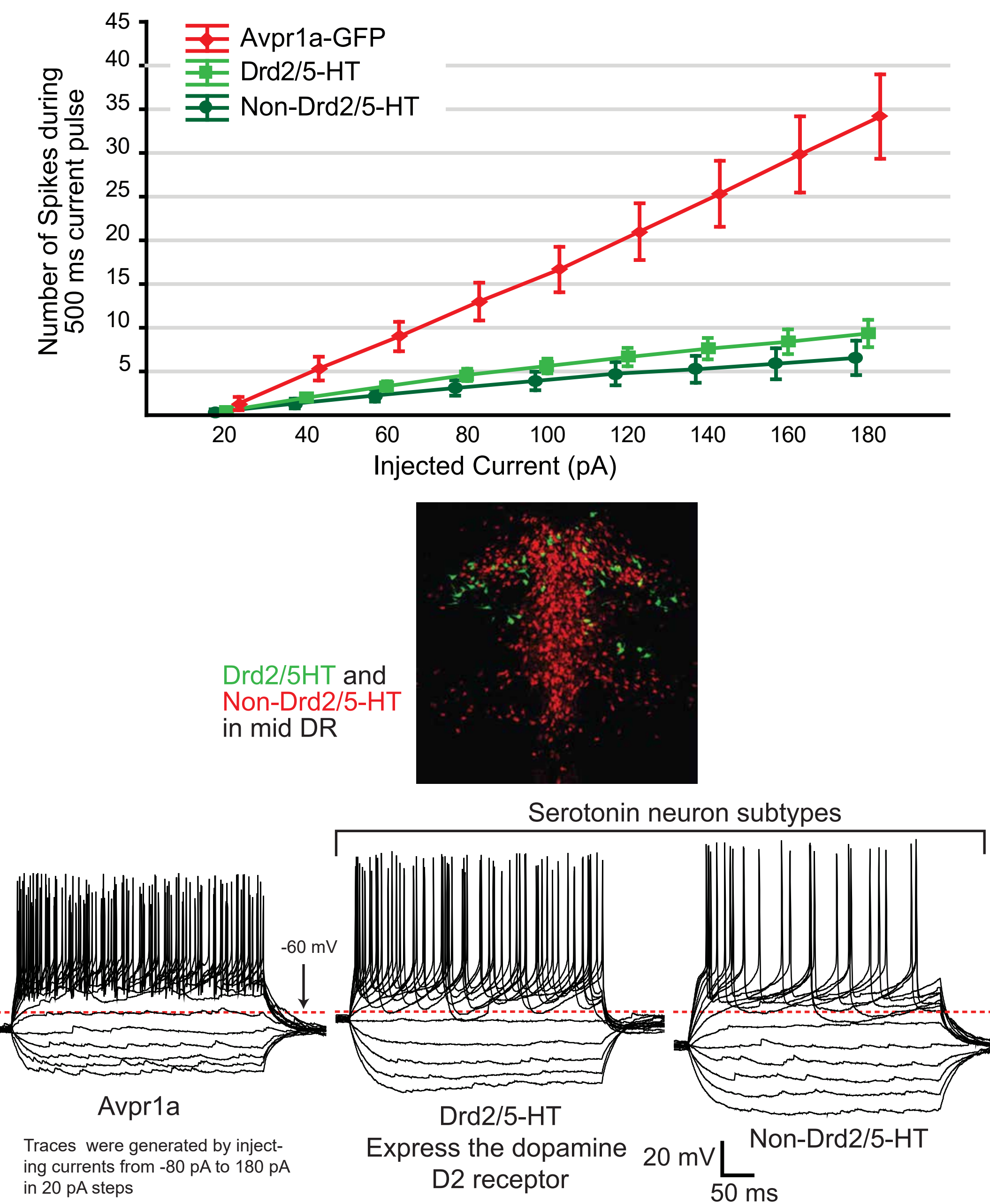


Overall increase in Fos expression induced by exposure to a female stimulus animal occurs largely in Avpr1a and non-Avpr1a, non-serotonergic neurons.

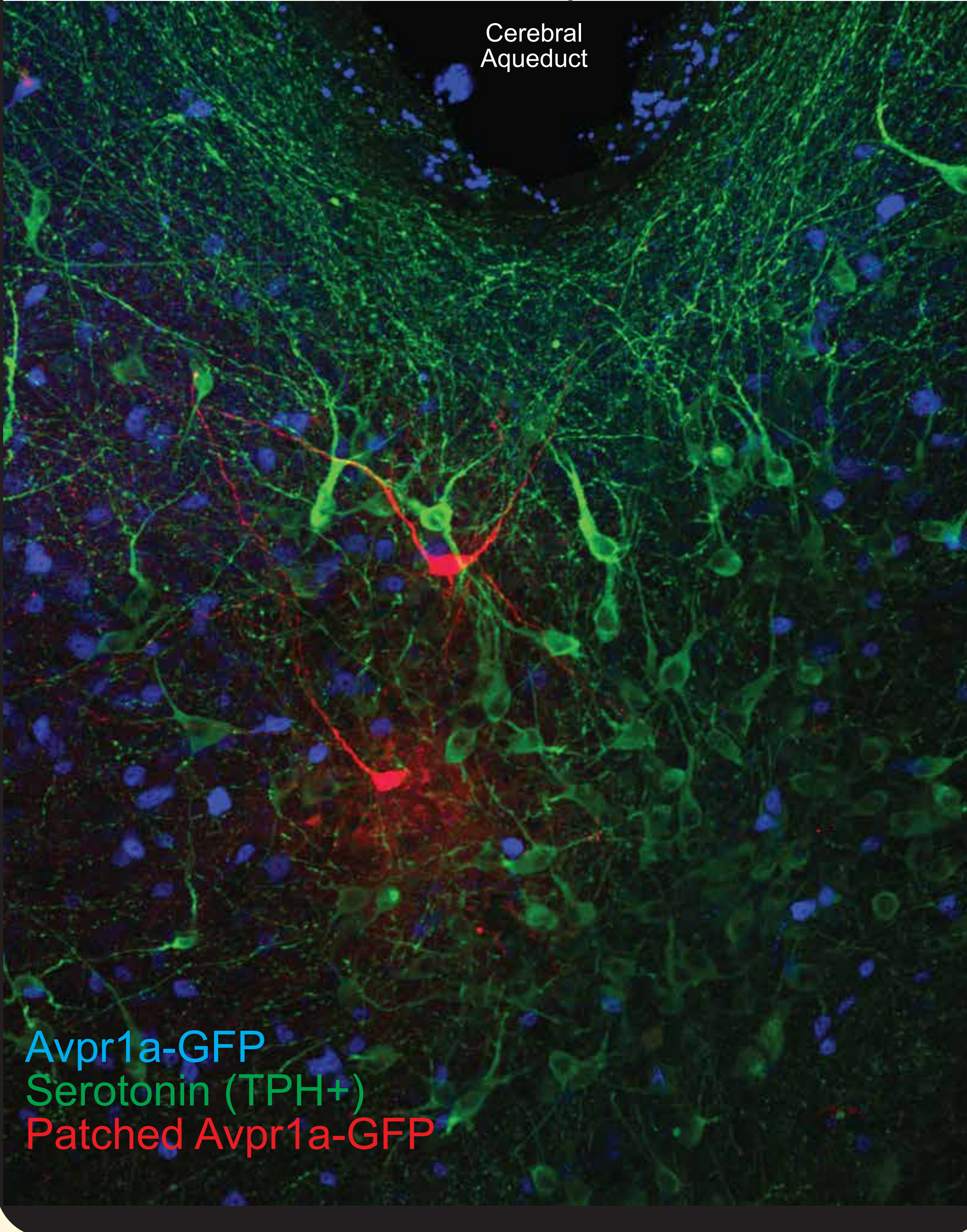
Avpr1a-GFP mouse: GFP expression mirrors AVP innervation zones and GFP+ neurons respond to vasopressin



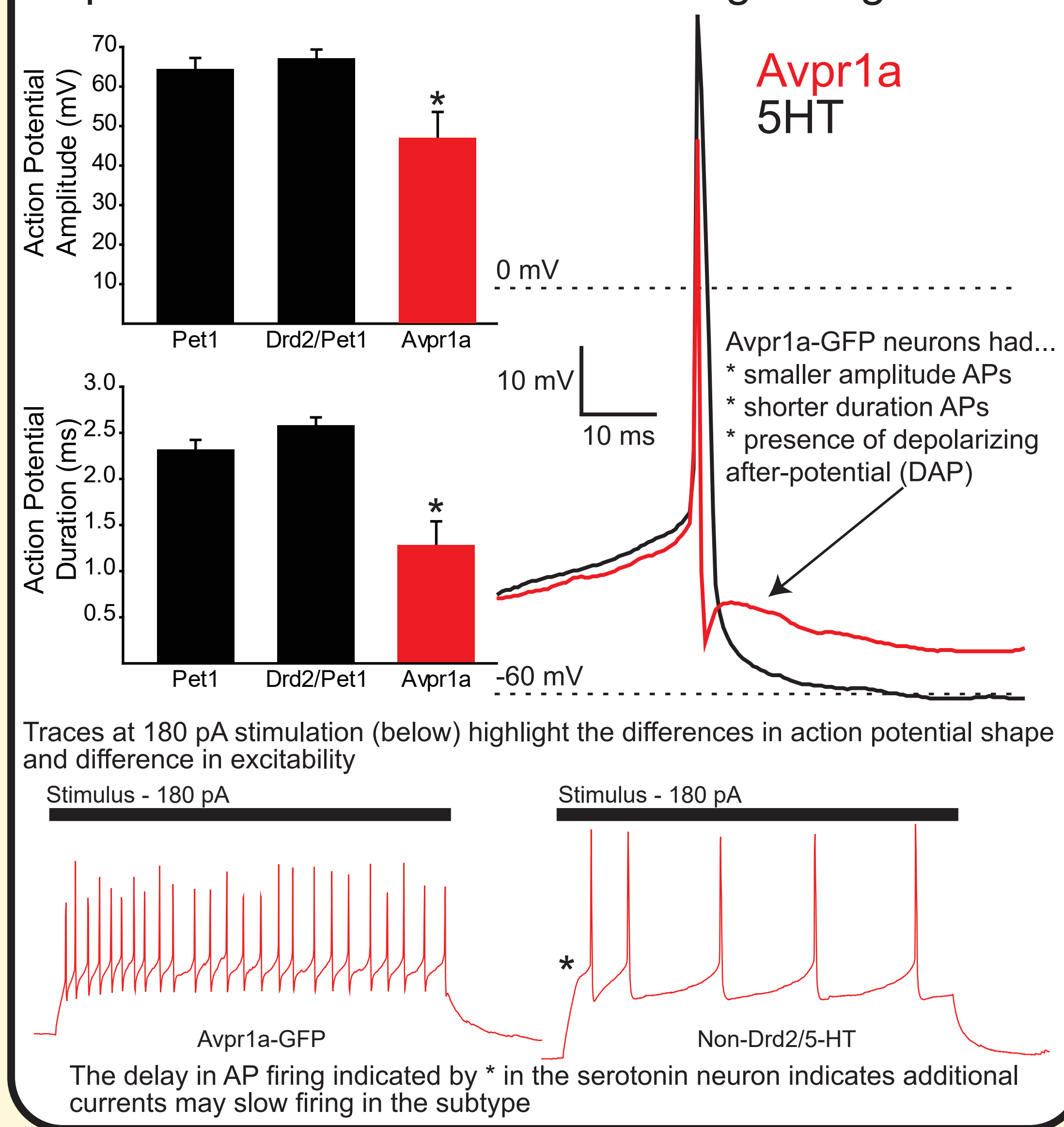
Avpr1a-GFP neurons are highly excitable compared to multiple subtypes of neighboring serotonin neurons



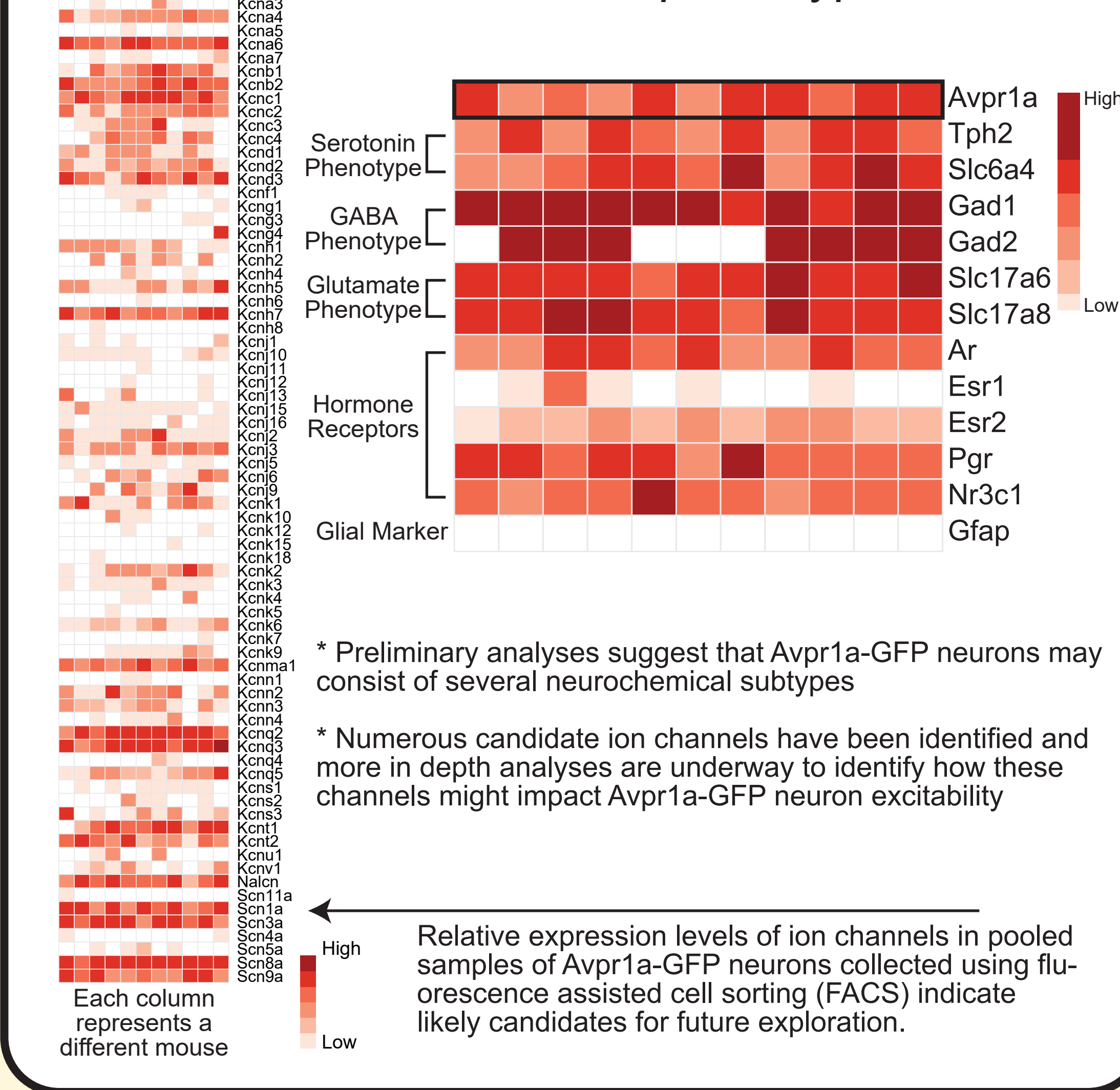
Who are the vasopressin responsive neurons of the dorsal raphe?



Action potentials differ between vasopressin-responsive neurons and serotonergic neighbors



Future directions: Use transcriptome analysis to identify genes that underlie Avpr1a-neuron excitability and neurochemical phenotype.



Results & Conclusions

Vasopressin neurons in the extended amygdala are activated by mating stimuli. A subset of neurons in the dorsal raphe, a target region of extended amygdala vasopressin neurons, is also activated by mating as measured by increases in c-fos.

In situ hybridization for Avpr1a, tryptophan hydroxylase, and c-fos mRNA (a gene up-regulated by neuronal activity) revealed that, in both male and female subjects, exposure to a female stimulus animal increased c-fos expression in the DR both in Avpr1a+ neurons and non-Avpr1a neurons.

Our data verify the existence of AVP-responsive neurons in the DR and suggest that activation of Avpr1a+ neurons in the DR is stimulus specific, and may be initiated by more affiliative, less antagonistic interactions.

Avpr1a neurons have distinct physiological properties compared to neighboring serotonin neurons. Avpr1a neurons have small amplitude short duration action potentials. During the after-hyperpolarization Avpr1a neurons have depolarizing after potential. These properties likely facilitate the high firing rates observed in these neurons.

Preliminary gene expression studies suggest a number of candidate ion channels that may underlie the hyper-excitability profile of dorsal raphe Avpr1a neurons.

Further study is needed to fully interrogate the function of AVP pathways, but one function of the BNST/MeA system appears to be activation of the neurons in the DR with potential excitatory influence on serotonin neurons.

Future work will focus on validating expression of specific ion channel genes and seek to identify the functional role of dorsal raphe Avpr1a neurons.

References

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Described Fos expression in BNST vasopressin neurons after mating in mice

Niederkofer et al. (2016) *Cell Reports*, 17(8):1934-49
First described the Drd2-expressing subset of serotonin neurons

Rood and De Vries (2011) *Journal of comparative Neurology*, 519(12):2434-74
Presented a comprehensive atlas of the mouse vasopressin system

Rood and Beck (2014) *Neuroscience*, 260:205-16
First demonstrated interaction between vasopressin and serotonin neurons in the dorsal raphe

Gong et al. (2003) *Nature*, 425(6961):917-25
GENSAT mouse program