



Menthol and other flavors promote or enhance addiction-related behaviors

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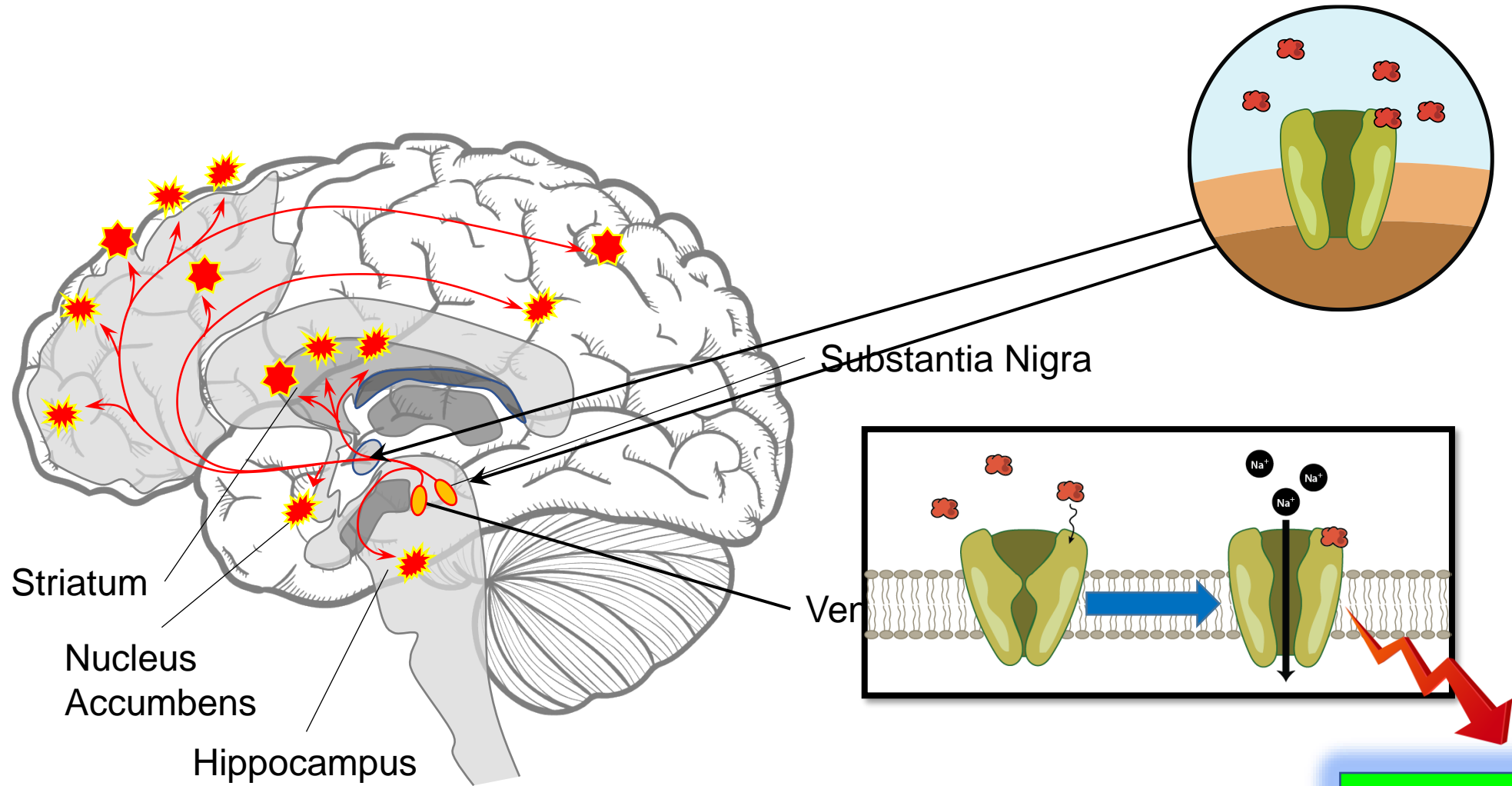
Co-Chair, Basic Science Network, Society for Research on Nicotine and Tobacco (SRNT)

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Disclosures

- Funding from the National Institutes of Health
 - K99/R00 – Characterization of Menthol and its impact on nicotine reward
 - R21 – Determination of the impact of green apple flavors on nicotine reward
 - R01 – Electronic cigarettes, adolescents, and changes in neurobiology

All Drugs of Abuse Alter Behavior by "Re-wiring" Dopamine Signaling



Euphoria or 'Feel Good' sensation

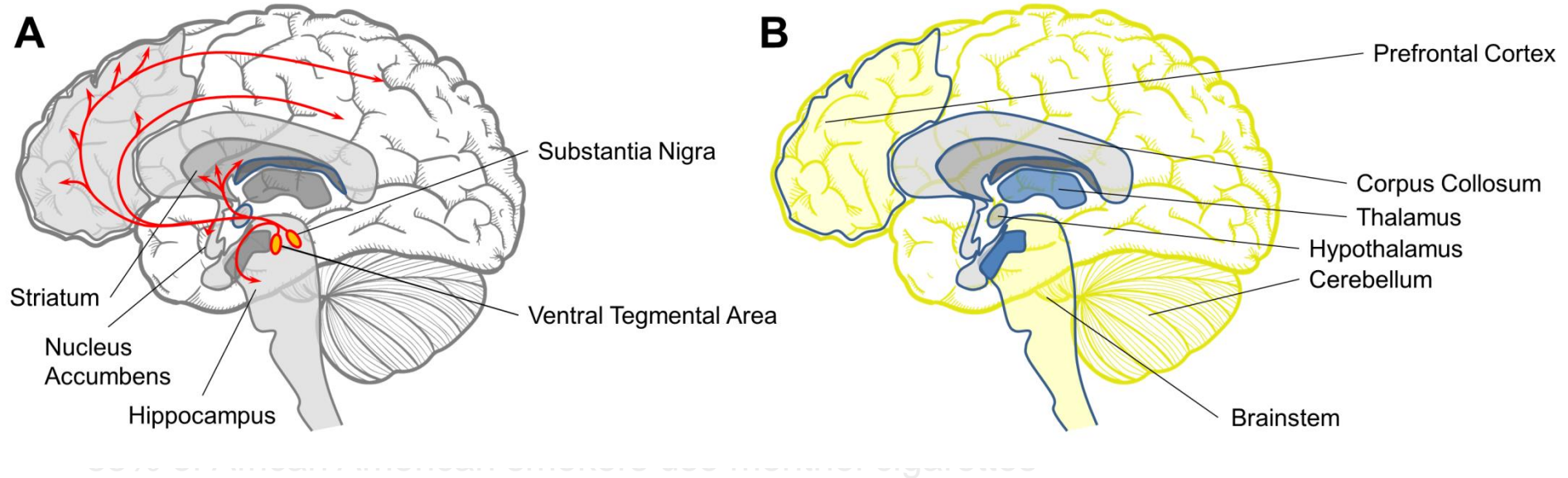
nAChRs and the Addiction to Nicotine

1. $\beta 2^*$ nAChRs are upregulated in human smokers, rodents, and cell lines
2. $\beta 2$, $\alpha 6$, and $\alpha 4$ knockout mice fail to self-administer nicotine
3. Selective activation of $\alpha 6$ or $\alpha 4$ nAChRs is sufficient for CPP and is blocked by selective antagonists

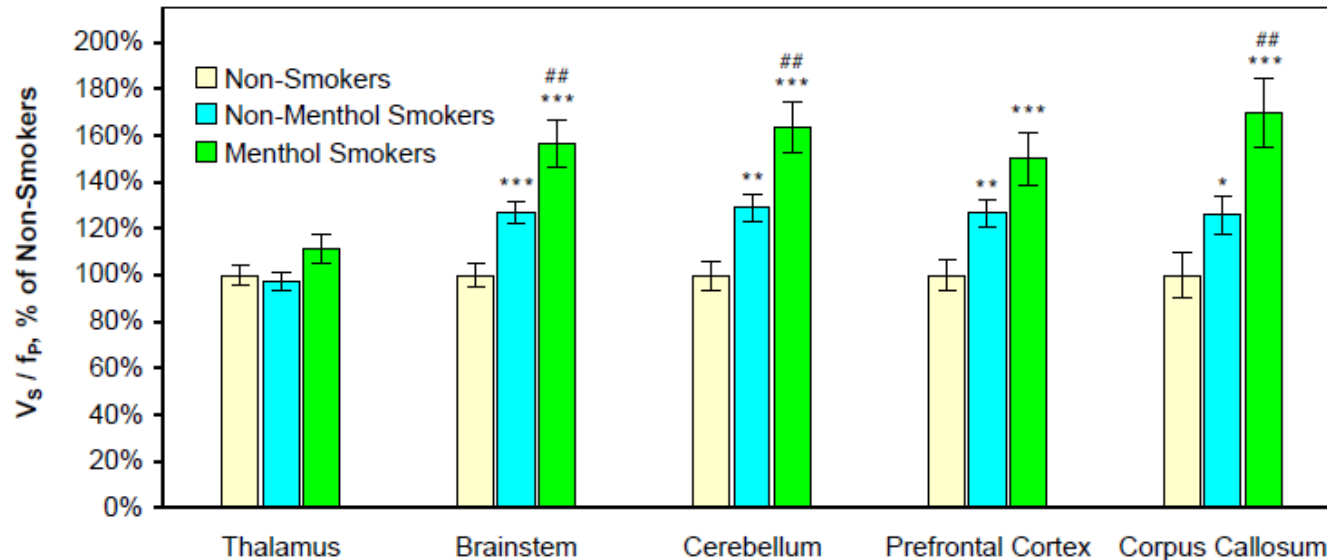


Henderson *et al.*, 2014, 2017
Drenan *et al.*, 2012 (SfN)
Kuryatov *et al.*, 2011
Pons *et al.*, 2008
Mukhin *et al.*, 2008
Nashmi *et al.*, 2007
Tapper *et al.*, 2004
Picciotto *et al.*, 1998
And many many more....

Why Study Menthol and Other Flavors?

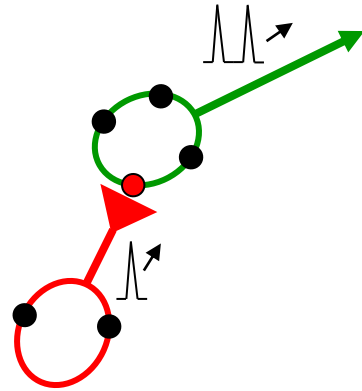


- Consumers of menthol cigarettes are less likely to quit smoking (~20% less)

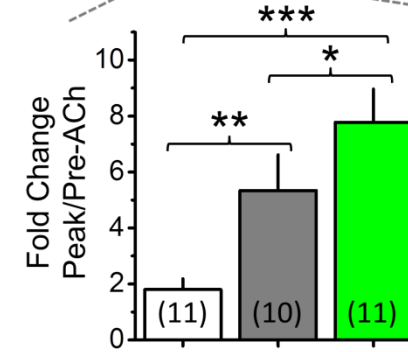
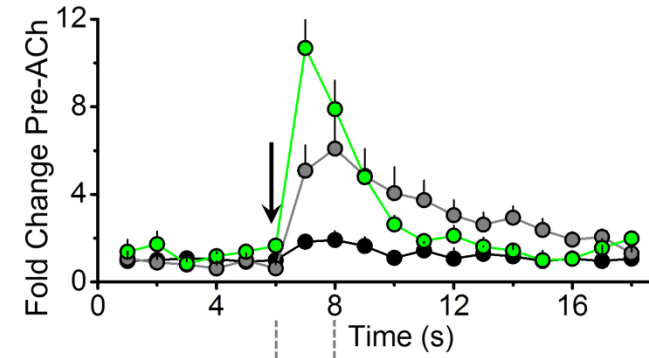
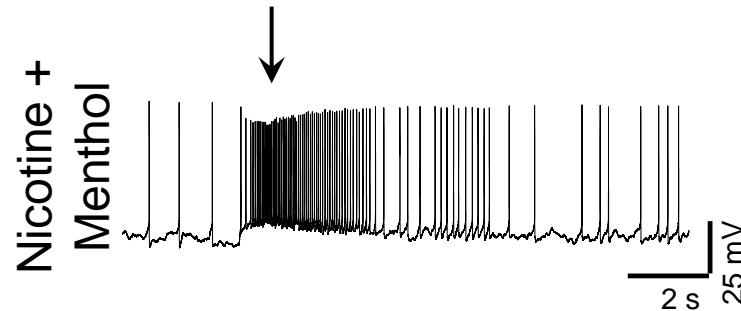
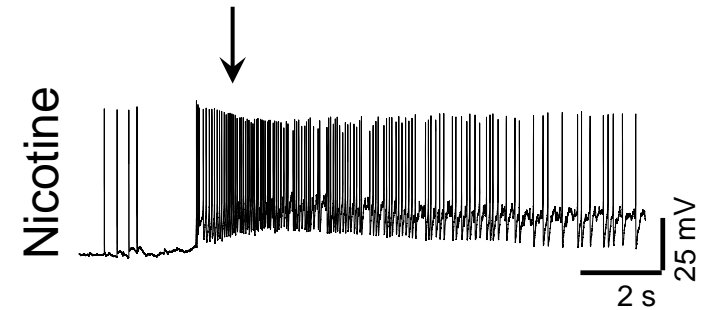
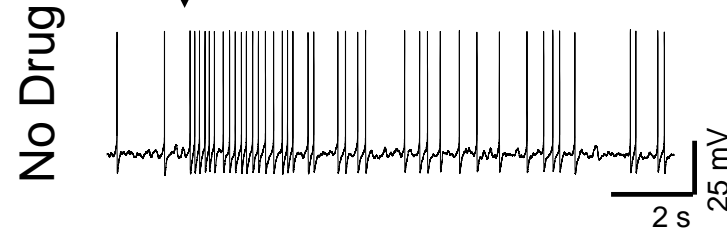


Nicotine and Nicotine + Menthol effect on midbrain neurons

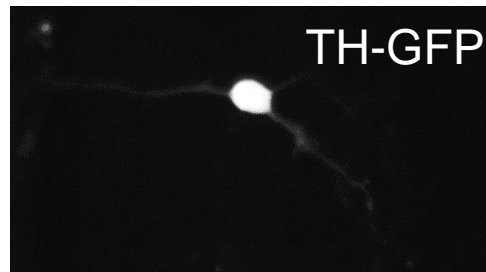
Baseline Physiology



arrows indicate, ACh puff
300 ms, 300 μ M

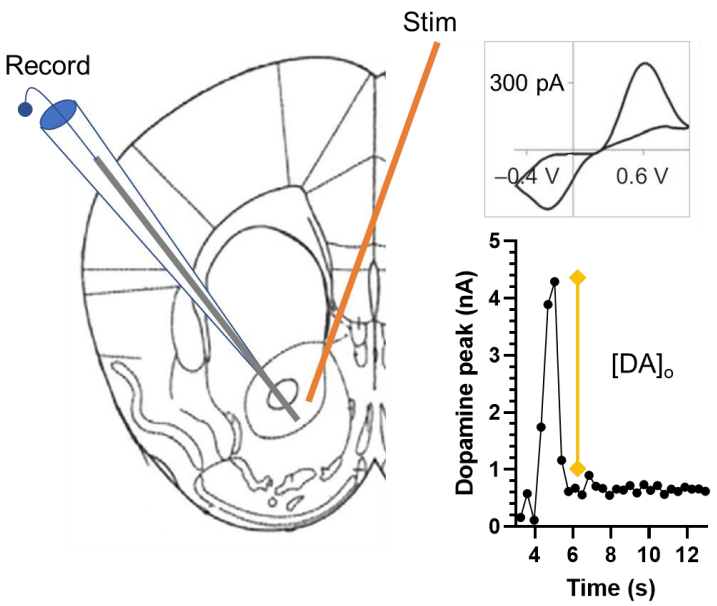


- No Drug
- Nicotine
- Nicotine + Menthol

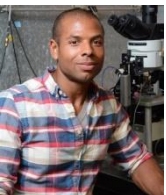
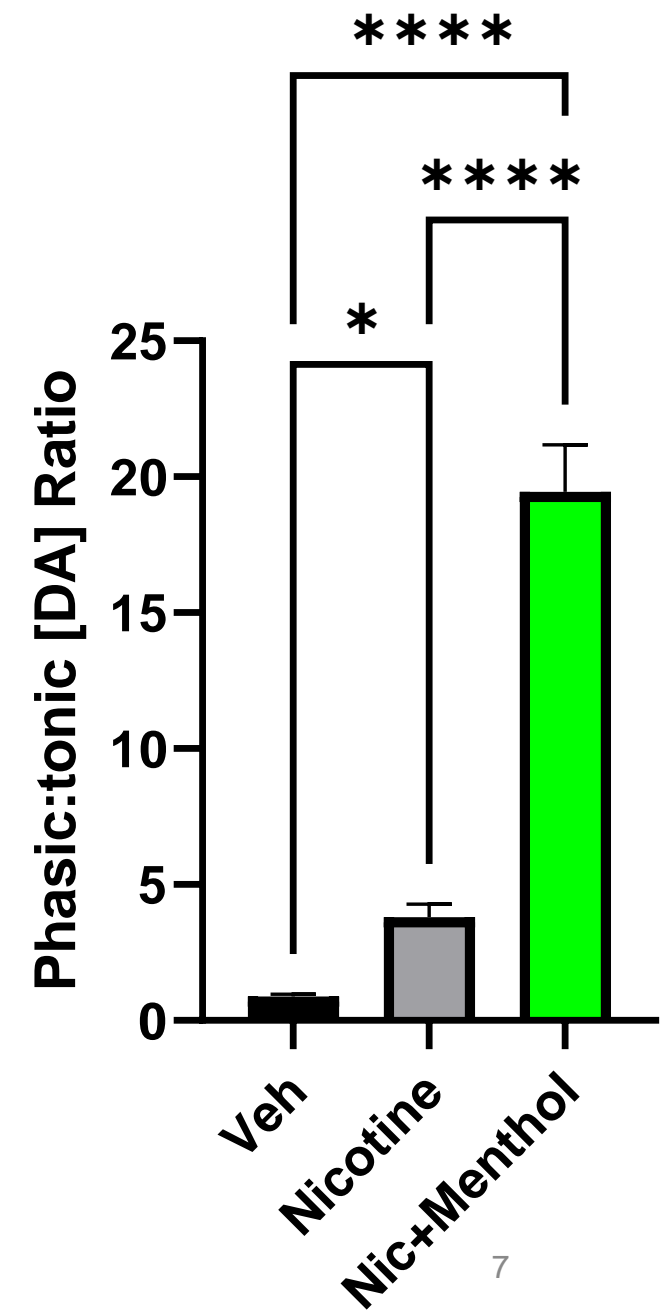
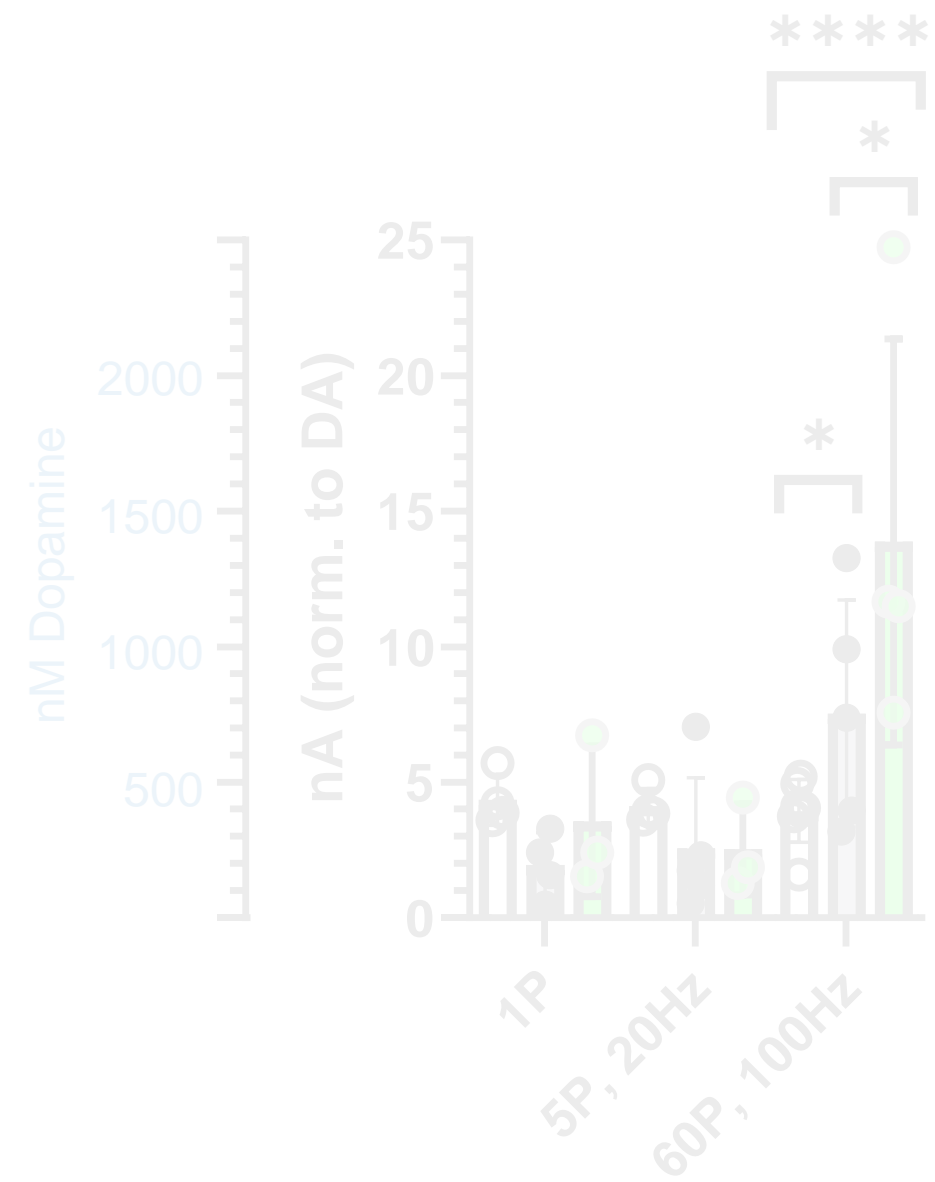


Henderson et al., 2017

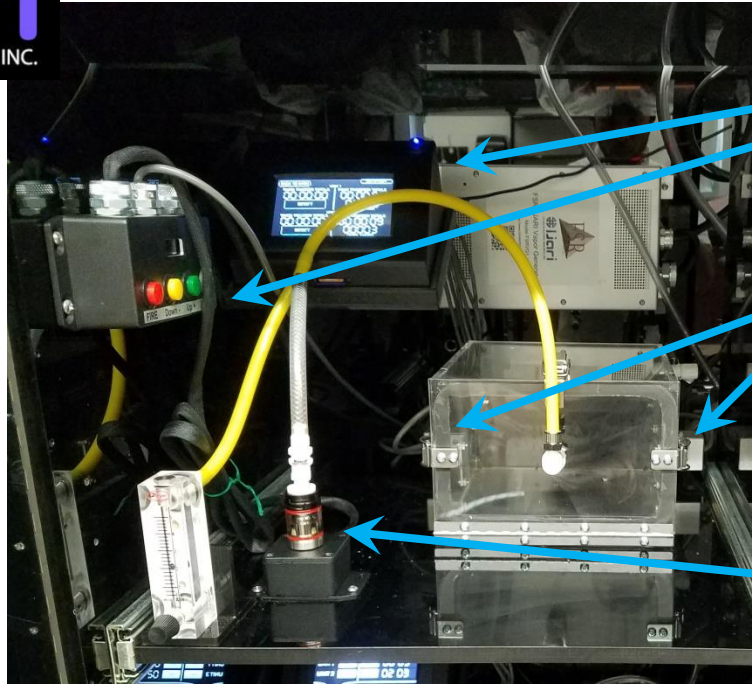
Nicotine and Nicotine + Menthol Condition-dependently Modulates Dopamine Release



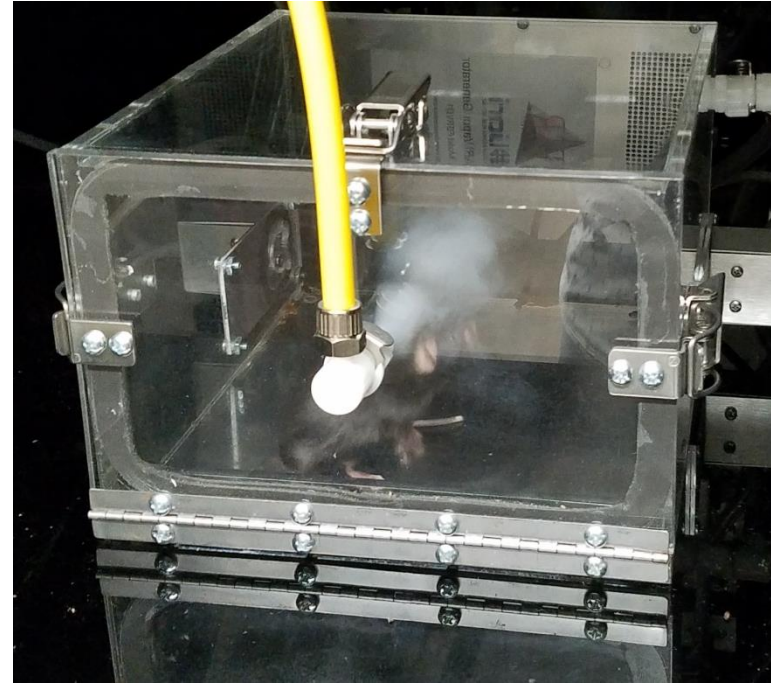
- Control
- Nic-Vape
- Nic+Men



Vapor Self-Administration in Mouse Models



Controllers
Nose Pokes
Vape Tank



*Sessions are M-F, with weekend break, 3 s delivery, 400 °F, 65 W

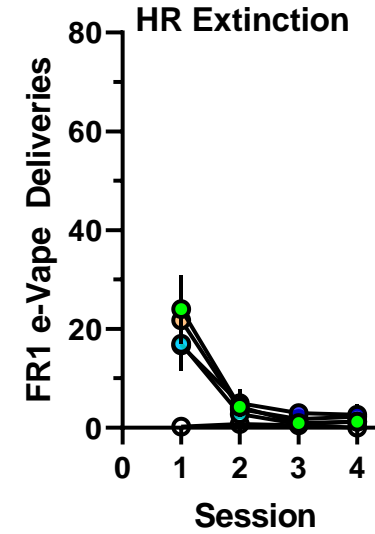
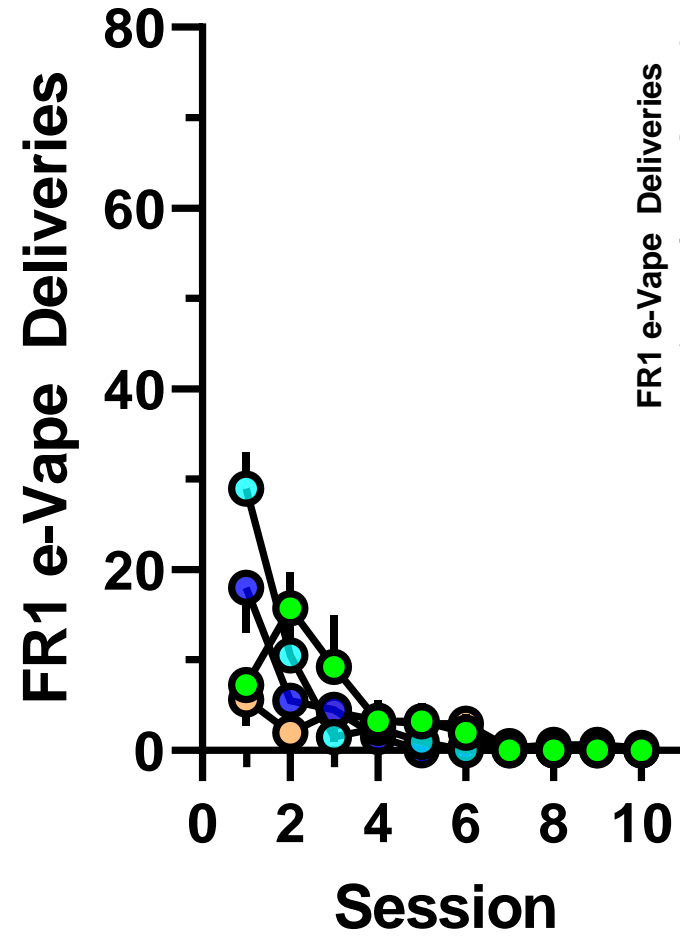
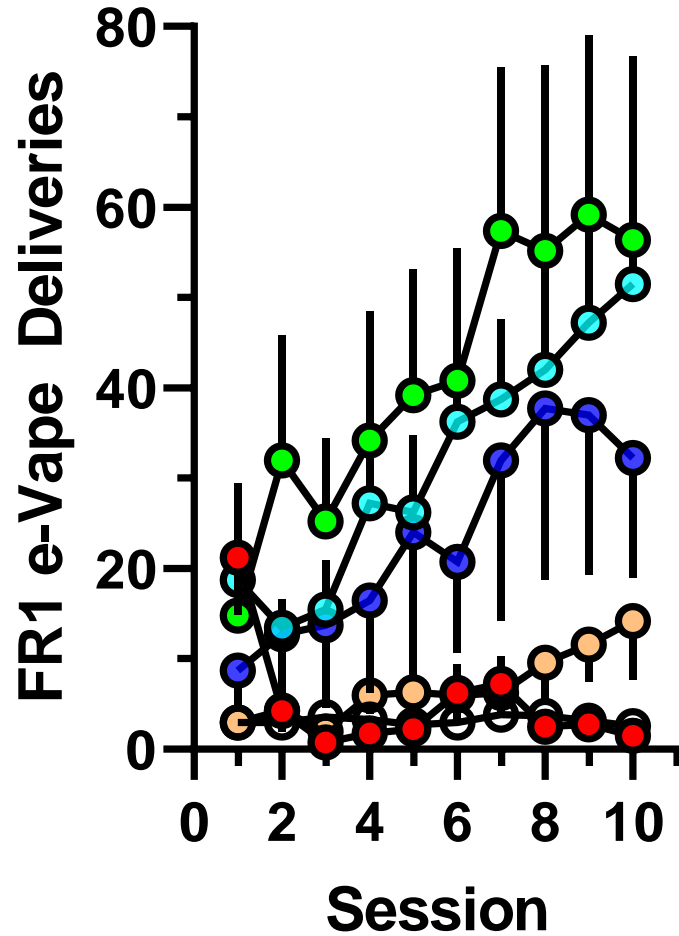
Henderson *et al.*, 2021

Cooper *et al.*, 2020, *Nic Tob Res*

Commercial E-liquids on Fixed-Ratio 1 (FR1)



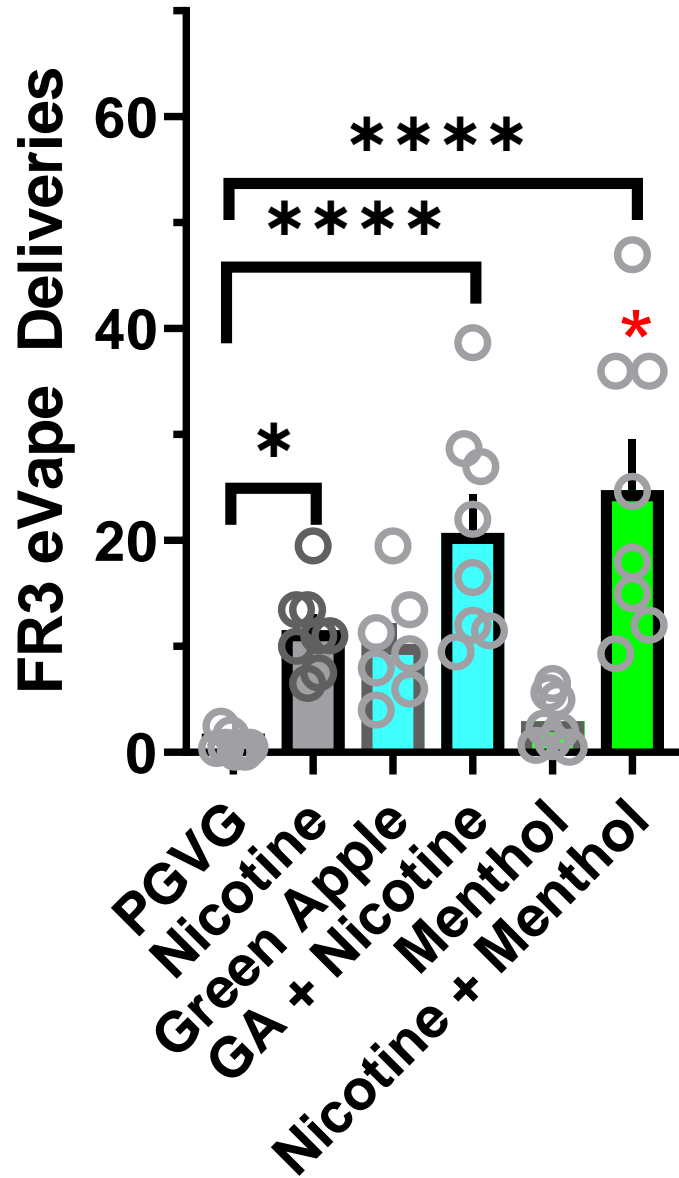
- Menthol + Nicotine
- Green Apple (GA)
- GA + Nicotine
- 6 mg/mL Nicotine
- PGVG
- Cue-Light

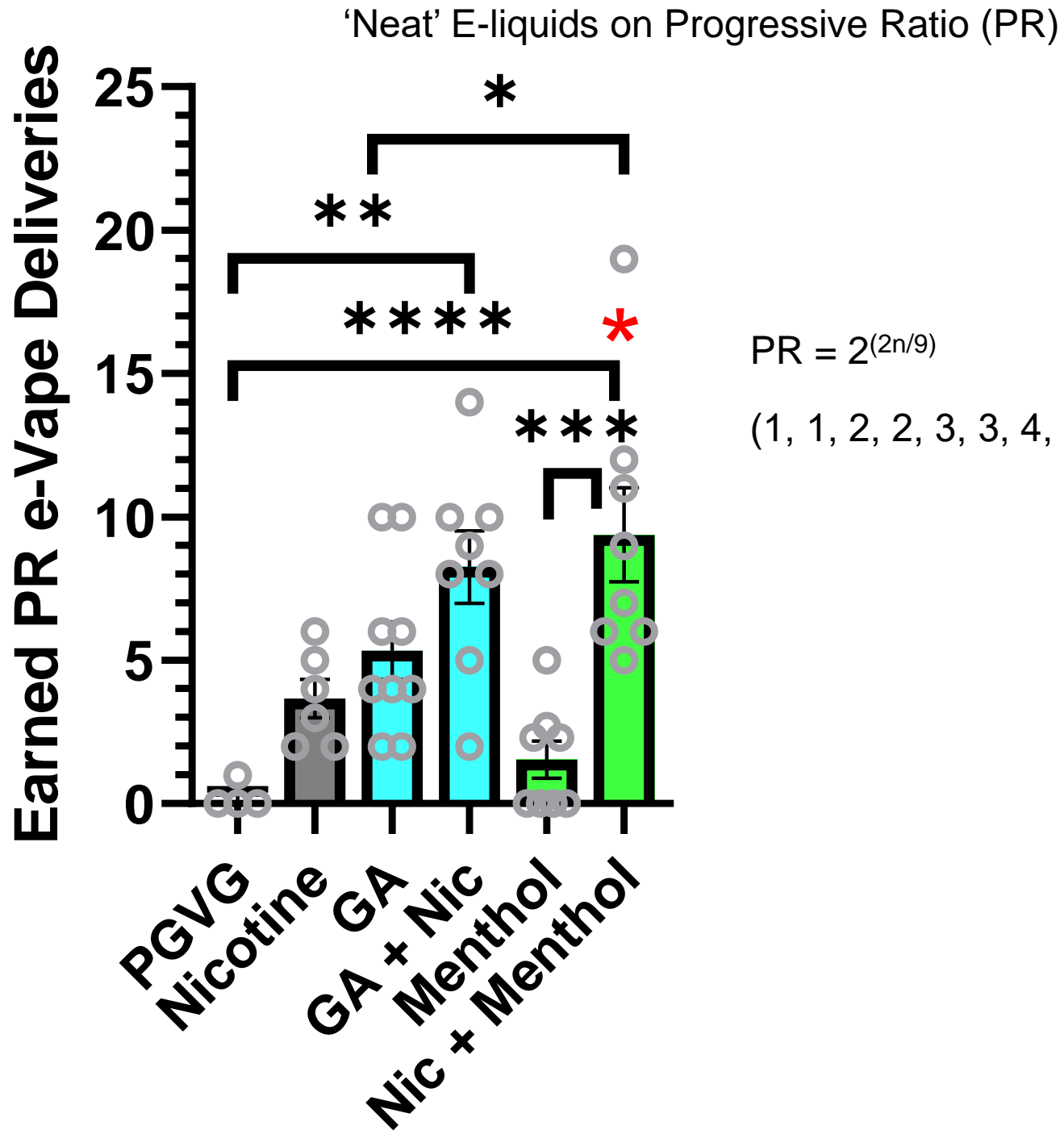


Active
Nosepoke

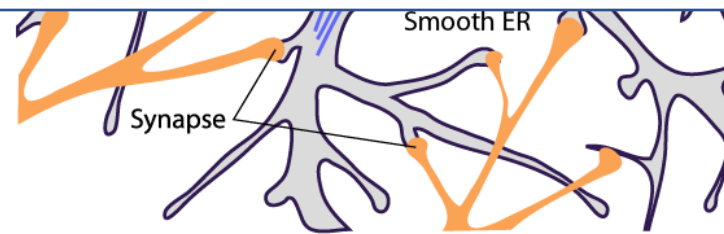
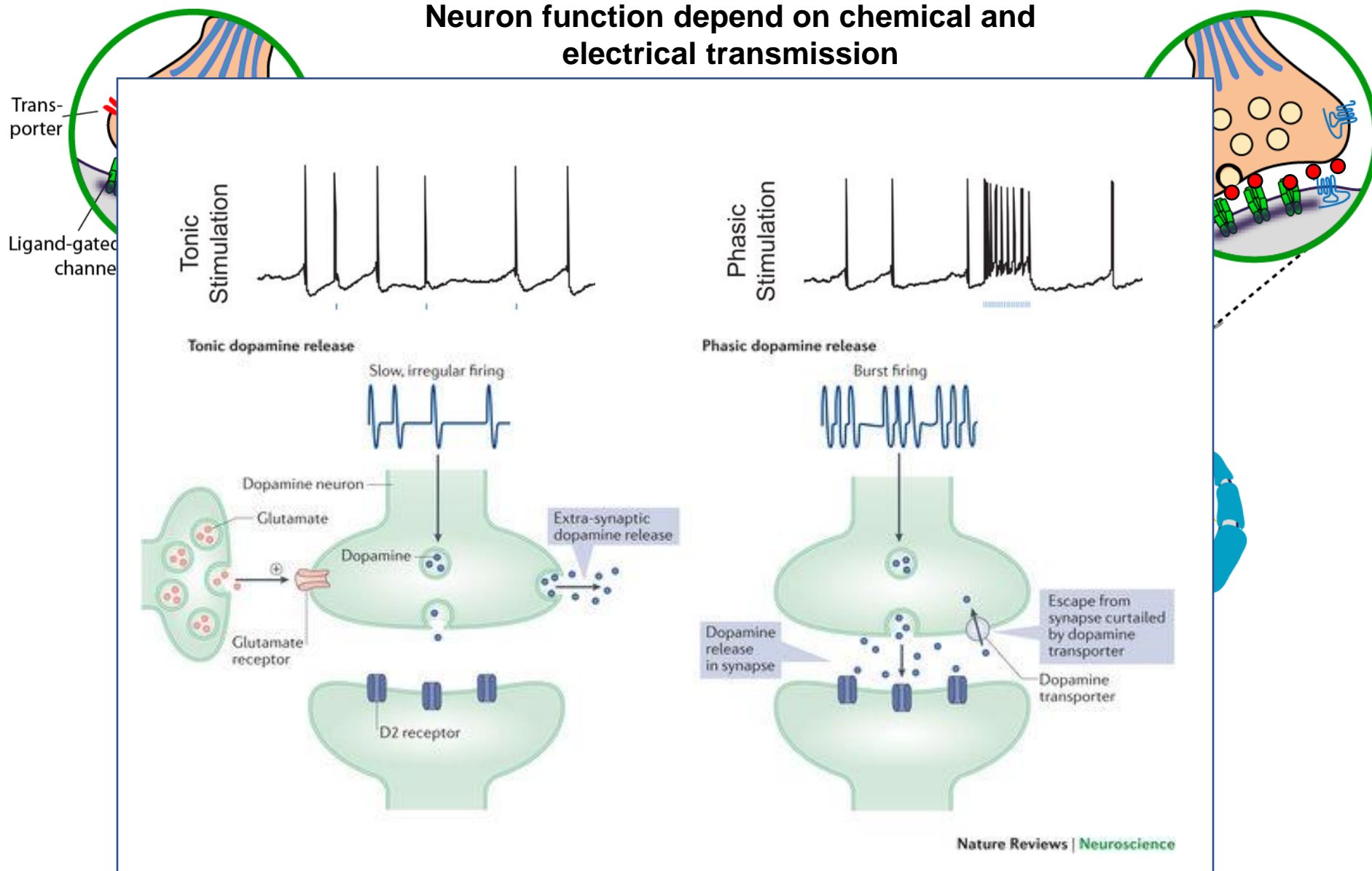
Inactive
Nosepoke

'Neat' E-liquids on Fixed-Ratio (FR3)



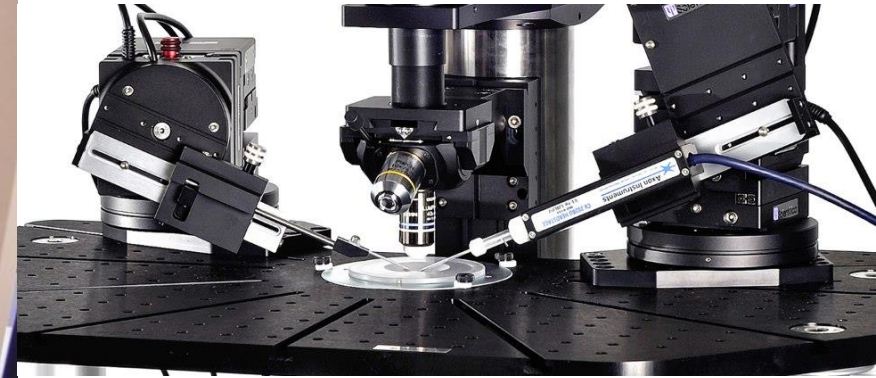


Neuron function depend on chemical and electrical transmission

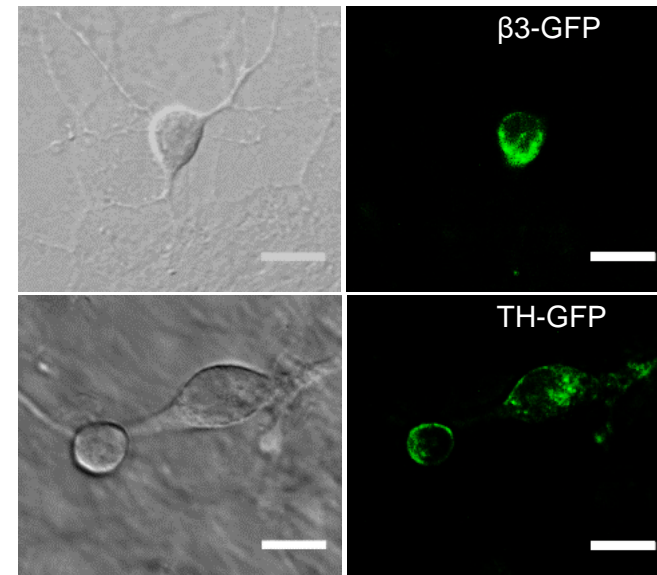
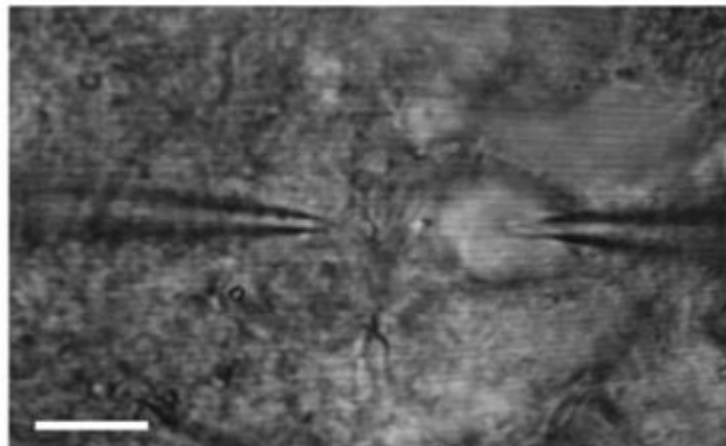


Electrical and chemical features can be studied with electrophysiology and electrochemistry

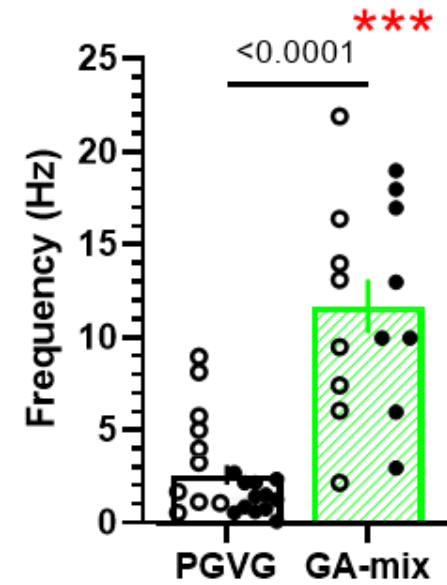
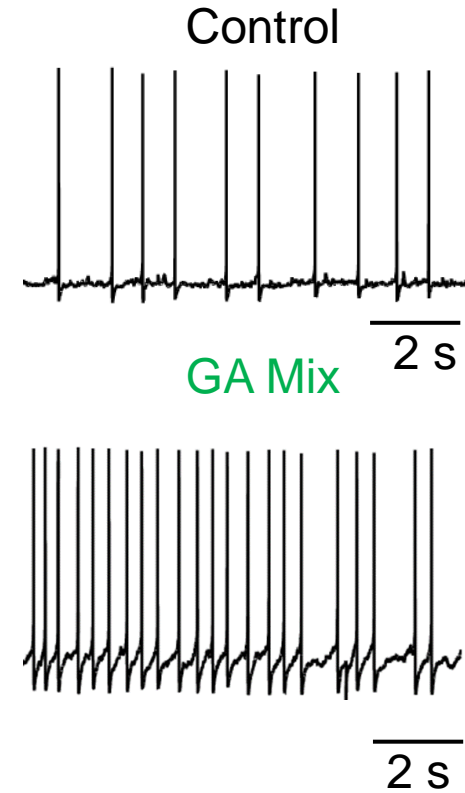
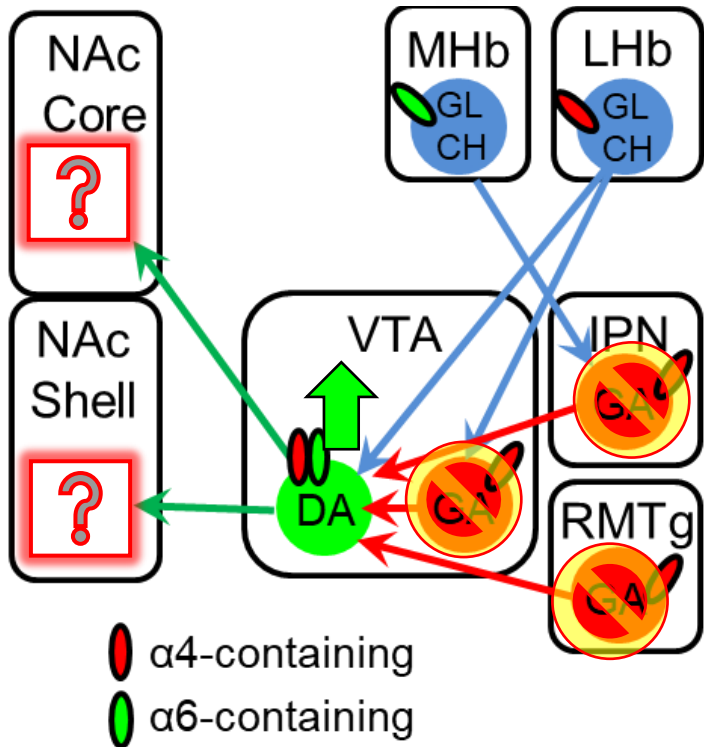
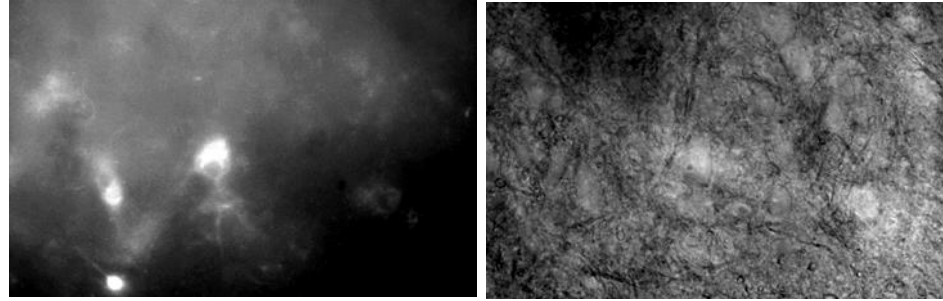
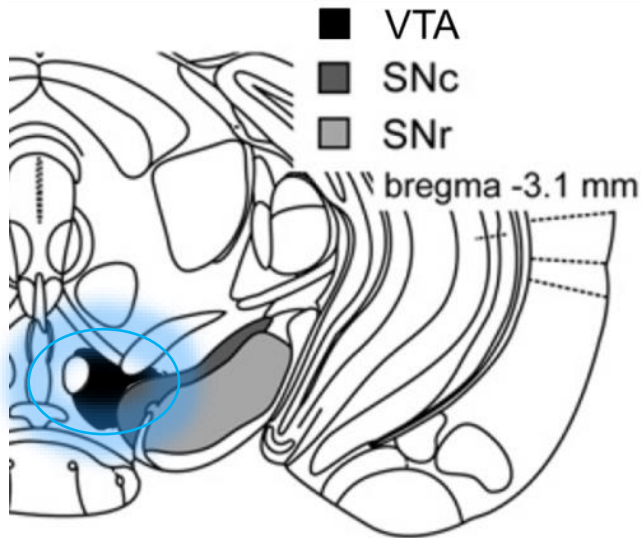
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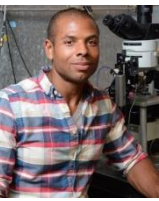


Scale bars, 20 μm

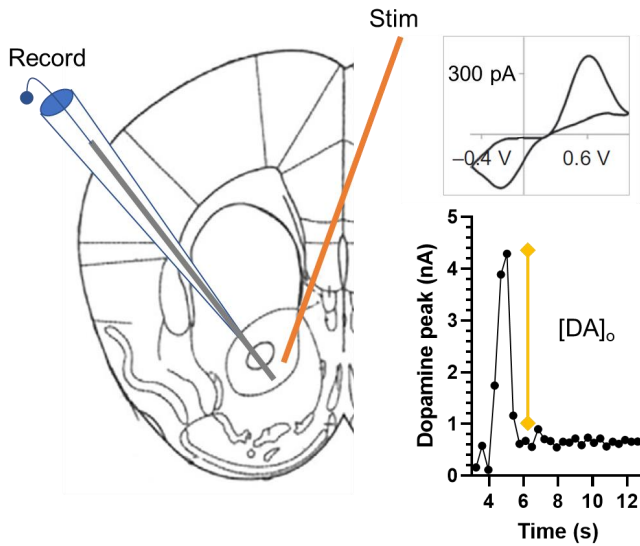


If GABA-resident nAChRs are low-sensitivity, then DA tone should be disinhibited



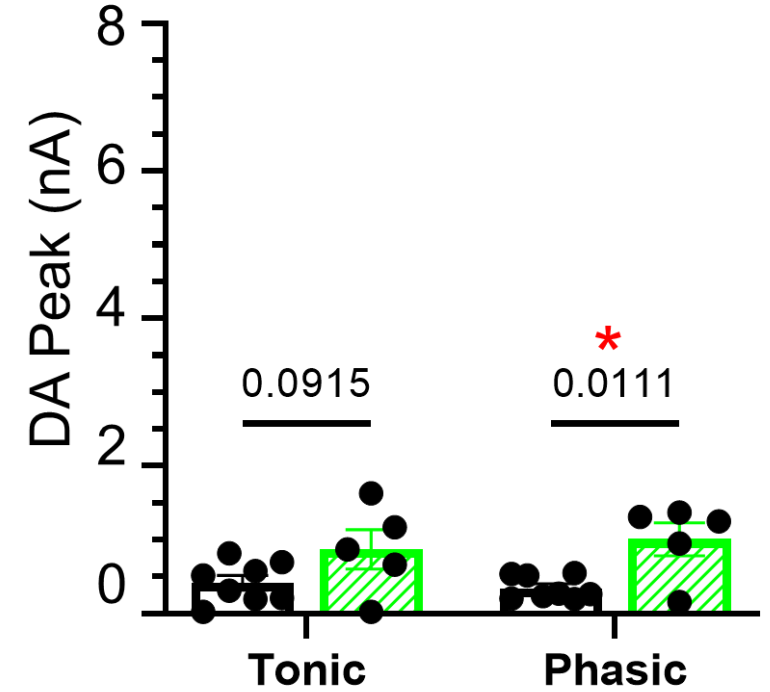
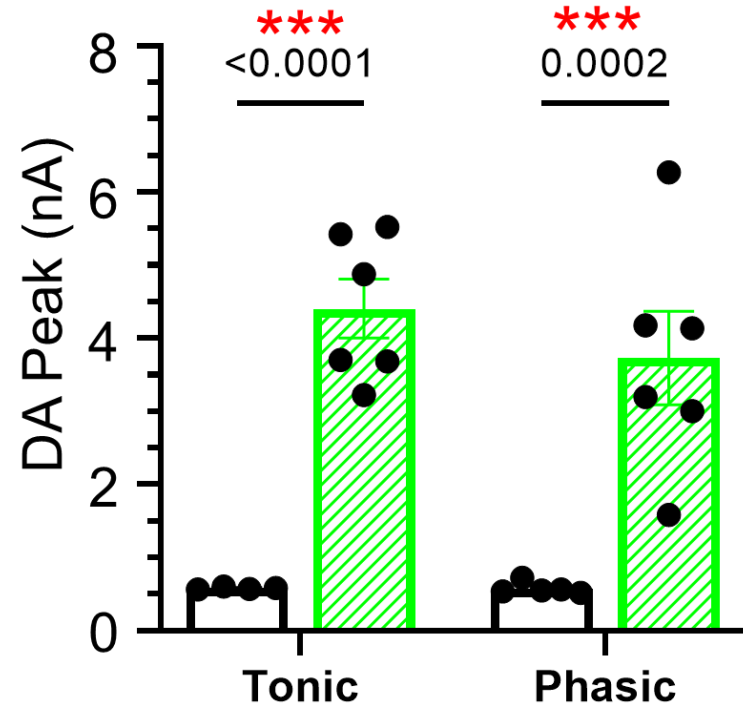


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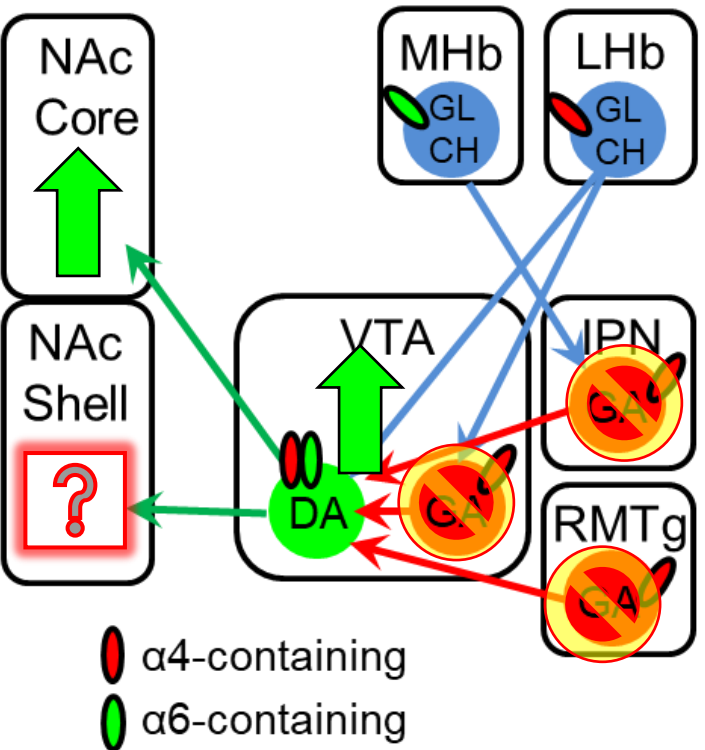
Males

Females



□ PGVG

▨ GA-mix



Summary

- Menthol enhances nicotine Addiction-related behavior
- Green Apple Flavors also enhance self-administration.
 - Green apple does both on its own
- Flavors alter dopamine neuron excitability and dopamine release
- This enhancement in dopamine neuron excitability may be a crucial component of flavor-induced reward.

