TEAM RITALIN

Research in Testing ADHD's Link to Impulsivity in Neuroscience

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Introduction

- Attention Deficit Hyperactivity Disorder (ADHD)
- Affects 5-10% of all school age children
- Twentyfold increase in prescription of ADHD drugs in past 30 years
- Limited research on the neurobiology of the disorder
- Diagnoses based on qualitative observations
- Frequent misdiagnoses and rising medical costs

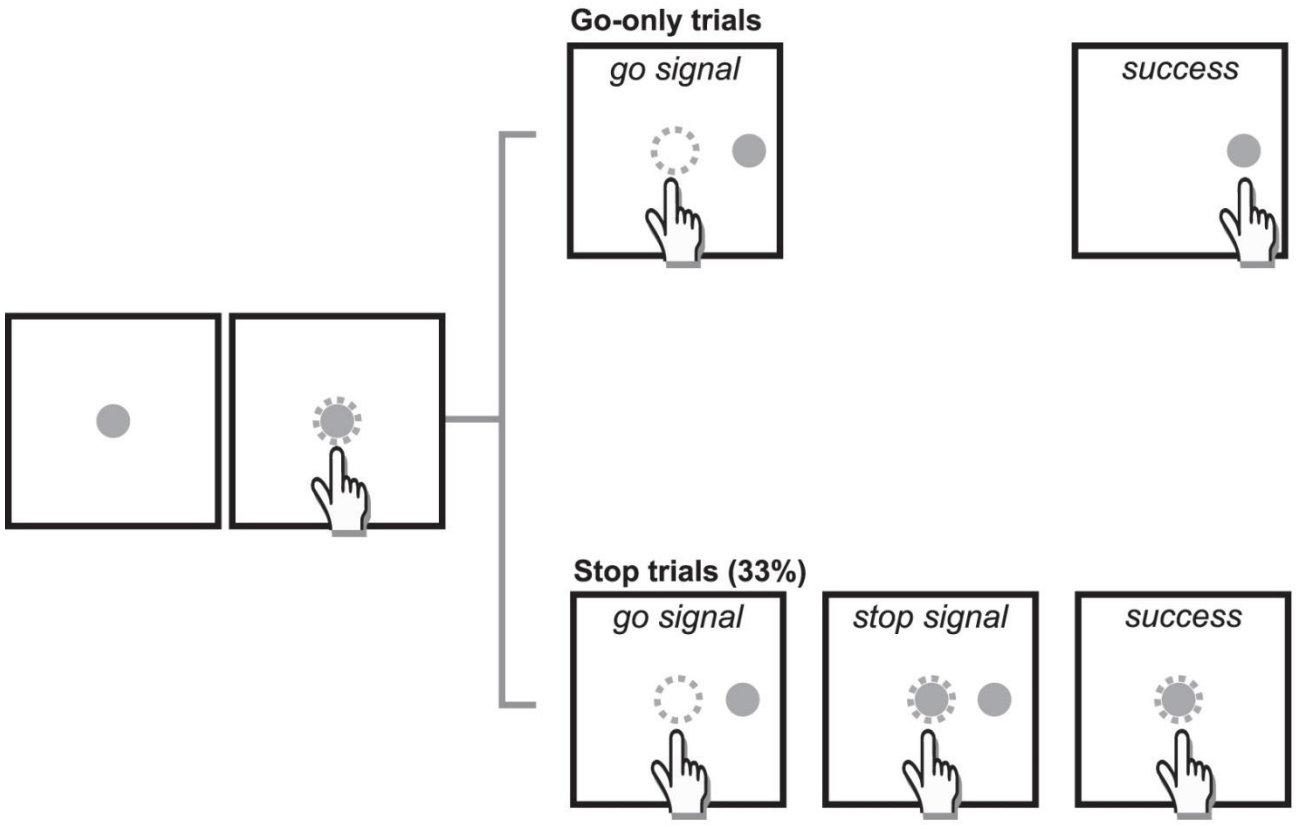
Prenatal Nicotine Exposure (PNE)

- PNE is linked to many psychiatric disorders
- Women who smoke during pregnancy are three times as likely to have children diagnosed with ADHD
- 1 in 5 women still smoke during pregnancy
- Several studies show behavioral, neuroanatomical, & neurochemical disturbances after PNE that are similar to ADHD
  - Benefits of methylphenidate point to PNE as a valuable animal model of impulsivity
  - PNE rats and humans with ADHD had similar deficits on behavioral tasks that measure impulsivity

Attention Deficit Hyperactivity Disorder (ADHD) & PNE

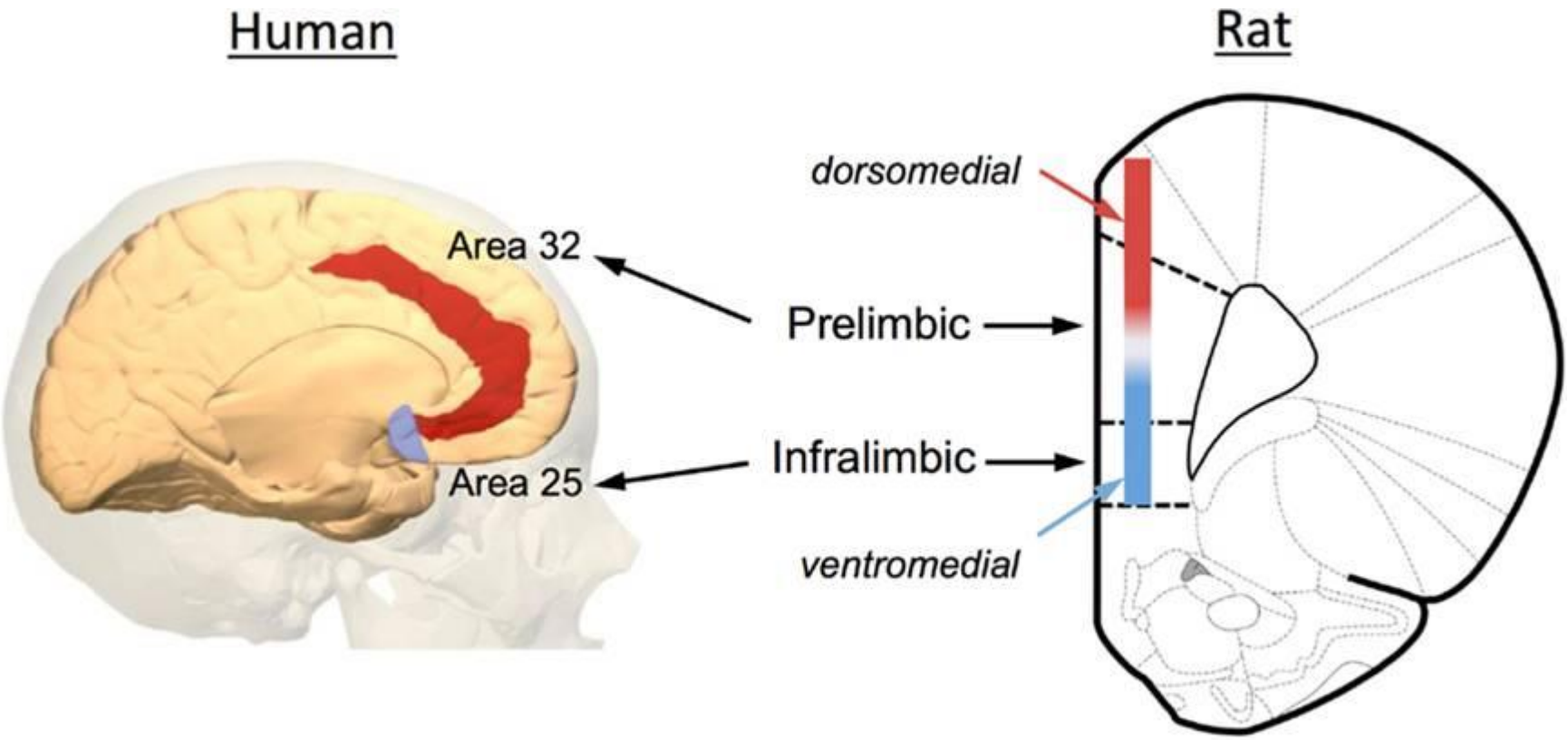
- PNE rats and humans with ADHD exhibit similar behavioral symptoms: inattention, hyperactivity, and impulsivity
  - **Inattention:** difficulty concentrating, distractibility, and problems completing tasks
  - **Hyperactivity:** high or excessive levels of motion
  - **Impulsivity:** tendency toward rapid, unplanned actions without considering the negative consequences of these actions

Human Stop-signal tasks measure impulsivity



Mirabella G, Iaconelli S, Modugno N, Giannini G, Lena F, et al. (2013) Stimulation of subthalamic nuclei restores a near normal planning strategy in parkinson's patients. PLoS ONE 8(5): e62793. doi:10.1371/journal.pone.0062793

Medial Prefrontal Cortex (mPFC)



Gass, J.T., & Chandler, L.J. (2013). The plasticity of extinction: contribution of the prefrontal cortex in treating addiction through inhibitory learning. *Frontiers in psychiatry,* 4(46): 1-13.

Our Approach

- Understanding of mPFC neural signaling is essential to treatment
- Experimental system will elucidate foundation of behavior
- Correlation between behavior and neural firing will allow us to pinpoint the signals involved in impulsive behavior

Our Goal

Hypothesis: PNE rat model is a valid model for the study of ADHD-like symptoms

1. Show that PNE rats are more impulsive during performance on a stop-signal task that measures the ability you inhibit unwanted responses

2. Demonstrate that activity in mPFC is correlated with performance on the stop-signal task

3. Evaluate neural signals in mPFC in PNE rats during performance of the stop-signal task

Rat Breeding & Selection

- 10 mothers total
- Acclimation to nicotine
  - 0.2 → 0.4 → 0.6 mg/mL
- 17 PNE and 23 control male pups
  - Cross-fostered to control mother

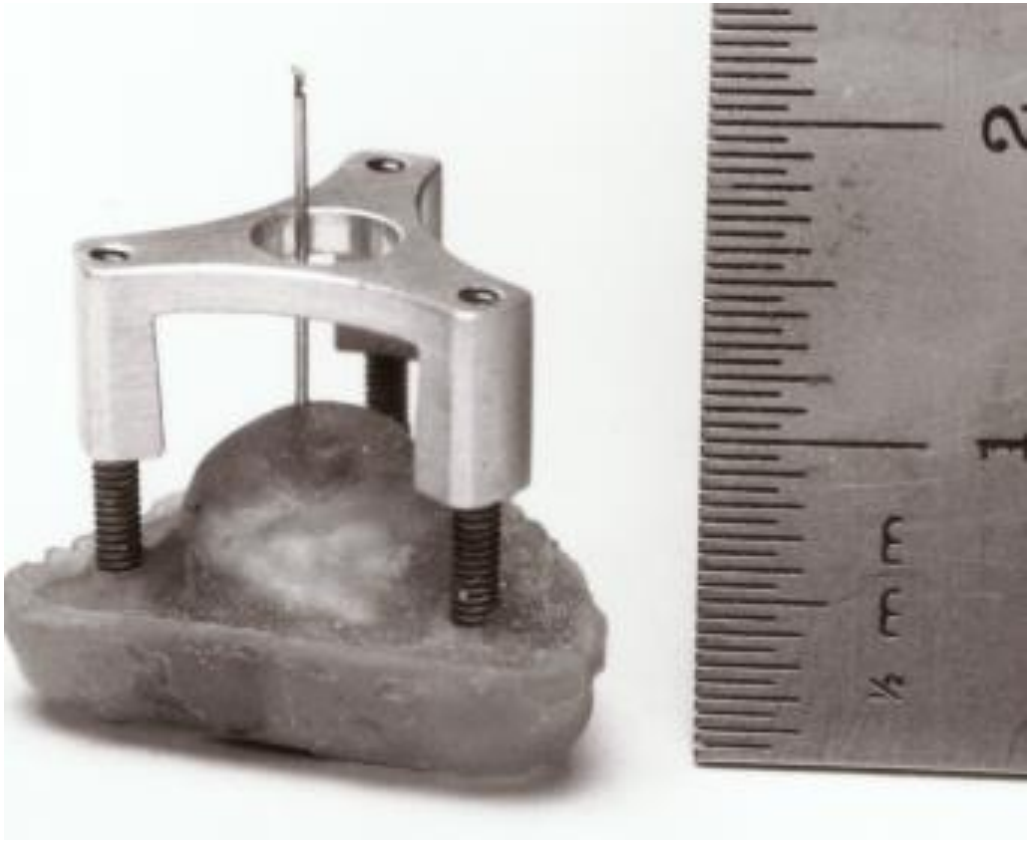
Rat Breeding & Selection

- No significant differences in pregnancy duration, pups per litter, pup birth weight, or hyperactivity (t-test; $p > 0.05$)

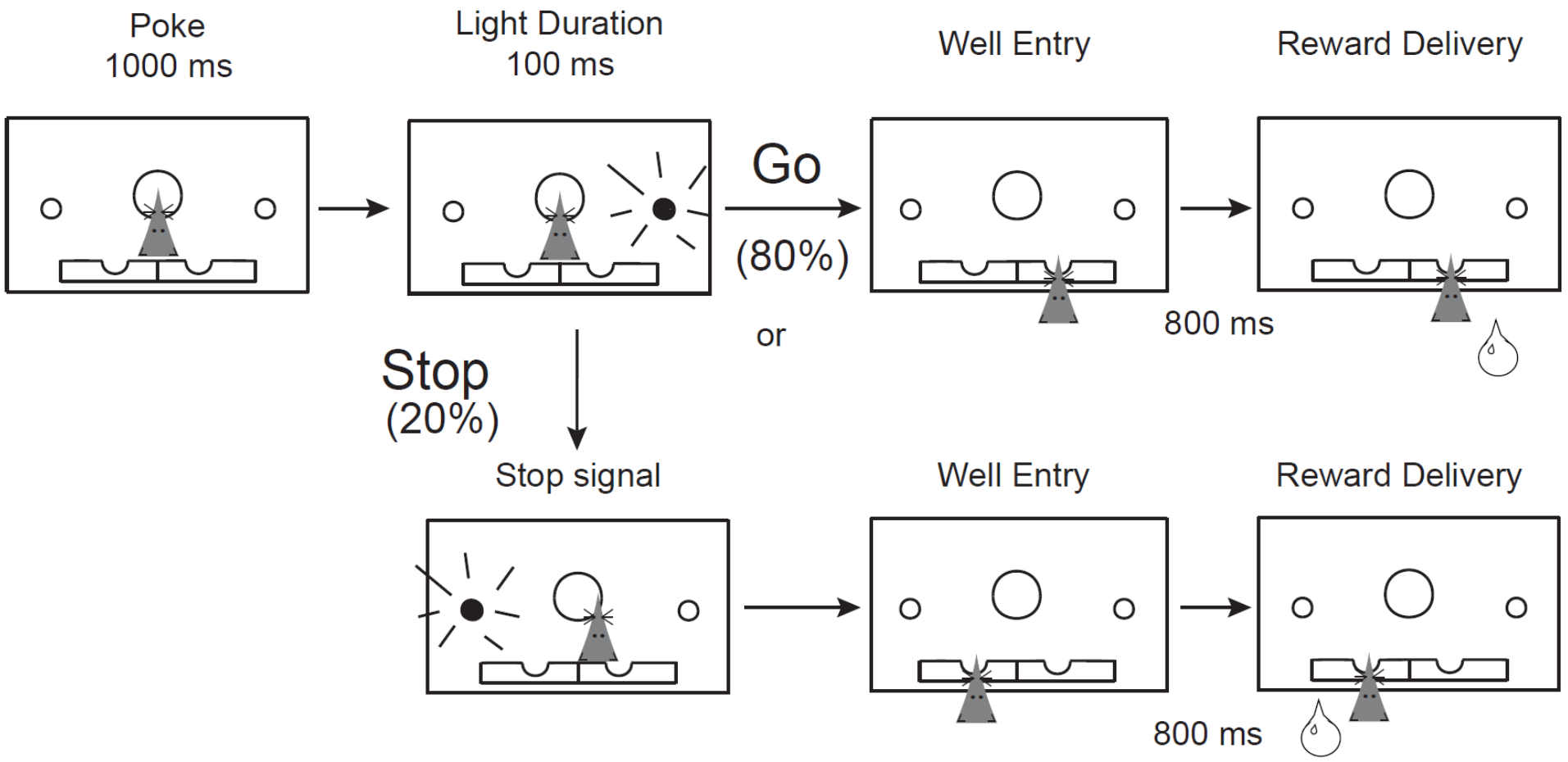
- Randomly selected 8 males each from 17 PNE pups (from 3 dams) and 23 control pups (from 3 dams)

Stop-signal Task Training & Surgery

Task Training → Implant electrodes

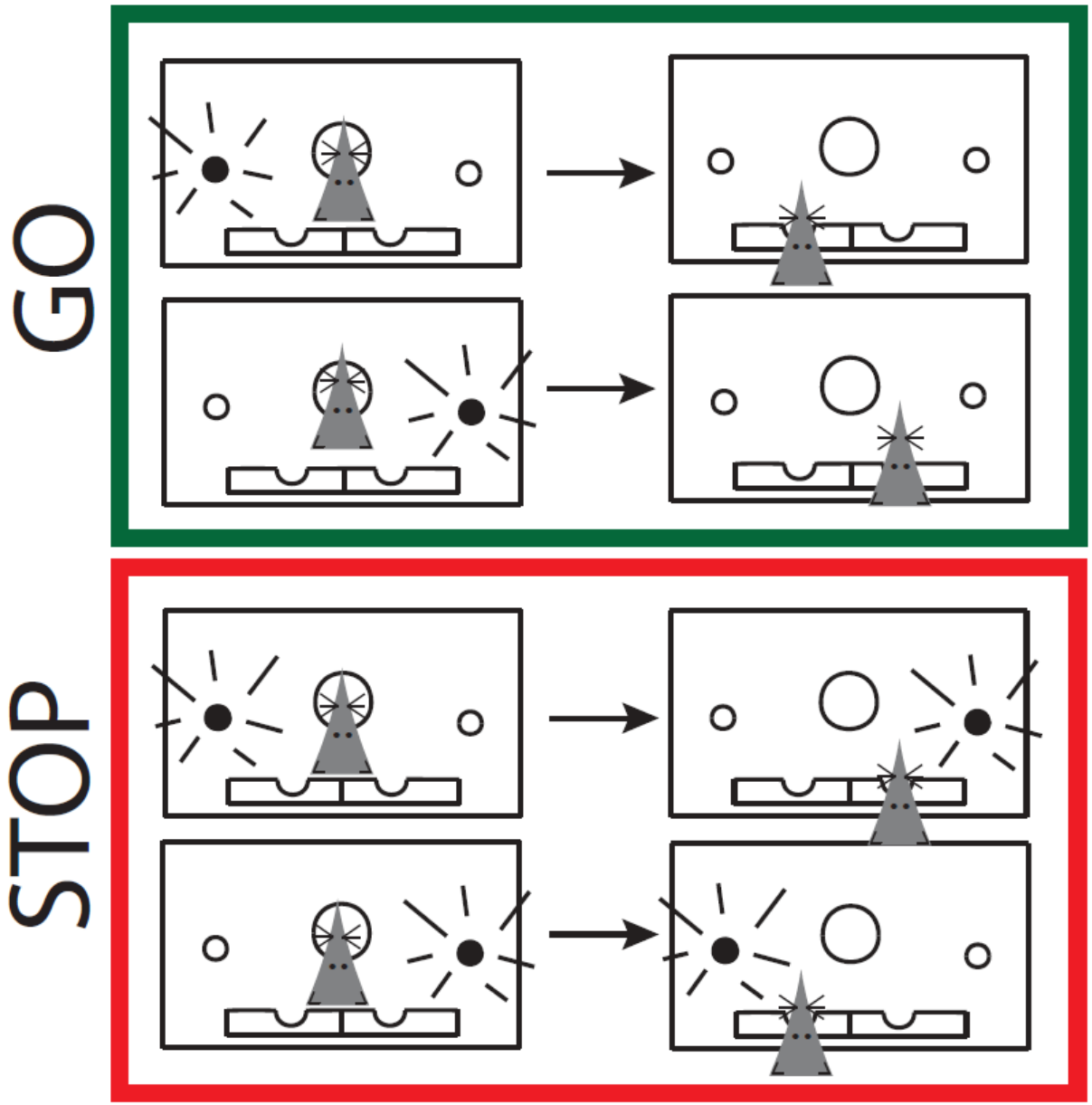


Rat Stop-signal task measures impulsivity

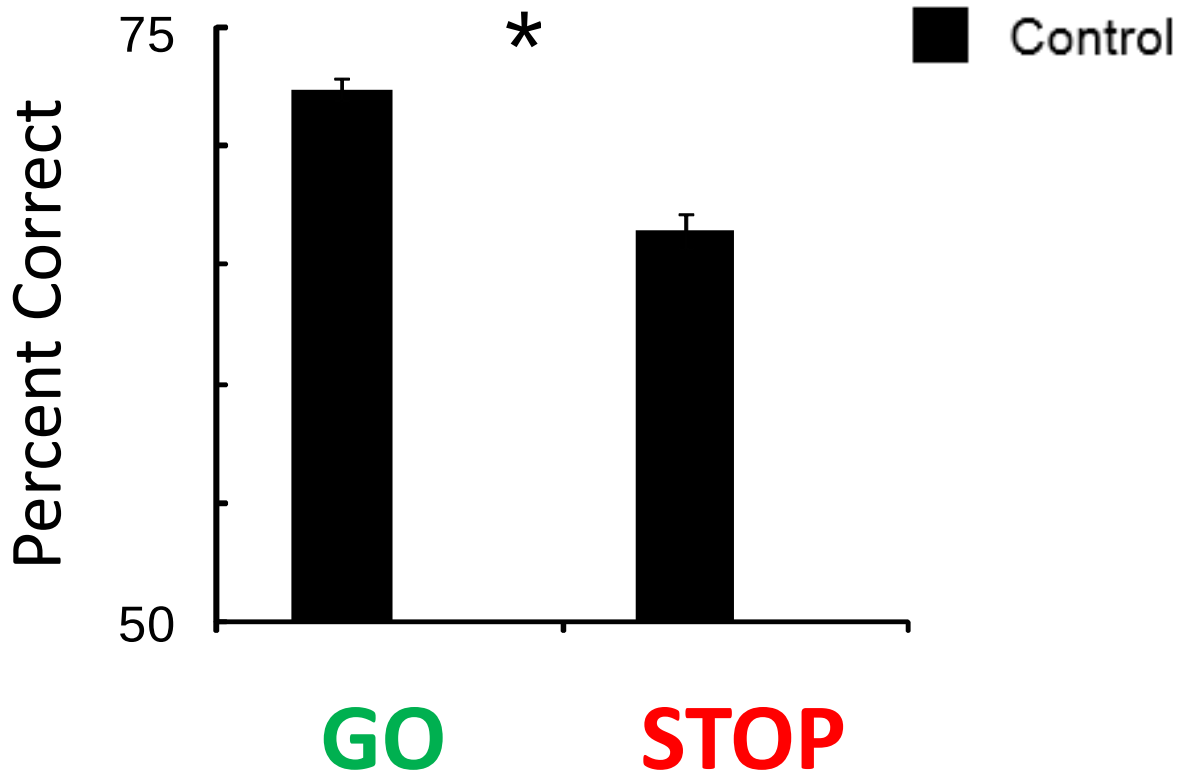


Bryden, D. W., Burton, A. C., Kashtelyan, V., Barnett, B. R., & Roesch, M. R. (2012). Response inhibition signals and miscoding of direction in dorsomedial striatum. *Front Integr Neurosci, 6*, 69. doi: 10.3389/fnint.2012.00069

Trial types

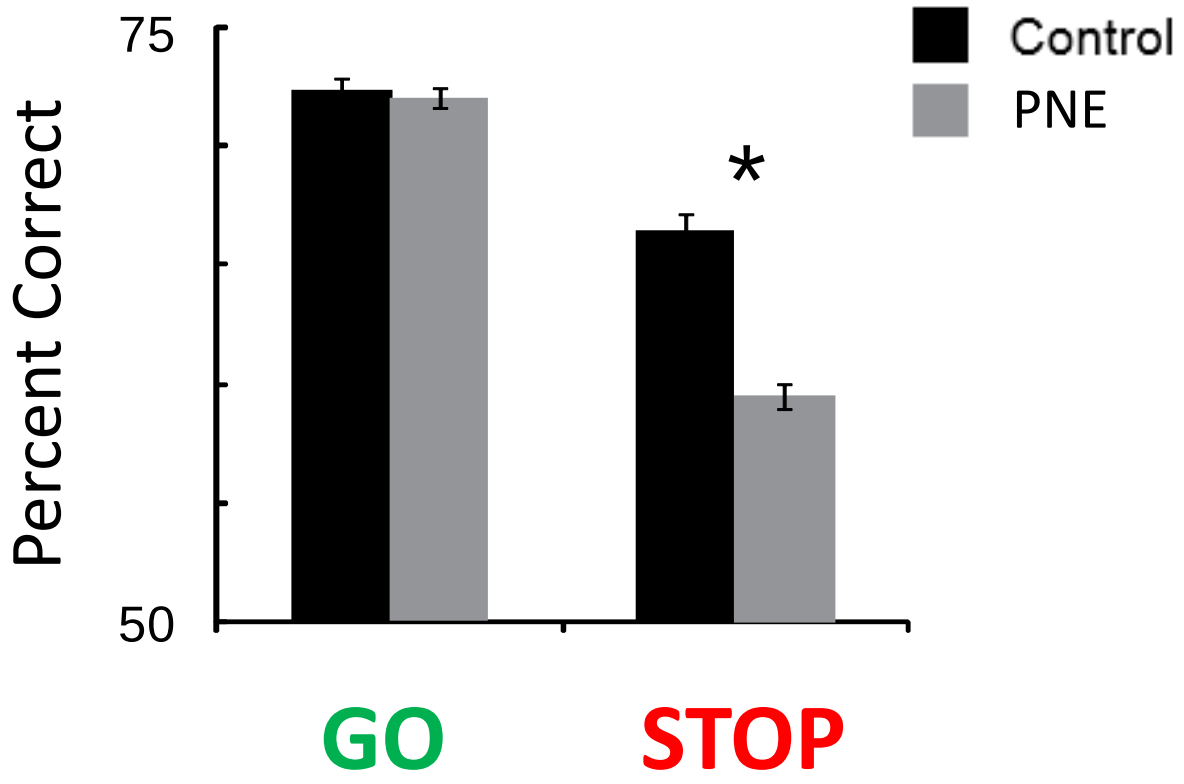


Rats performed significantly worse on STOP trials compared to GO trials



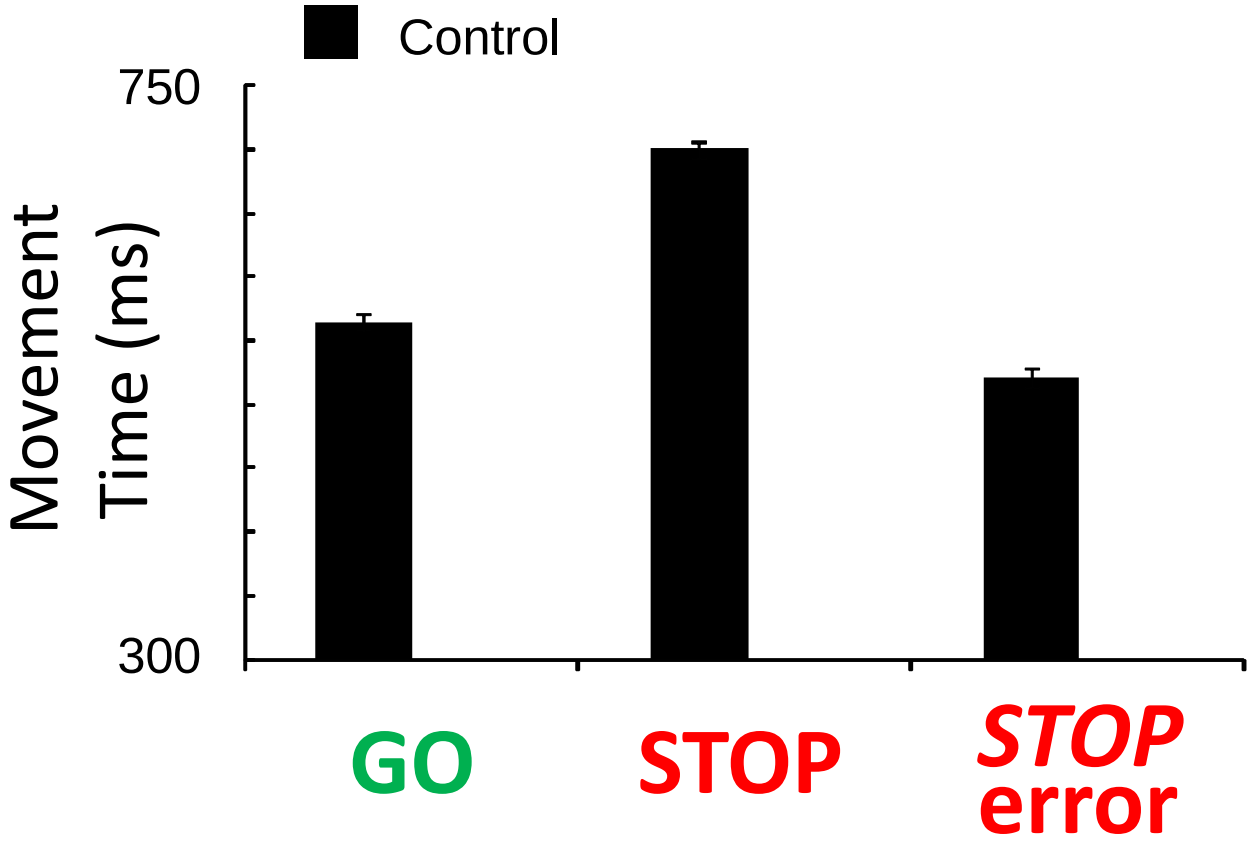
*(t-test; $p < 0.05$)

PNE Rats performed significantly worse on STOP trials compared to controls

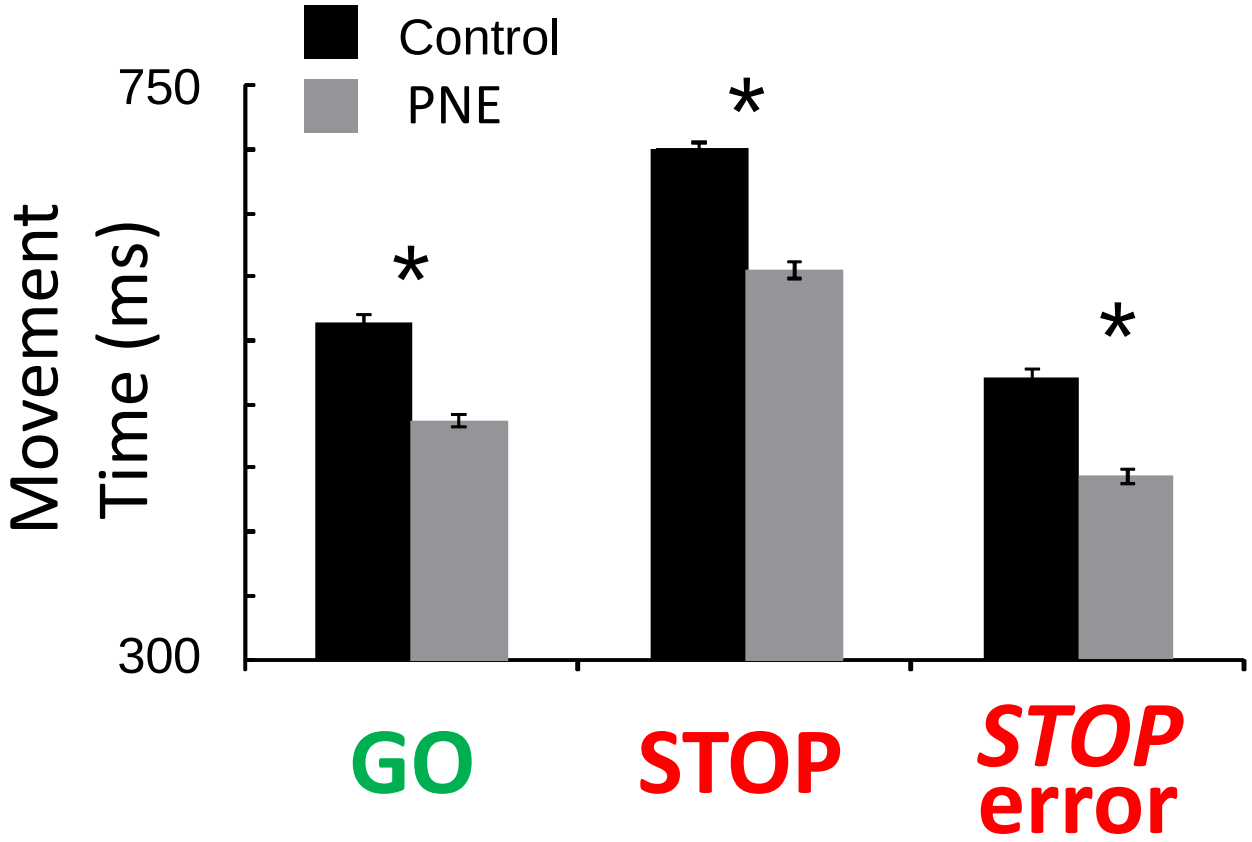


* (t-test; $p < 0.05$)

Rats were slower on correct STOP trials

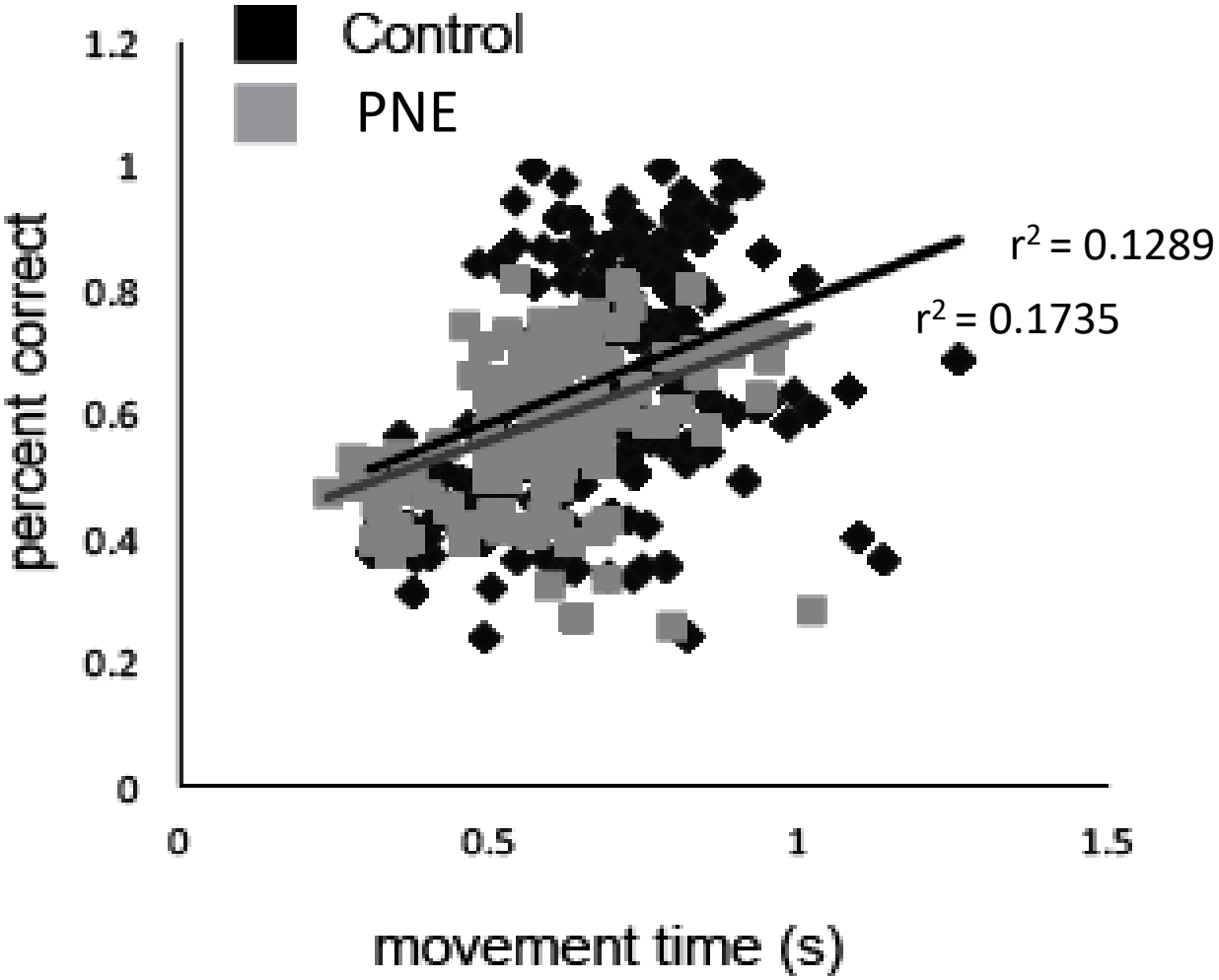


PNE rats were significantly faster on all trial-types



* (t-test; $p < 0.05$)

Speed-Accuracy Tradeoff: When rats were slower, they performed better



p < 0.0001

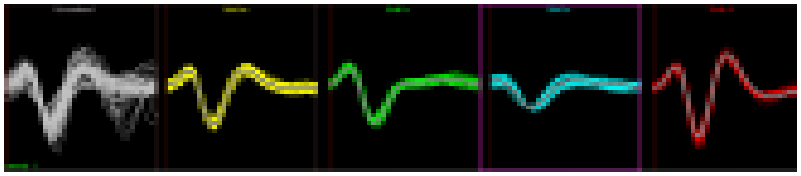
Summary

- **Behavior**
  - PNE rats were more impulsive (reduced stop accuracy)
  - PNE rats were faster on STOP and GO trials
  - When rats were slower they were better at inhibiting behavior (speed-accuracy tradeoff)

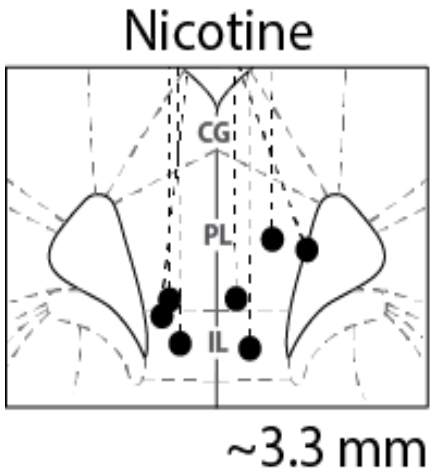
Neural Recording & Analysis

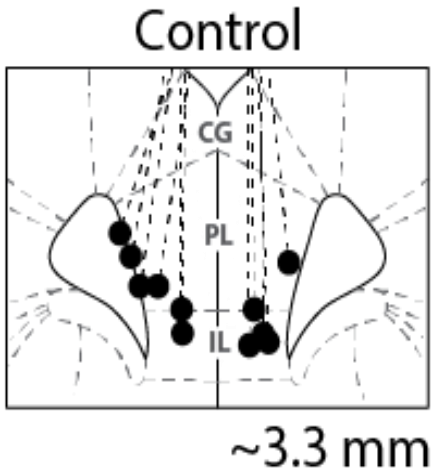
Neural Recording → Histology → Data Analysis

- 16 rats in total from the control and PNE groups performed 349 sessions, over which we collected neural firing data from 631 and 552 cells, respectively

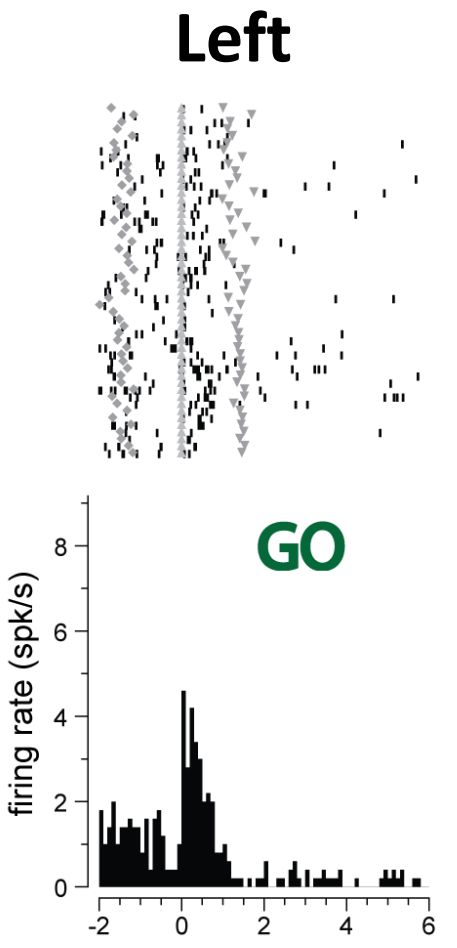


Plexon

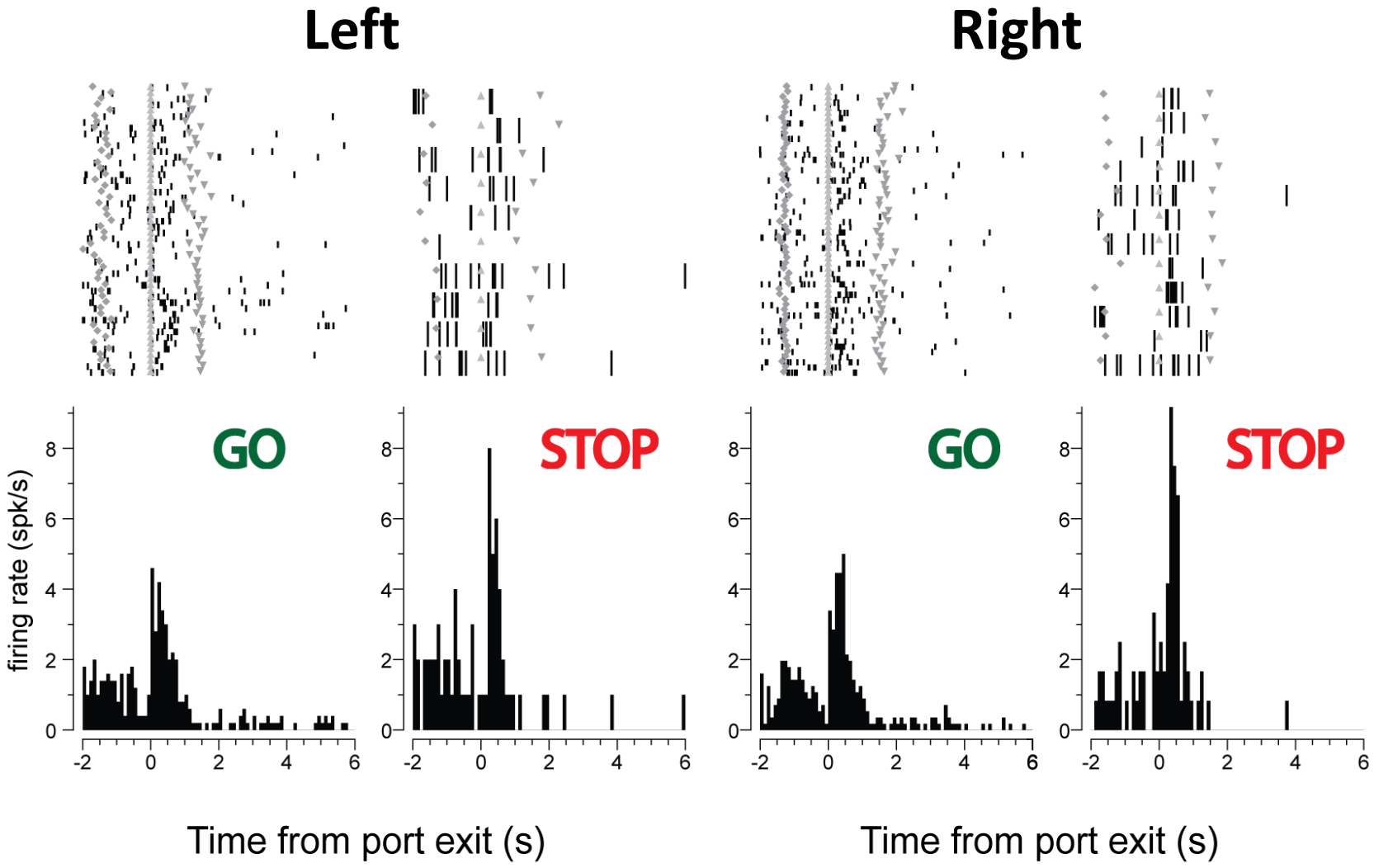




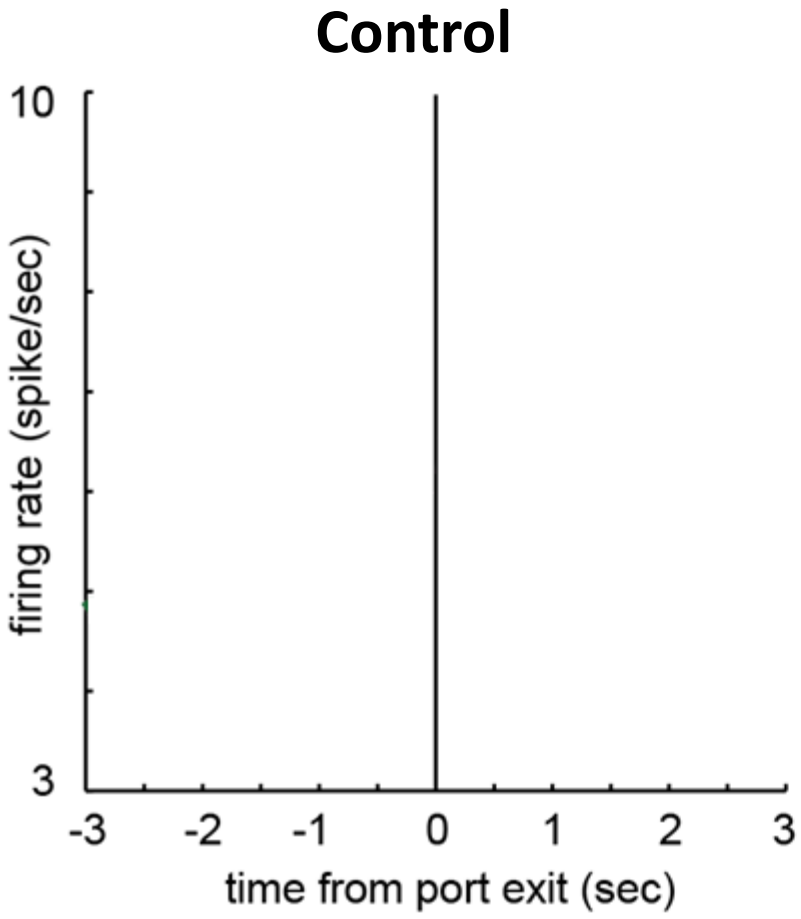
Single cell example of a neuron that increased firing during the task

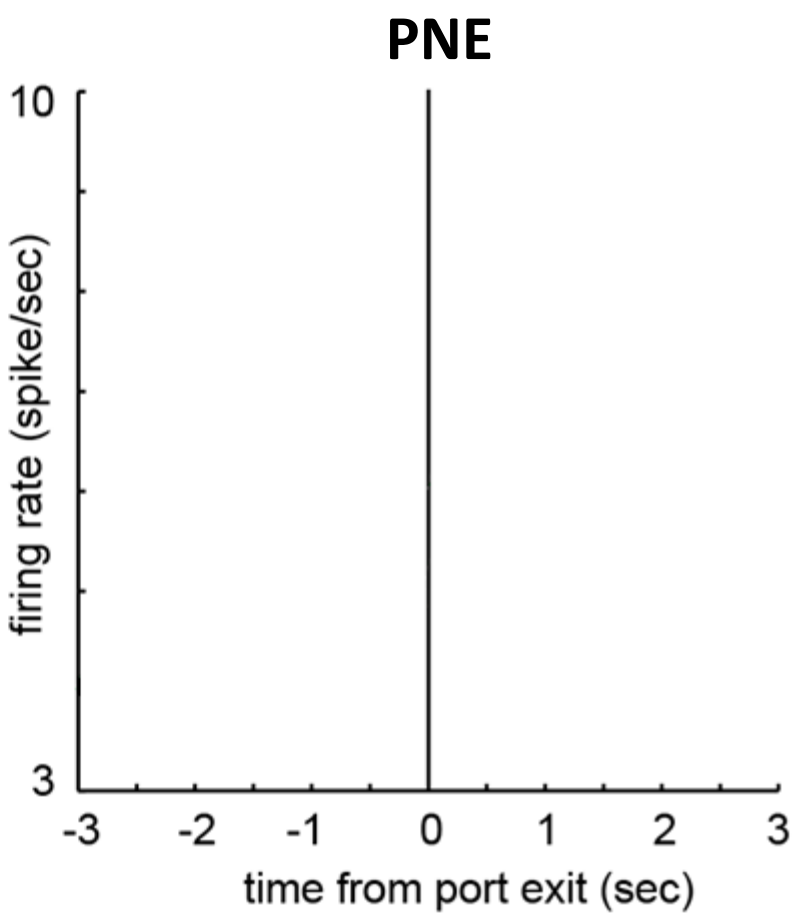


Activity was stronger on STOP trials when behavior had to be inhibited

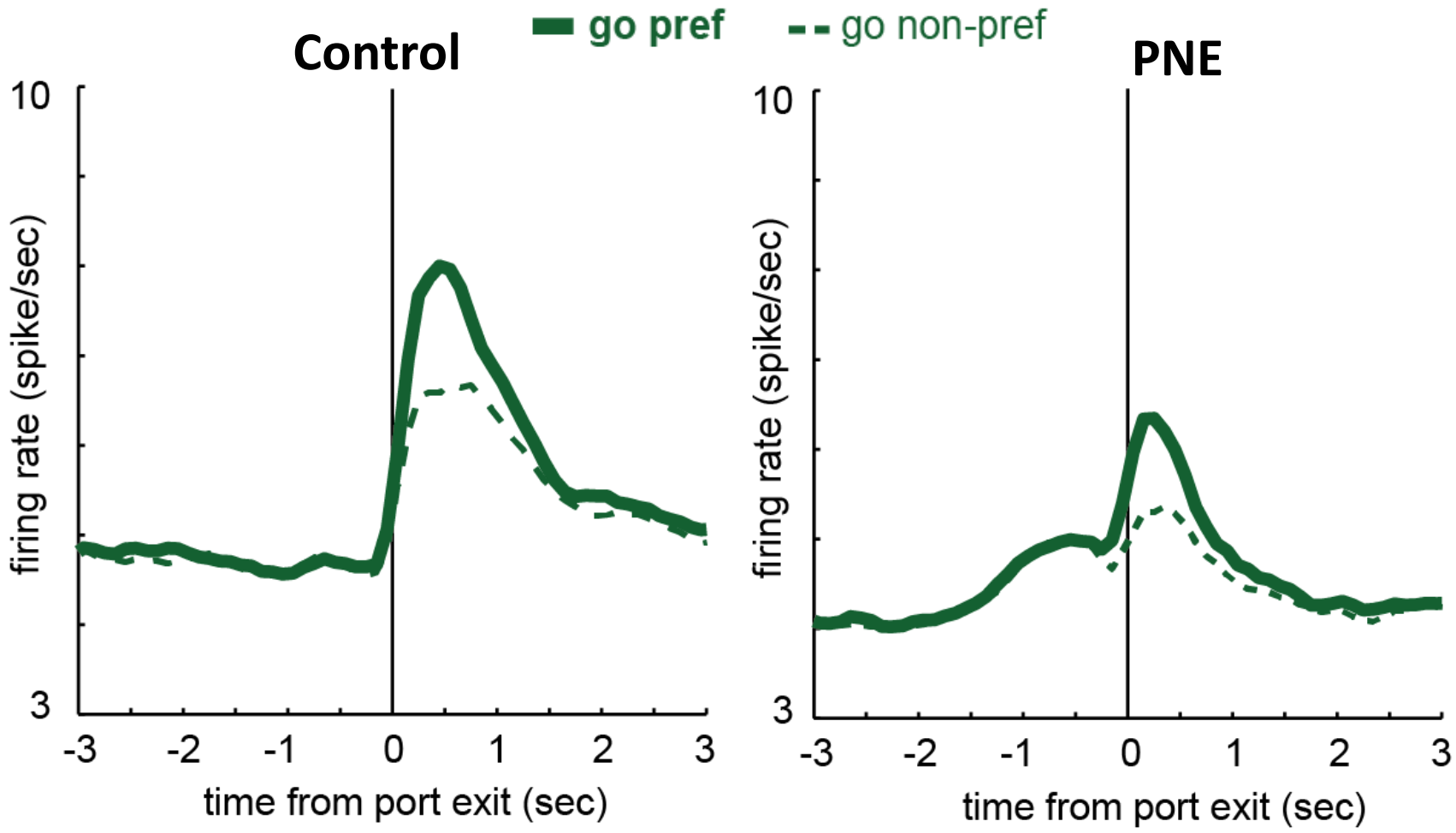


Average neural firing over all ‘increasing-type’ neurons (Control: n = 121; PNE: n = 131)

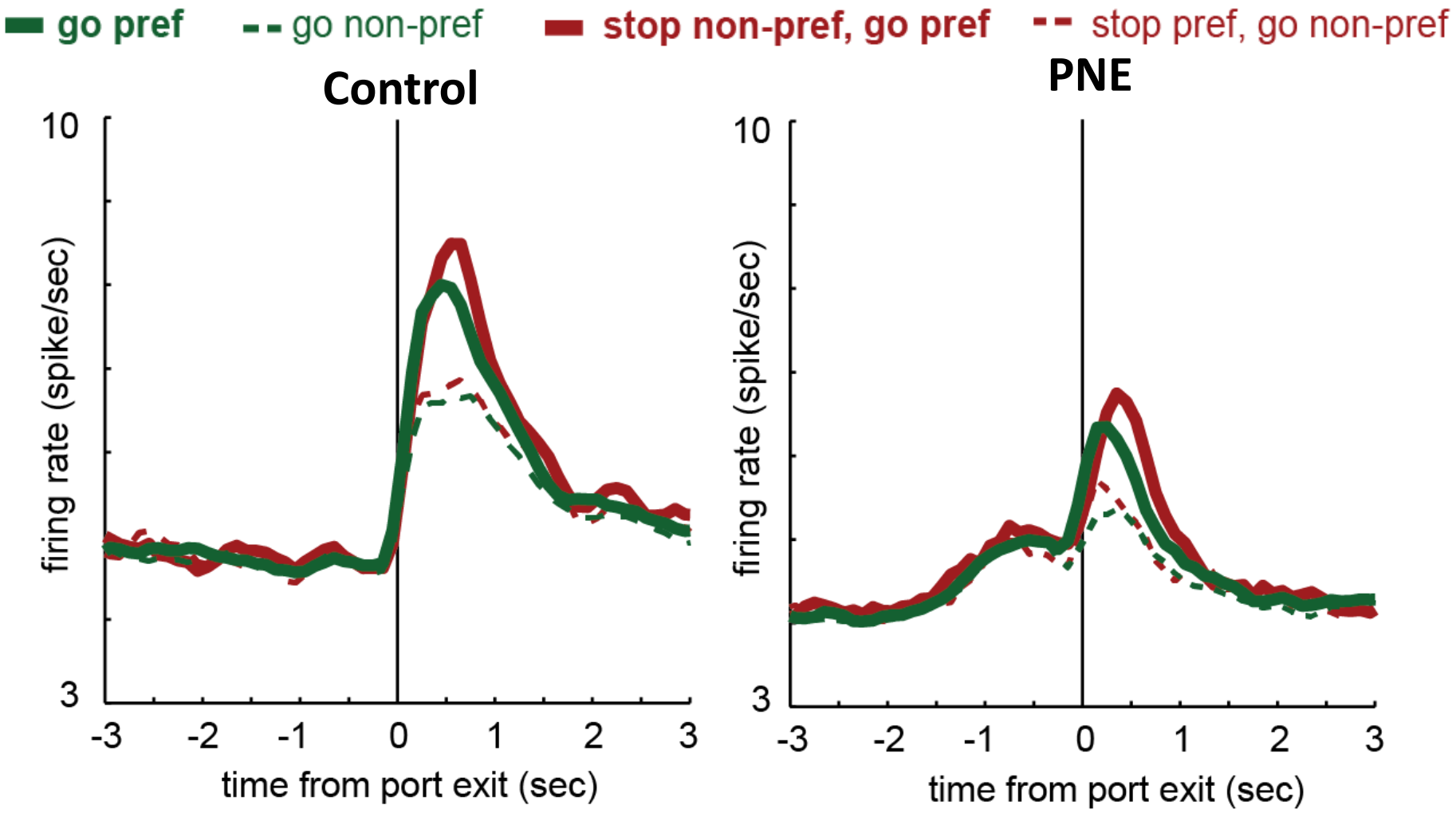




Average neural firing was modulated by response (solid versus dashed) on GO trials

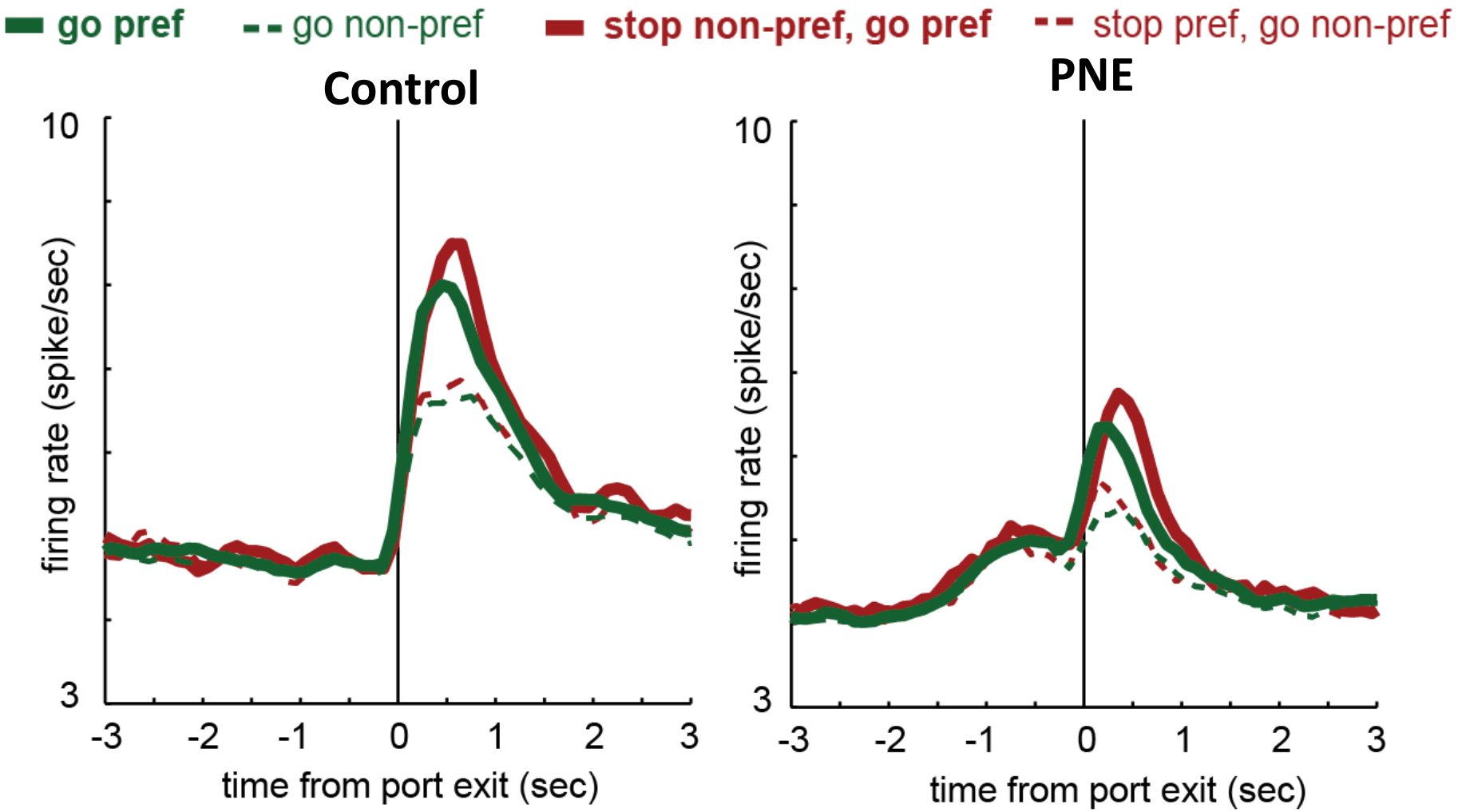


Average neural firing was stronger on STOP trials in both control and PNE rats



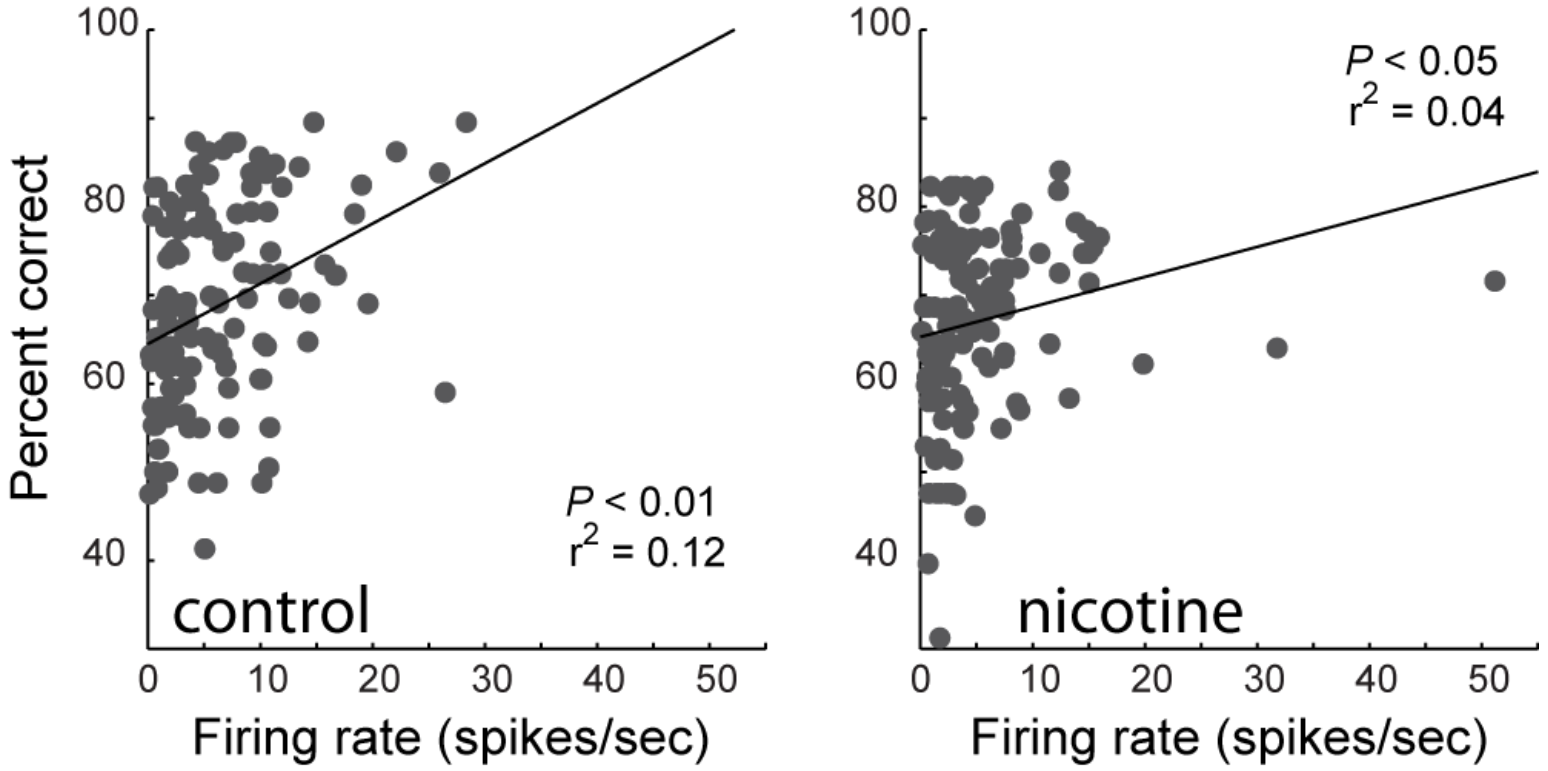
(Wilcoxon; $p < 0.001$)

However, overall firing was significantly *reduced* in PNE rats relative to controls



(Wilcoxon; $p < 0.001$)

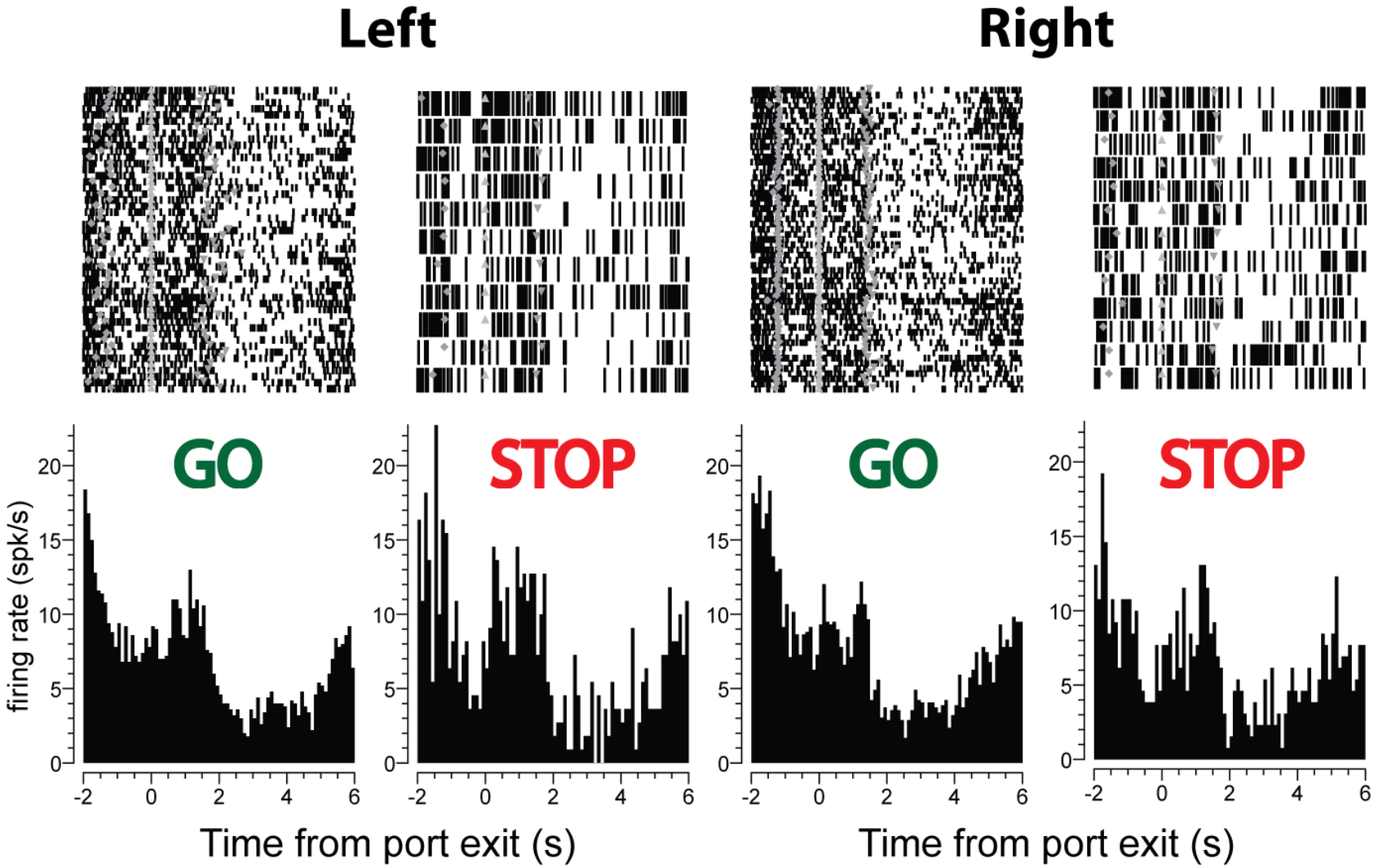
mPFC firing was positively correlated with percent correct (higher firing = better behavior)



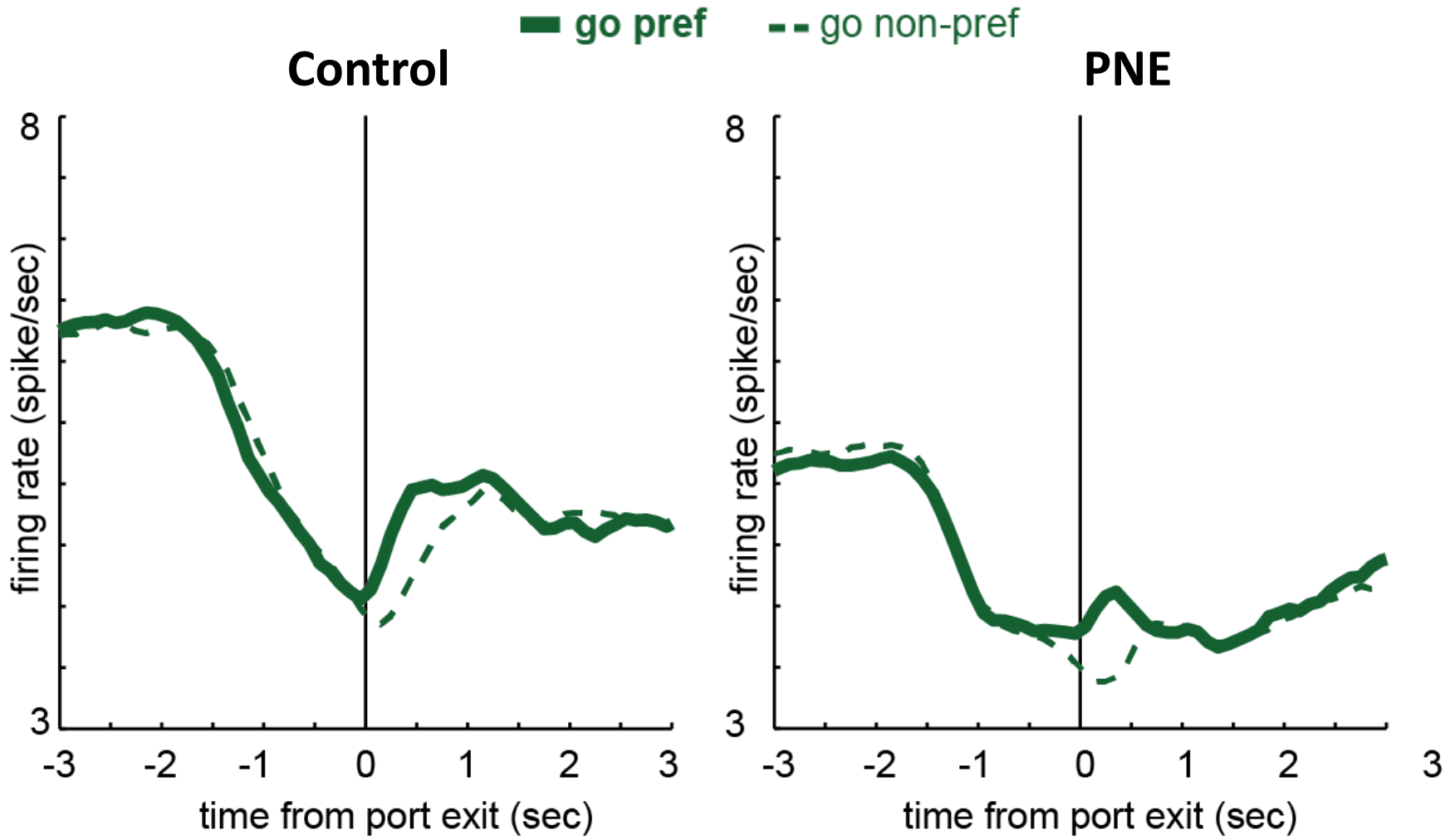
Summary

- **Increasing-type cells**
  - Neural activity was modulated by response direction
  - Neural activity was stronger during STOP trials
  - Neural activity was correlated with behavioral performance
  - Neural activity was significantly reduced in PNE rats compared to controls

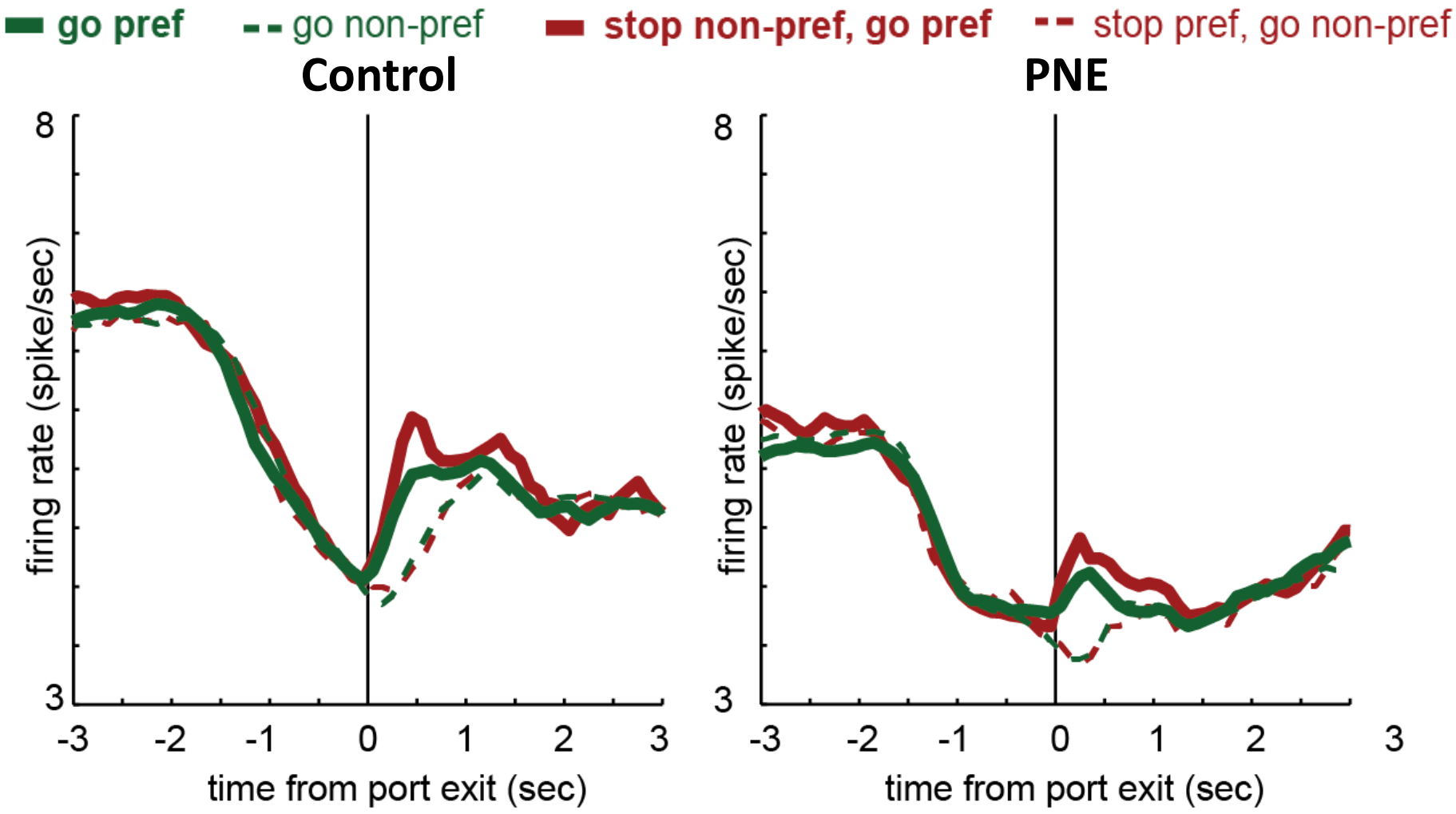
Other neurons decreased firing during performance of the task



Average neural firing over all ‘decreasing-type’ neurons (Control: n = 182; PNE: n = 174)

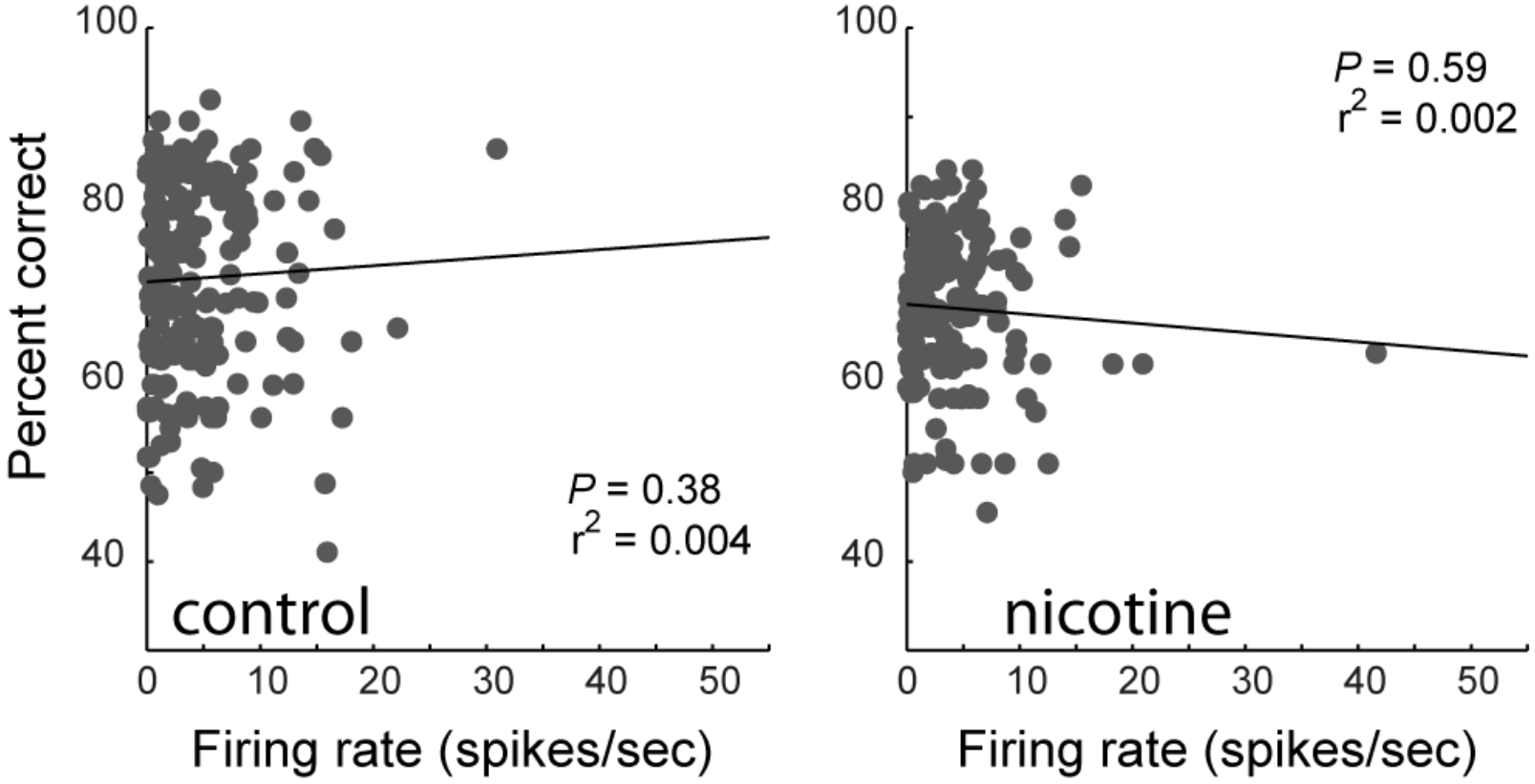


‘Decreasing-type’ neurons also fired more strongly on STOP versus GO trials

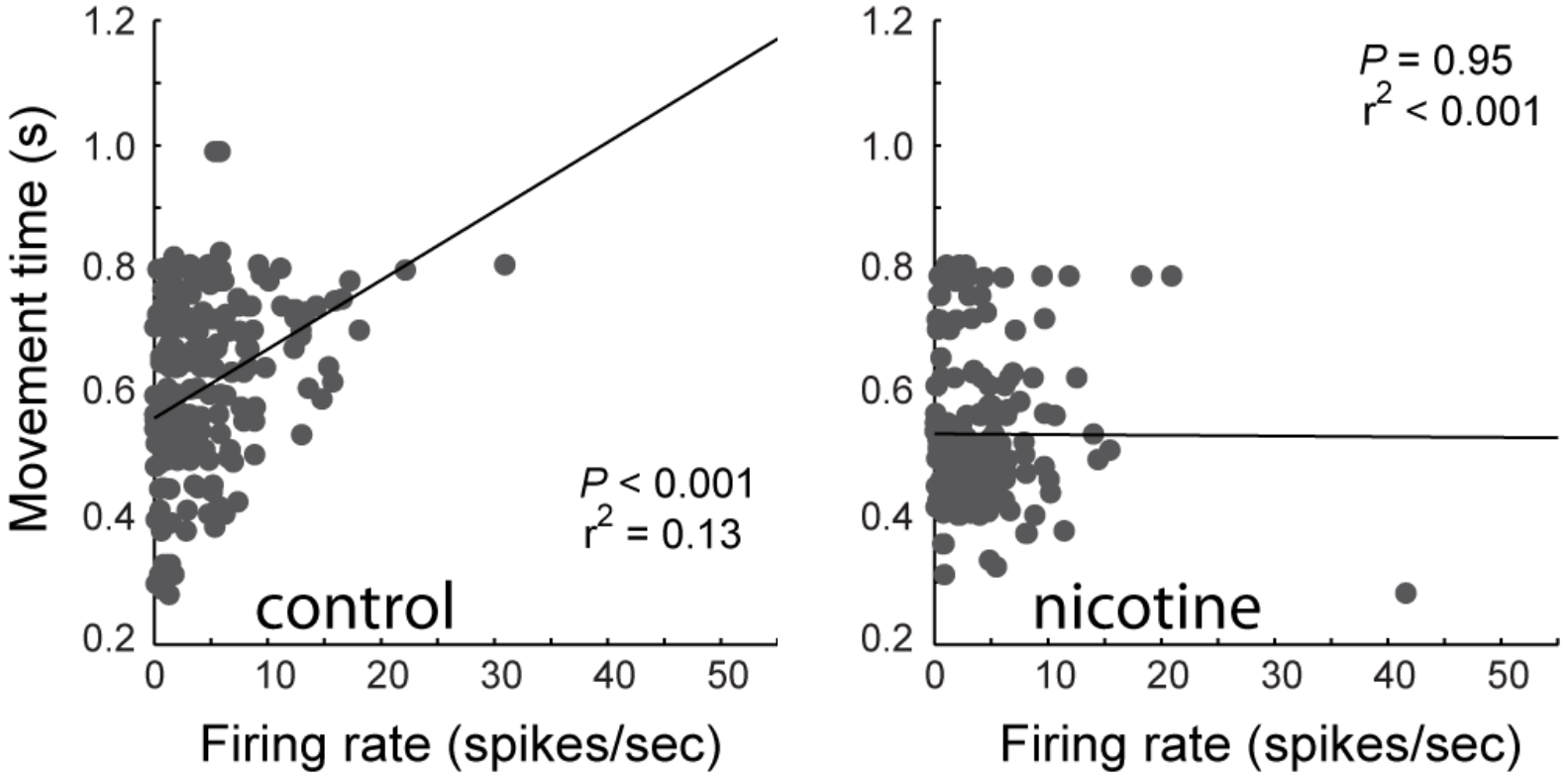


(Wilcoxon; $p < 0.05$)

However, the activity of 'decreasing-type' was not correlated with percent correct



Instead, neural activity was positively correlated with movement time (high firing = slower)



Summary

- **Decreasing-type cells**
  - Neural activity was modulated by response direction
  - Neural activity was stronger during STOP trials
  - Neural activity was correlated with motor output in controls only
  - Neural activity was significantly reduced in PNE rats as compared to controls

Conclusions

- **Behavior**
  - PNE rats were more impulsive (reduced stop accuracy)
  - PNE rats were faster than controls on both STOP and GO trials
- **Neural recordings**
  - Neural activity in mPFC was stronger during STOP trials during which rats had to inhibit behavior
  - Neural activity in mPFC was correlated with performance and speed
  - Neural activity of mPFC neurons was significantly attenuated in PNE rats as compared to controls
- **PNE rat model** is a useful model to study the neural underpinnings of impulsive-like behavior observed in ADHD

Future Directions

Studies should target mPFC. Specifically, artificially increasing neural activity in mPFC should alleviate impulsivity in PNE rats.

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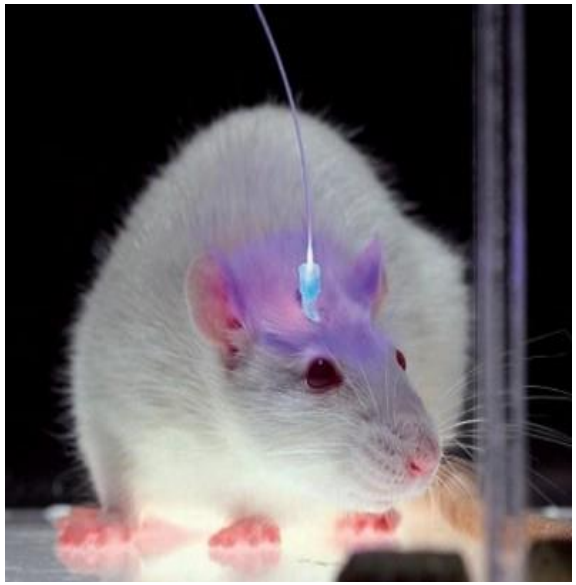

Courtesy of Deisseroth lab

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  - Ms. Amanda Burton
  - Ms. Ronny Gentry
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  - Ms. Nina Lichtenberg
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Questions?

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