Impact of prenatal nicotine exposure on impulsivity and neural activity in medial prefrontal cortex

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Abstract Prenatal nicotine exposure (PNE) remains an important issue today. A recent study (2012) from the Substance Abuse & Mental Health Services Administration reports that 1 in 5 white women smoke cigarettes during pregnancy. Exposure to nicotine during pregnancy is linked to a large number of psychiatric disorders, including, obesity, conduct disorder, drug abuse, and attention-deficit hyperactivity disorder (ADHD). Behavioral, neuroanatomical, and neurochemical disturbances described after PNE, and the benefits observed after methylphenidate (MPH) treatment, have pinpointed PNE as a valuable animal model for studying the neural underpinnings of abnormal impulse control as observed in patients with ADHD. Current literature suggests that core deficits observed in ADHD reflect abnormal inhibitory control governed by prefrontal cortex, which has been shown to be structurally altered by PNE. Here, we ask if PNE impacts behavior and neural signals in medial prefrontal cortex (mPFC) as rats perform a stop-signal task that tests the ability to inhibit an ongoing movement. To address these issues, we administered nicotine to pregnant rats via drinking water. After birth rats were cross fostered to control mothers that were not exposed to nicotine. At age ##, rats were trained on our stop-signal task and then implanted with drivable electrodes above mPFC. Consistent with our hypothesis, we found that PNE made rats more impulsive. Surprising, however, we also found that PNE rats were better at performing basic task procedures such as responding to spatial cue lights. Consistent with these changes in behavior, we found that signals related to stopping in mPFC were diminished after PNE and that signals related to the direction of the required behavioral response were attenuated relative to controls.

Questions & Hypotheses

Research Questions:
- Is there a relationship between neural firing in the medial prefrontal cortex (mPFC) and impulsivity in control rats?
- Is neural firing in the mPFC cortex disrupted and impulsivity increased in fetal nicotine rats?

Hypotheses:
- mPFC will exhibit increased firing during correct stop-signal trials
- Fetal nicotine rats will exhibit reduced neural firing in the mPFC cortex and increased impulsivity

Methods

- Female Long-Evans rats were acclimated to nicotine through water and mated; nicotine exposure continued throughout gestation.
- Pups were selected from PNE litters and control litters and cross-fostered to control mothers.
- After rat pups matured, they were trained on the stop-signal task (SST) daily for a month. After a month of training, the performance of the control and PNE rats was evaluated, and electrodes were implanted in the mPFC. We performed neural recordings during the stop-signal task. The electrode was advanced 40µm following each session to traverse the mPFC (Bryden et al., 2011).
- We analyzed data using MATLAB to obtain firing and behavioral information and performed histological analysis to confirm that the electrodes were placed in the mPFC during surgery.

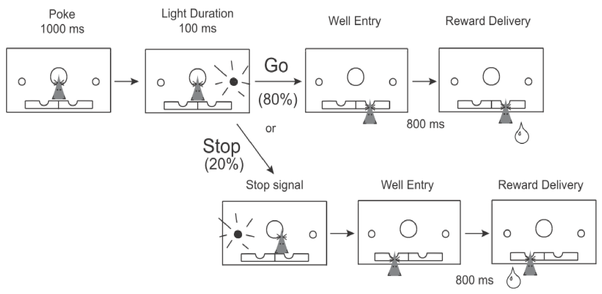

Figure 1. Diagram of the stop-signal task. The rat enters the odor port and initiates a response towards well on the side of the first light (go trial). On 20% of trials, a stop light on the opposite side appears, and the rat must stop the initial response and move towards the opposite well for reward. (Bryden et al, 2012)

Results

When the rats were 10-12 weeks old, they performed a locomotion task to test for any preliminary deficiencies. In this task, rats were individually placed into boxes with eight infrared beams across the box, and when the rat crossed the beam, it was recorded as a crossing. The number of crossings were then analyzed with a t-test. Control rats averaged 92.9 crossings in a two hour period, while PNE rats averaged 69.3 crossings. PNE rats moved around significantly less than control rats.

During the neural recordings, the movement time from the odor port to the reward well was recorded, in addition to the percent correct responses made by each rat. From Figure 4, it can be seen that both groups moved significantly more slowly on stop trials, but control rats moved more quickly than PNE rats on both sets of trials. Additionally, both groups had significantly fewer percent correct trials on stop trials than on go trials. The stop change reaction time (SCRT) was computed as the difference between the average movement times for stop and go trials for each group. This is a measure of the rats' ability to halt an existing response and change direction. The SCRT among both types of rats was comparable.

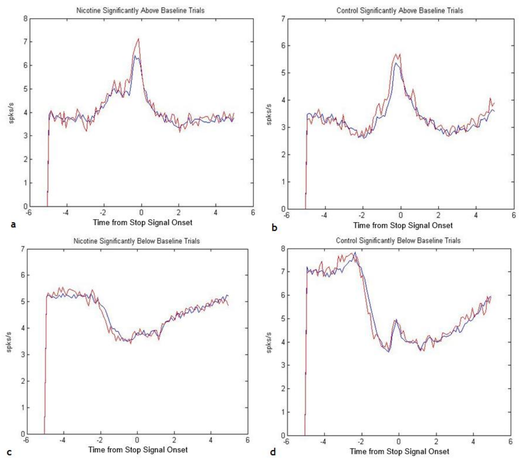

Figure 2. Baseline firing is described as the neural activity before the trial time begins. Firing rate plots are aligned on port exit. X-axis is time from stop-signal onset, measured in seconds. Y-axis is spike rate, defined as spikes or action potentials per second. Blue lines are go trials, and red lines are stop trials. Data was analyzed in Matlab to determine average firing frequency over time.

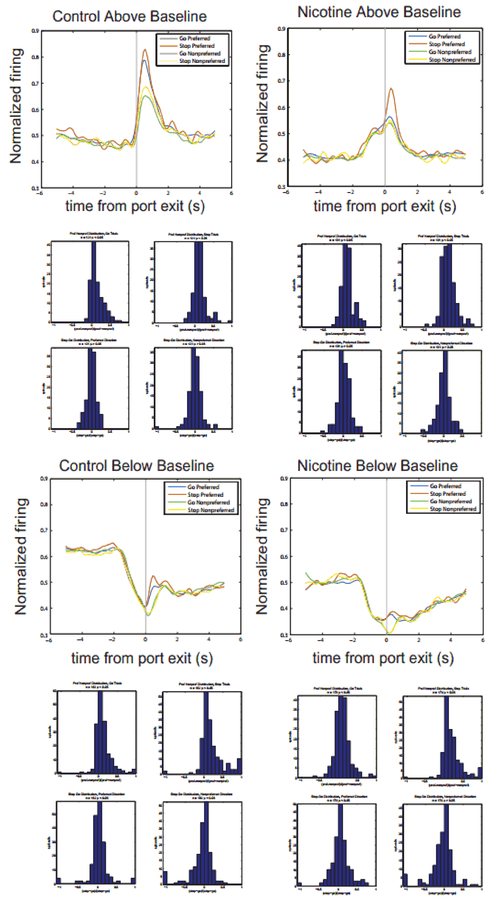

Figure 3. a) On both Stop and Go trials, the cells fire significantly more in the Preferred direction. In the Preferred and Nonpreferred directions, neural firing rates are not significantly different for Stop or Go trials.
b) Cells fire significantly more in the Preferred direction on both Stop and Go trials. In the Preferred direction, cells fire significantly more during Stop trials when going, but there is no significant difference in firing rate between Stop or Go trials in the Nonpreffered direction.
c) On both Stop and Go trials, cells fired at a significantly greater rate in the Preferred direction. In the Preferred and Nonpreferred directions, firing rate was not significantly different for Stop or Go trials.
d) During both Stop and Go trials, cells fired at a significantly greater rate in the Preferred

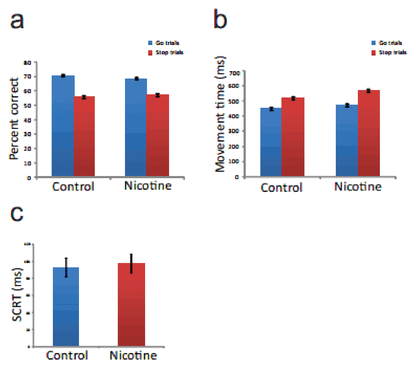

Figure 4. Analyzed in Excel to determine movement time and percent correct for Go and Stop trials. Error bars represent the standard error of the mean.

Conclusions

Twelve rats from the control and PNE groups performed 157 sessions, over which we collected neural firing from 346 cells. Overall, we found that control and PNE groups performed the same number of trials per session. As expected, we found that PNE rats had longer stop change reaction times (SCRTs), which were measured by the difference in movement times on STOP and GO trials. Control rats' average SCRT was 78.67ms and PNE rats' average SCRT was 97.78ms. This statistic provides evidence that the PNE rats are more impulsive than control rats. However, we found that PNE rats were better on more simple aspects of the tasks. Specifically, they were faster and more accurate on GO and STOP trials. Thus, although PNE rats took longer to inhibit an ongoing movement, they were better at simple stimulus driven actions (i.e., respond in the direction of the light).

Analysis of neural activity is currently ongoing. Since PNE rats took longer to alter behavior on STOP trials (SCRT) we predict that activity in mPFC, which we think is necessary for stopping,, will be decreased in PNE rats. Since PNE rats were better at responding to spatial signals that instruct behavior, we expect that activity in mPFC of PNE rats was more spatially tuned as compared to controls.

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