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# Abstinent smokers show reduced brain responses to positive feedback and enhanced responses to negative feedback

## Introduction

Cigarette smokers attempting to quit often fail due to nicotine withdrawal symptoms [1]. These symptoms include anxiety, **irritability (enhanced sensitivity to negative outcomes)**, and **anhedonia (reduced sensitivity to positive outcomes)** [2-3]. As such, we examined the impact of nicotine withdrawal and nicotinic acetylcholine receptor (nAChR) agonist administration (i.e., varenicline and nicotine) on brain activity in a task designed to probe positive and negative feedback processing. We expected that brain activity linked with feedback processing in our sample of smokers and nonsmokers would replicate a previous implementation of this task in a sample of healthy controls [4]. When considering group effects (smokers vs. nonsmokers), we hypothesized that abstinent smokers would show elevated brain activity to negative feedback (irritability) and reduced brain activity to positive feedback (anhedonia). Lastly, we considered the impact of nAChR agonist administration on behavioral task measures to confirm expected drug effects on task performance (i.e., percent of correct and no response trials).

## Methods

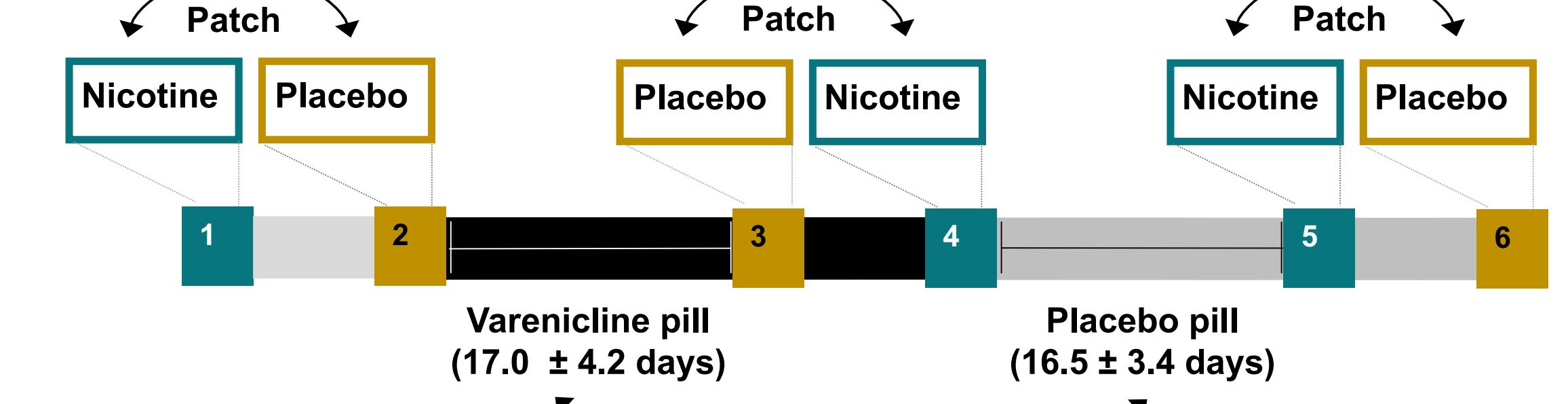
- Participants.** Right-handed and 18-55 years of age. Smokers ( $n=24$ ) and nonsmoking controls ( $n=20$ ). Smokers were non-treatment seeking and reported 10 or more cigarettes per day for a minimum of 2 years. Carbon monoxide (CO) levels confirmed overnight abstinence.

- Drug manipulations.** Scanned at 6 time points in a two-drug, placebo-controlled pharmacological administration study (Fig. 1A). Order of drug conditions was counterbalanced across participants.
  - 3 varenicline pill conditions (PILL factor: pre-pill vs. varenicline vs. placebo).
  - 2 transdermal nicotine patch conditions (PATCH FACTOR: nicotine vs. placebo).

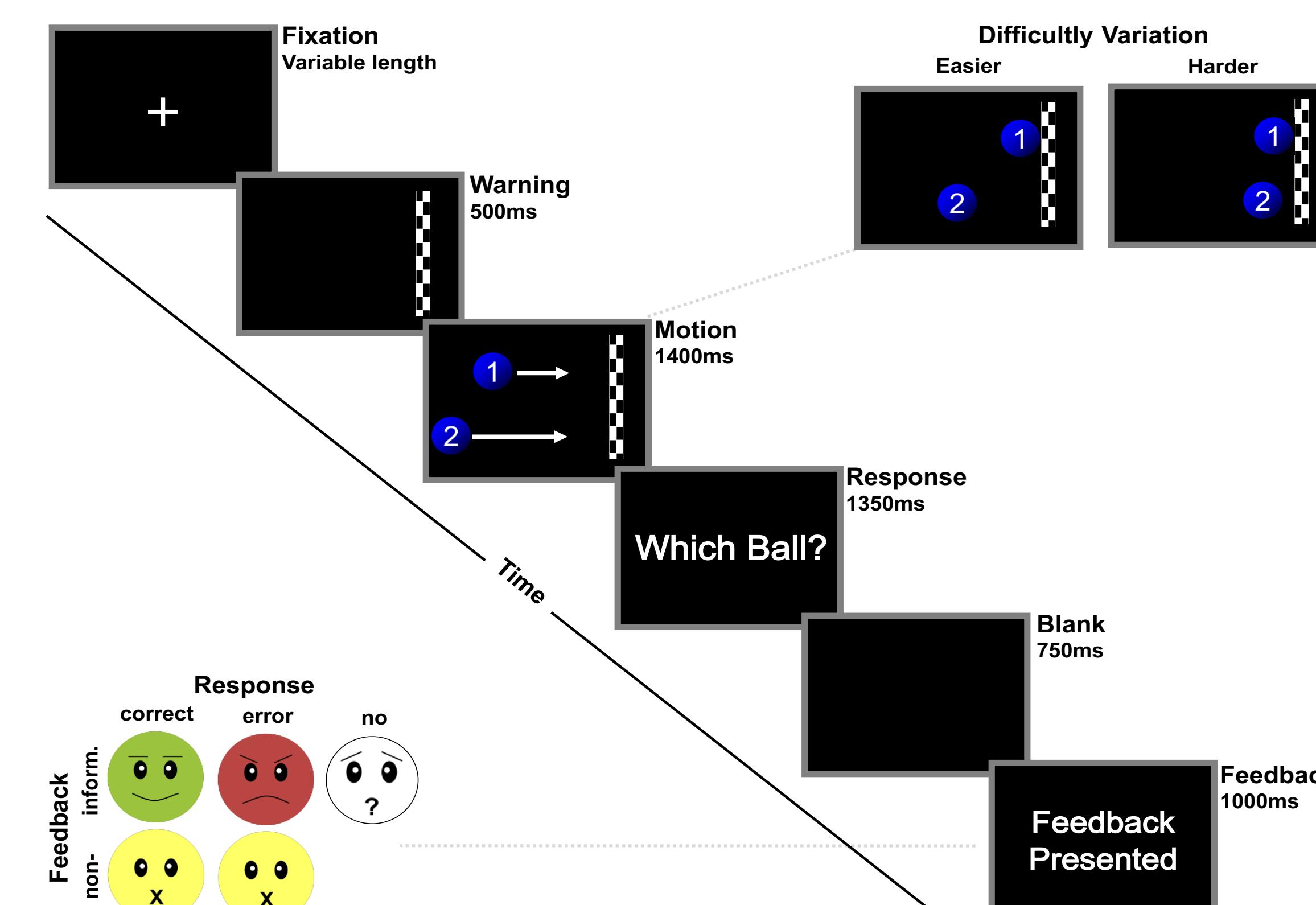
- Task.** Performed a fMRI performance feedback task called the motion prediction (MP) task [4].
  - Positive and negative performance feedback (RESPONSE: correct vs. error) presented that did, or did not, provide information about trial outcomes (FEEDBACK: informative vs. non-informative; Fig. 1B).
  - Difficulty levels individually, dynamically adapted to maintain ~35% error rate.
  - Behavioral measures:** percent of error, correct, and no response trials.

- fMRI data preprocessing and analysis.** AFNI
  - Five task-related regressors time-locked to feedback-onset (informative-correct, informative-error, non-informative-correct, non-informative-error, and no response trials).

- Task effect:** Whole-brain, group-level,  $t$ -test: informative-correct vs. informative-error ( $p_{\text{corrected}} < 0.001$ ).
- Group effects:** Group-level  $t$ -test (smokers vs. nonsmokers) within *a priori* defined volume of interest. Given our hypothesis of group effects within brain regions associated with positive and negative outcome processing, we applied a familywise error correction within a composite mask of interest ( $p_{\text{corrected}} < 0.05$ ) including the bilateral nucleus accumbens, caudate, putamen, amygdala, anterior cingulate cortex, bilateral insula, and orbitofrontal cortex [5].

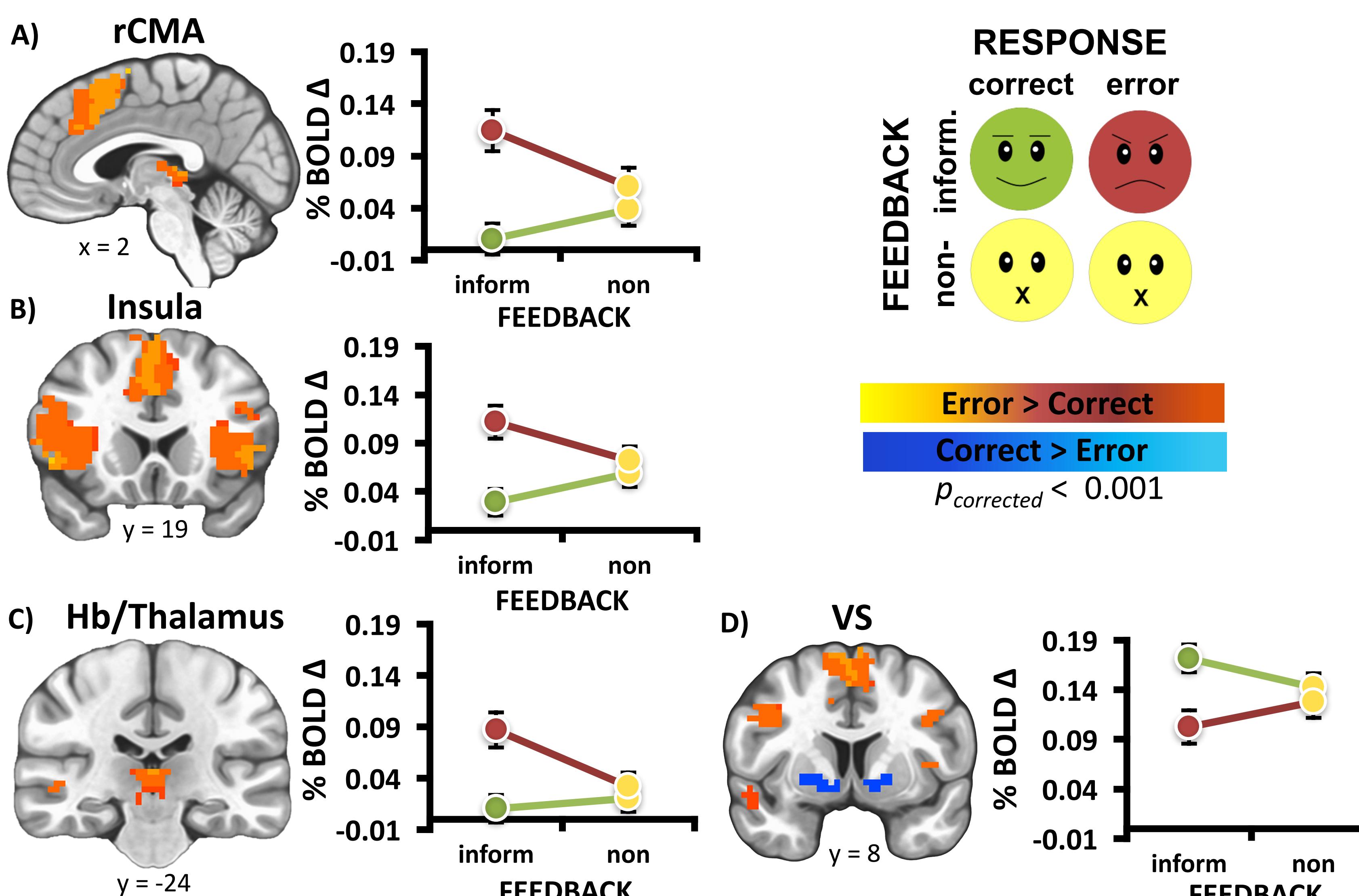


**Figure 1A.** Drug administration paradigm.

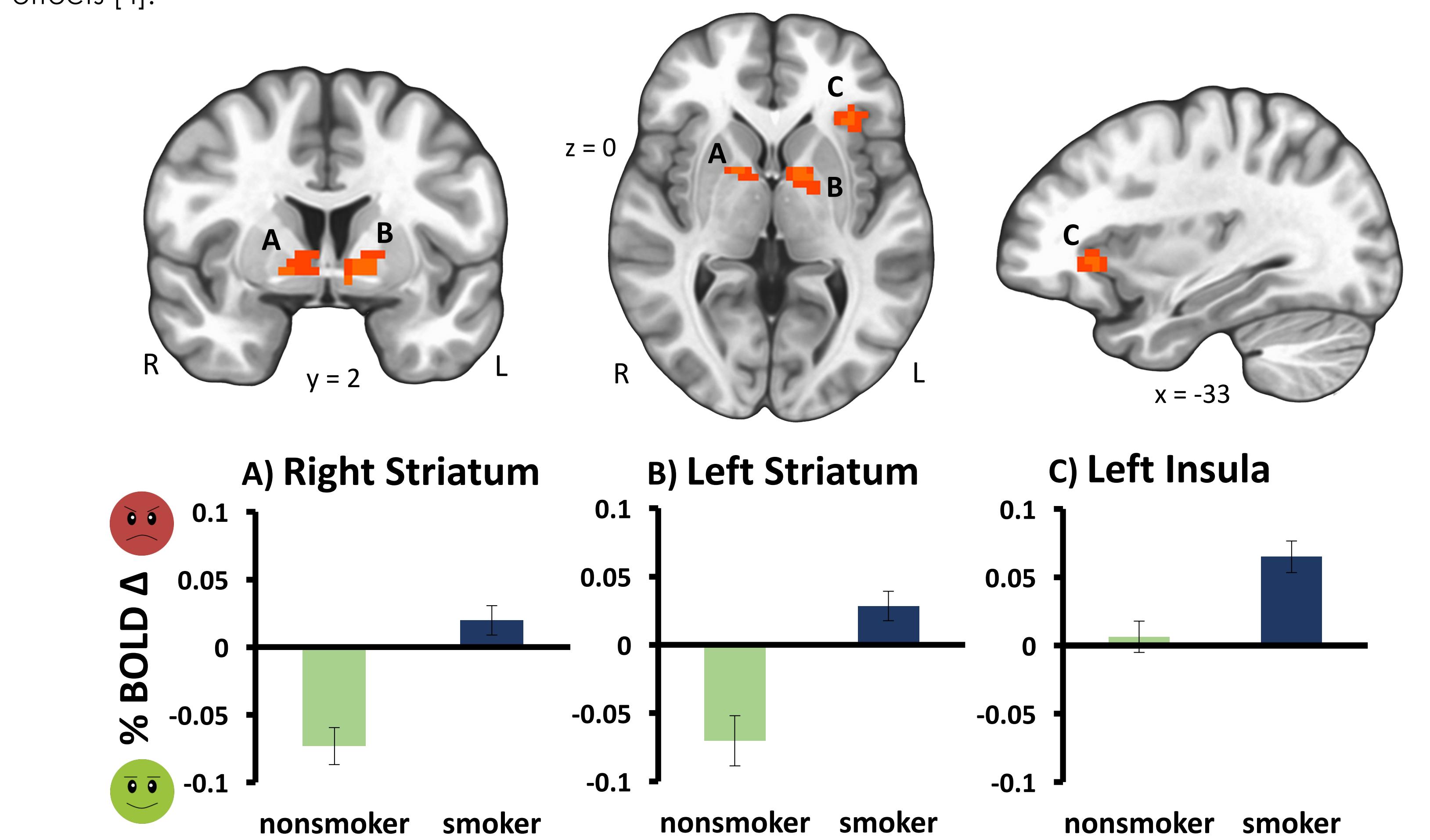


**Figure 1B.** Schematic diagram of one trial in the motion prediction task.

## Results



**Figure 2. Imaging Task Effects:** Mean percent signal change for each feedback-type demonstrated differential responses on error-trials versus correct-trials followed by informative, but not non-informative feedback. A whole-brain, group-level,  $t$ -test identified regions showing greater activity following negative feedback (orange/red) in the (A) rostral motor cingulate area/supplementary motor area (rCMA), (B) insula, and (C) a habenular (Hb)/thalamic region. The same whole-brain  $t$ -test identified greater activity following positive feedback (blue) in (D) bilateral ventral striatum (VS). These results replicate previously reported task effects [4].



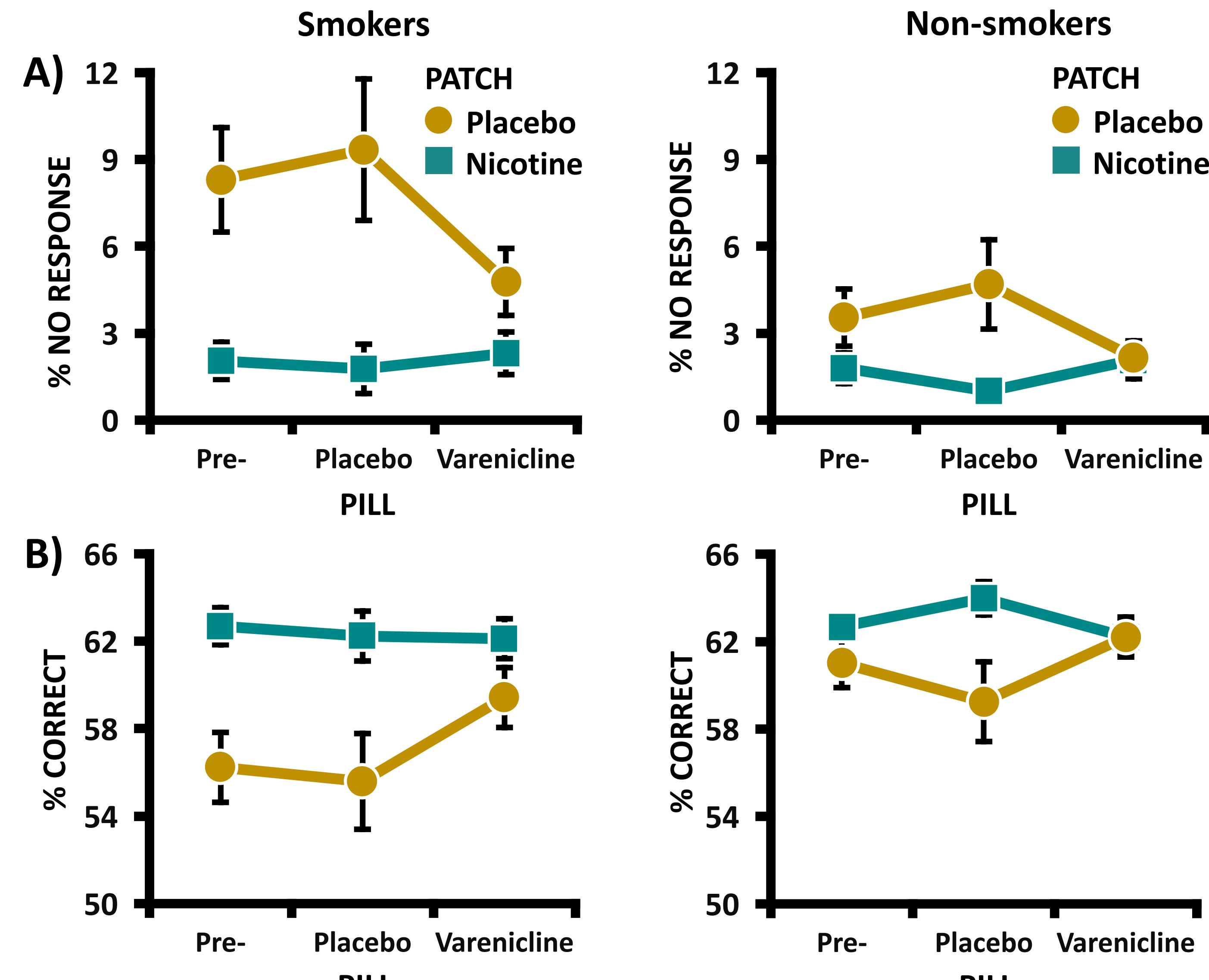
**Figure 3. Imaging Group Effects:** Smokers, compared to nonsmokers, displayed significantly less activity in the (A) right striatum and (B) left striatum following positive feedback and significantly more activity in (C) the left insula following negative feedback.

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**Figure 4. Behavioral Drug Effects:** Expected drug effects were observed when considering the percent of (A) 'no response' and (B) 'correct response' trials in the motion prediction task across drug conditions among smokers (left) and nonsmokers (right). Specifically, we observed a significant GROUP x PATCH interaction for both the 'no response' [ $F(1, 42) = 5.783, p < 0.05$ ] and 'correct response' trials [ $F(1, 42) = 5.058, p < 0.05$ ]. Furthermore, among smokers, a hypothesized PILL x PATCH interaction was observed when considering 'no response' [ $F(1.688, 38.827) = 4.62, p < 0.05$ ] and 'correct response' trials [ $F(1.998, 45.956) = 4.293, p < 0.05$ ]. Among nonsmokers, a PILL x PATCH interaction was also observed when considering 'correct response' trials [ $F(1.714, 32.569) = 4.224, p < 0.05$ ].

## Significance

These results replicate previously reported task effects [4] and extend the body of extant literature on human habenula activity. The observed group differences (smoker vs. nonsmoker) speak to the impact of an extended smoking history on feedback-related brain activation. Specifically, smokers' reduced VS activation following positive feedback is consistent with the view that a hypodopaminergic state during nicotine withdrawal leads to under-prioritization of non-drug rewards and anhedonia [6-7]. Additionally, smokers' enhanced brain activation following negative feedback suggests that altered brain function may also underlie the aversive symptoms of nicotine withdrawal (i.e. anxiety, irritability) [2-3]. Behavioral MP task performance measures confirmed expected nicotine withdrawal and pharmacological manipulation effects allowing for future investigation of these two smoking cessation aids' (varenicline and nicotine) impact on feedback-related brain activity.

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## References:

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