Habenula activity following positive and negative feedback among abstinent cigarette smokers

Neuroinformatics and Brain Connectivity Lab

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Introduction

The habenula (HB) inhibits dopamine-releasing neurons following the absence of an expected reward [1, 2], possesses a high density of nicotinic acetylcholine receptors (nAChRs) [3], and is linked with reward processing and the aversive effects of nicotine withdrawal and high nicotine doses [3, 4].

While preclinical evidence has demonstrated the HB's role in nicotine withdrawal [4, 5], the small size of the HB limits assessment of this region in human fMRI studies.

Here, we examined a response-feedback task shown to differentially activate the HB as well as the insula, anterior cingulate cortex (ACC), and ventral striatum (VS) among nonsmoking participants [6]. As an initial step towards characterizing the impact of smoking status on the activity of the HB and these other regions, we aimed to confirm task-related fMRI effects among abstinent smokers.

Methods

fMRI DATA COLLECTION:

- 24 overnight-abstinent smokers (biochemically verified) each participated in 6 fMRI sessions
- Double-blind, placebo-controlled, two-drug (nicotine and varenicline) study

MOTION PREDICTION TASK:

- Participants predicted which of two moving balls would reach a finish line first **(Fig. 1)**
- Task difficulty was dynamically-adapted to maintain a ~35% error rate and create performance uncertainty
- Participant RESPONSES (correct vs. error) were followed by performance FEEDBACK that did, or did not provide information about trial outcomes (informative vs. non-informative)

BEHAVIORAL & IMAGING MEASURES:

- Reaction time (RT), error rates, and missed response rates
- Differential % signal change on error-trials versus correct-trials followed by informative, but not non-informative feedback (i.e., a whole-brain RESPONSE x FEEDBACK interaction, $p_{corrected}<0.01$)

Results & Discussion

BEHAVRIOAL RESULTS:

- % trial type: correct: 59.6±1.1%, errors: 35.6±0.2%, no response: 4.8±1.0% of the trials **(Fig. 2A)**
- RT: slower for erroneous responses (620±17ms) than for correct responses (583±17 ms), $F(1,22) = 63.9$, $p < 0.001$ **(Fig. 2B)**

IMAGING RESULTS:

- Whole-brain RESPONSE x FEEDBACK interaction identified differential activations following positive versus negative feedback in the HB, insula, ACC and VS
  - HB, ACC and insula activity was increased following informative negative feedback relative to positive feedback, whereas no difference was observed following non-informative feedback **(Fig. 3A-C)**
  - HB activity was localized within the structurally-defined HB locations from each participant's anatomical MRI **(Fig. 3A)**
  - VS activity was increased following informative positive feedback relative to negative feedback **(Fig. 3D)**

CONCLUSIONS:

- Data support HB's role in processing performance feedback and suggest the feasibility of this paradigm to further probe the impact of smoking status and drug effects on such brain activity.

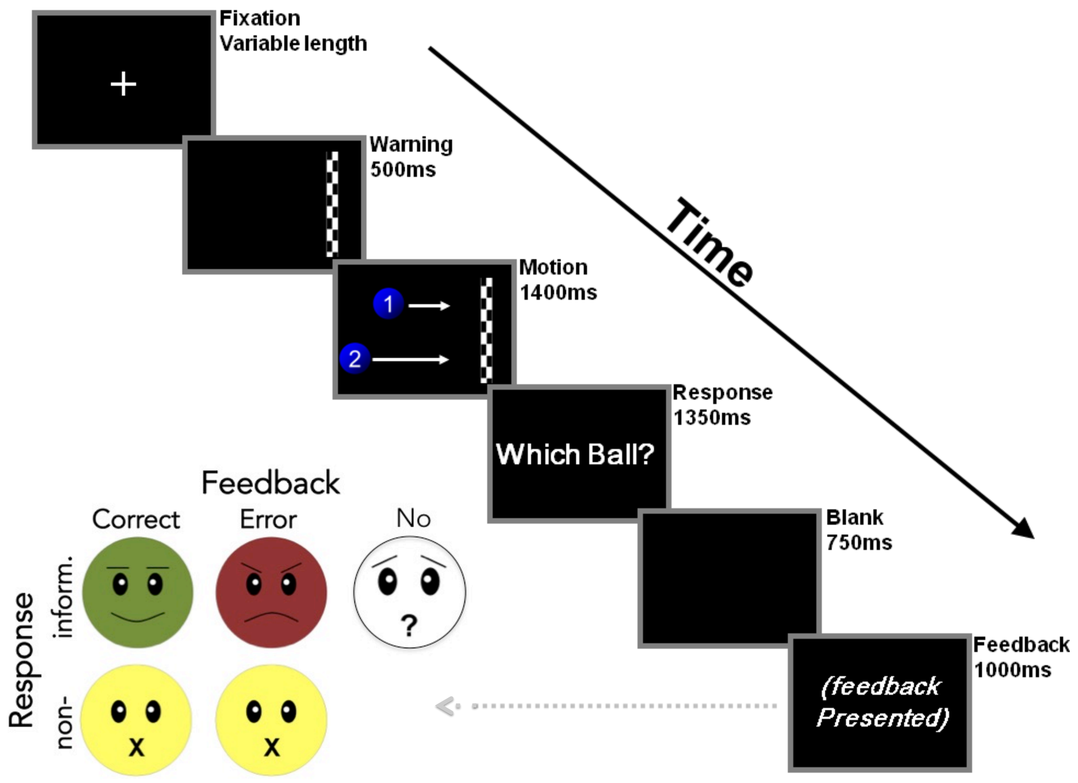

Figure 1. Schematic diagram of the motion prediction task

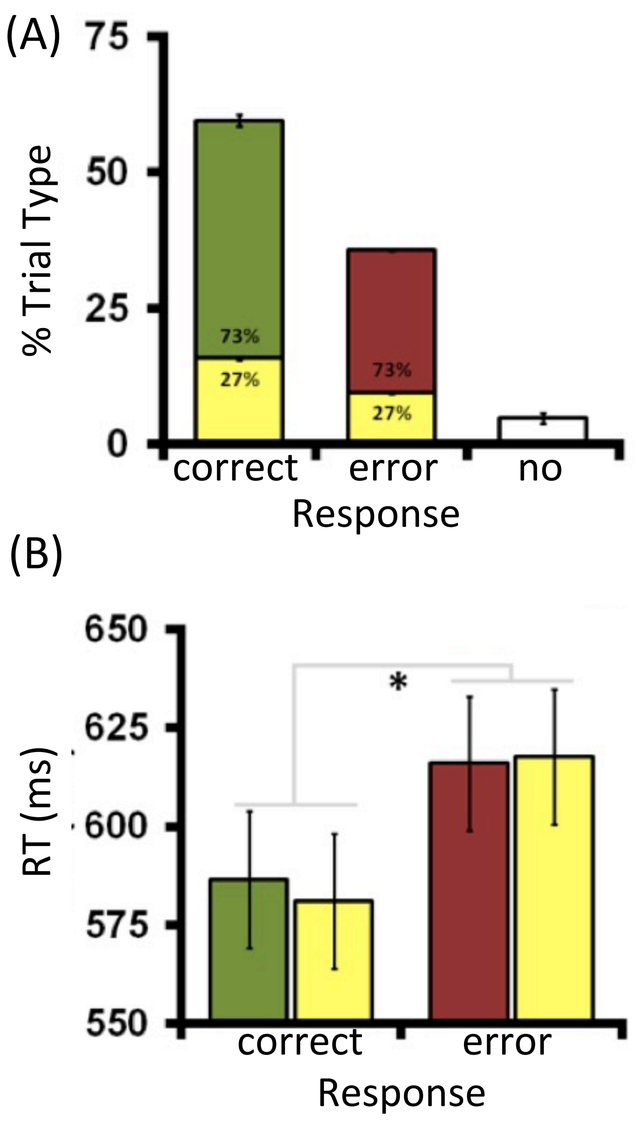

Figure 2. Behavioral outcomes: (A) average percentage of trial types, (B) average reaction times across trial types

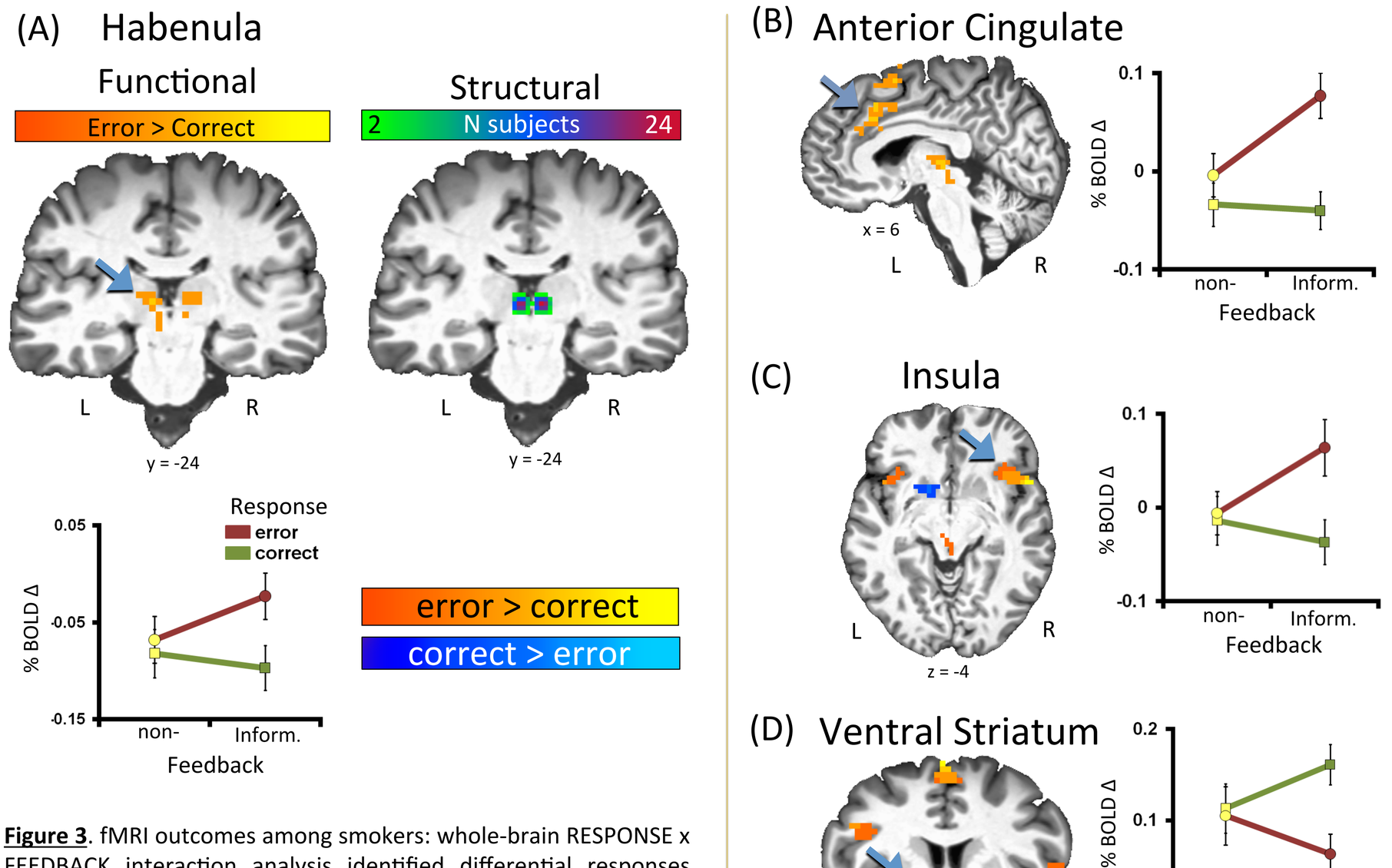

Figure 3. fMRI outcomes among smokers: whole-brain RESPONSE x FEEDBACK interaction analysis identified differential responses following positive and negative (informative) feedback in the: (A) habenula (which overlapped with the structurally-defined location of this region), (B) ACC, (C) Insula, and (D) ventral striatum

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