Neurochemical and neurophysiological measurements during goal directed behavior for natural reinforcement - comparison to cocaine self-adminstration.

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Introduction

The nucleus accumbens (Acb) and its dopaminergic projection are critically involved in goal directed behavior

Acb neurons exhibit patterned, phasic discharges time-locked to operant responding for drug and “natural” reinforcement

Dopamine (DA) blockade reduces operant responding for a variety of reinforcers

Acb DA increases over minutes during operant responding for a variety of reinforcers

DA functions in the Acb on a subsecond level

DA modulates the excitability of Acb neurons

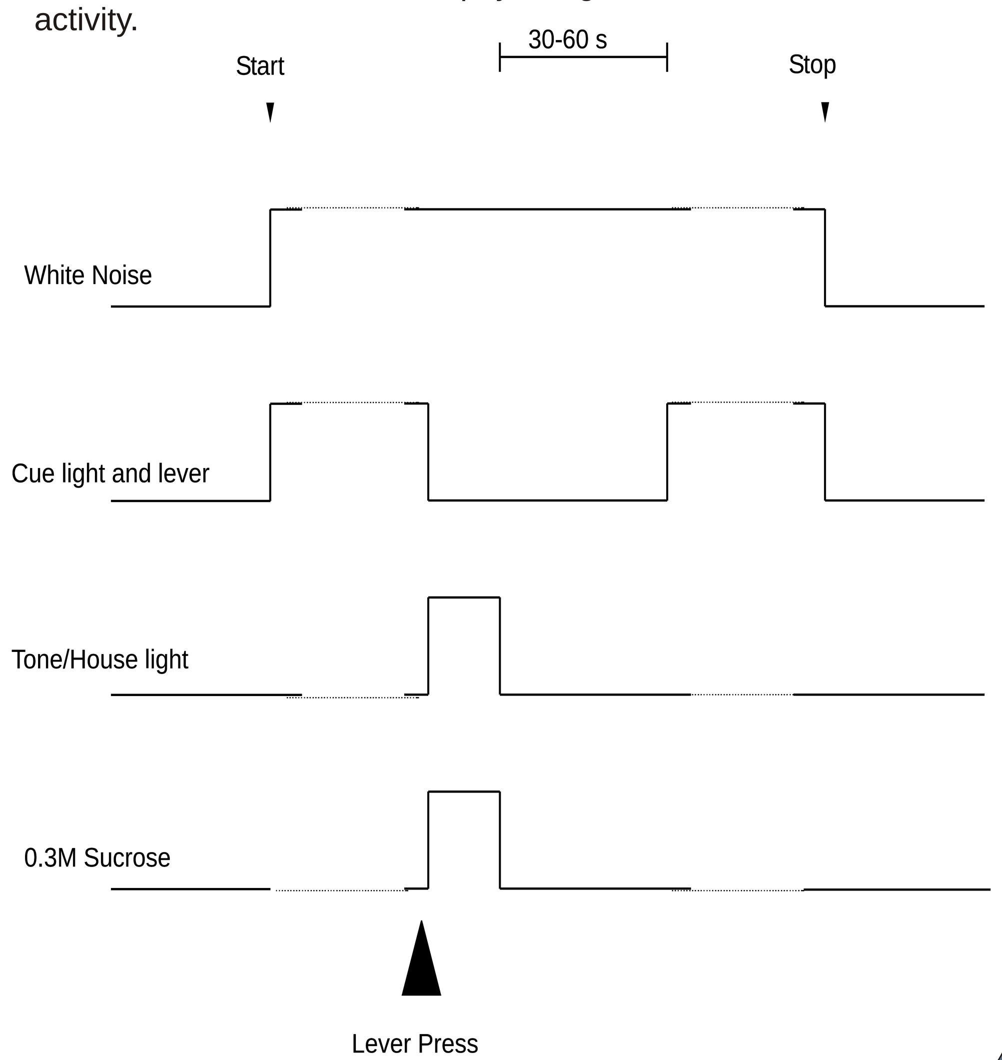
DA neurons exhibit phasic discharges time-locked the delivery of food rewards, stimuli that predict them and operant responding for food rewards

Phasic increases in extracellular Acb DA have been detected over ***seconds*** and are correlated with social interaction as well as operant responding for cocaine.

Can phasic fluctuations in Acb DA be detected during operant responding for food reward and how does the response differ from that of responding for cocaine?

Methods

Rats were surgically implanted with bilateral intra-oral catheters. Following recovery, rats were trained to press a lever for delivery of 0.3M sucrose (6s, 200µl per press) using the paradigm depicted in Figure 1. Training lasted between 2-3 weeks when stable rates of operant responding were observed. Following training, rats were surgically implanted for either voltammetric measurement of DA or electrophysiological measurement of Acb activity.

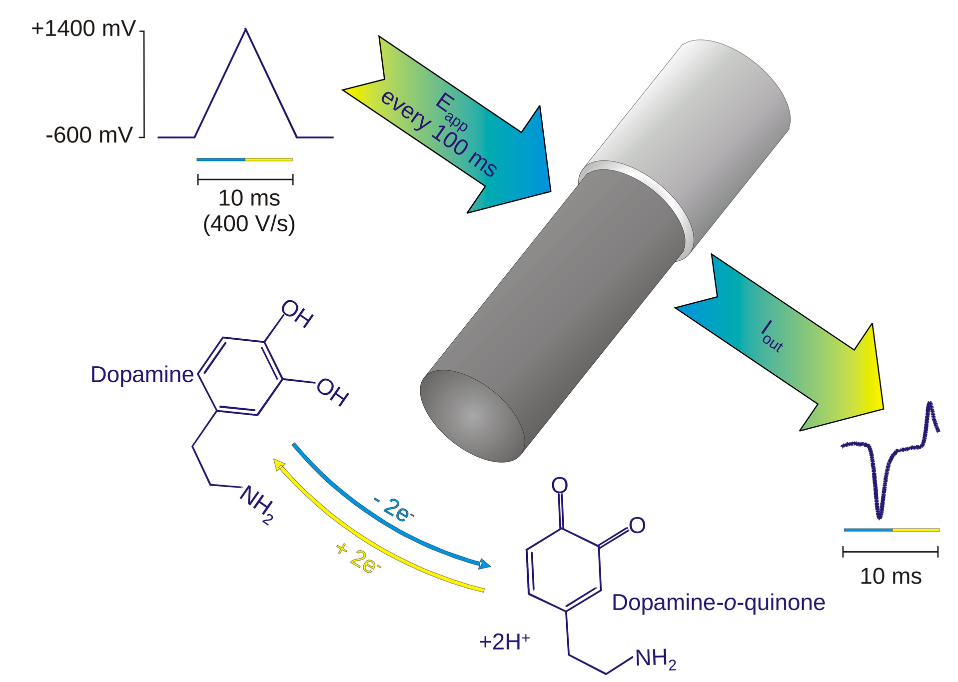


Detection of dopamine

Dopamine was monitored using fast-scan cyclic voltammetry (FSCV) at carbon fiber microelectrodes.

A triangular waveform (E_{app}) was applied to the electrode every 100 ms.

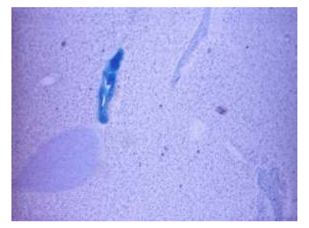
In the presence of dopamine, the output current (I_{out}) consists of a negative (oxidation) peak followed by a positive (reduction) peak.



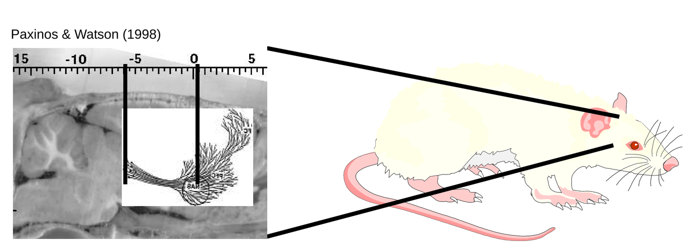
When this is plotted against the input potential, a cyclic voltammogram (CV) is produced, which allows for chemical identification.

Temporal changes in extracellular dopamine concentration were quantified from the current at the potential where the peak oxidation reaction occurred (~0.6 V vs Ag/AgCl), normalized to an *in vitro* electrode calibration.

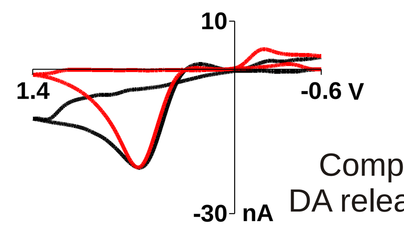
Verification of DA Signal



Histological



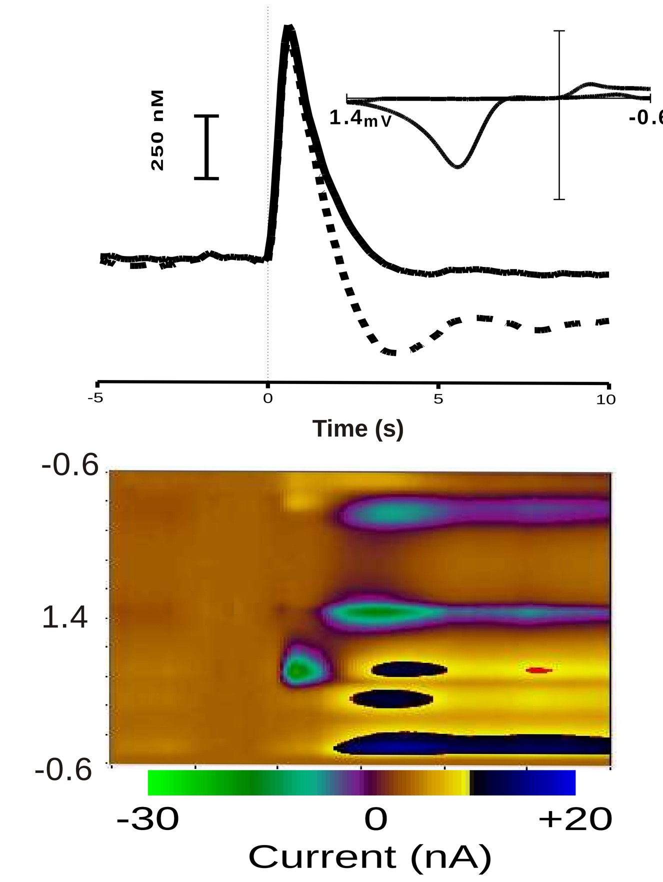
Anatomical



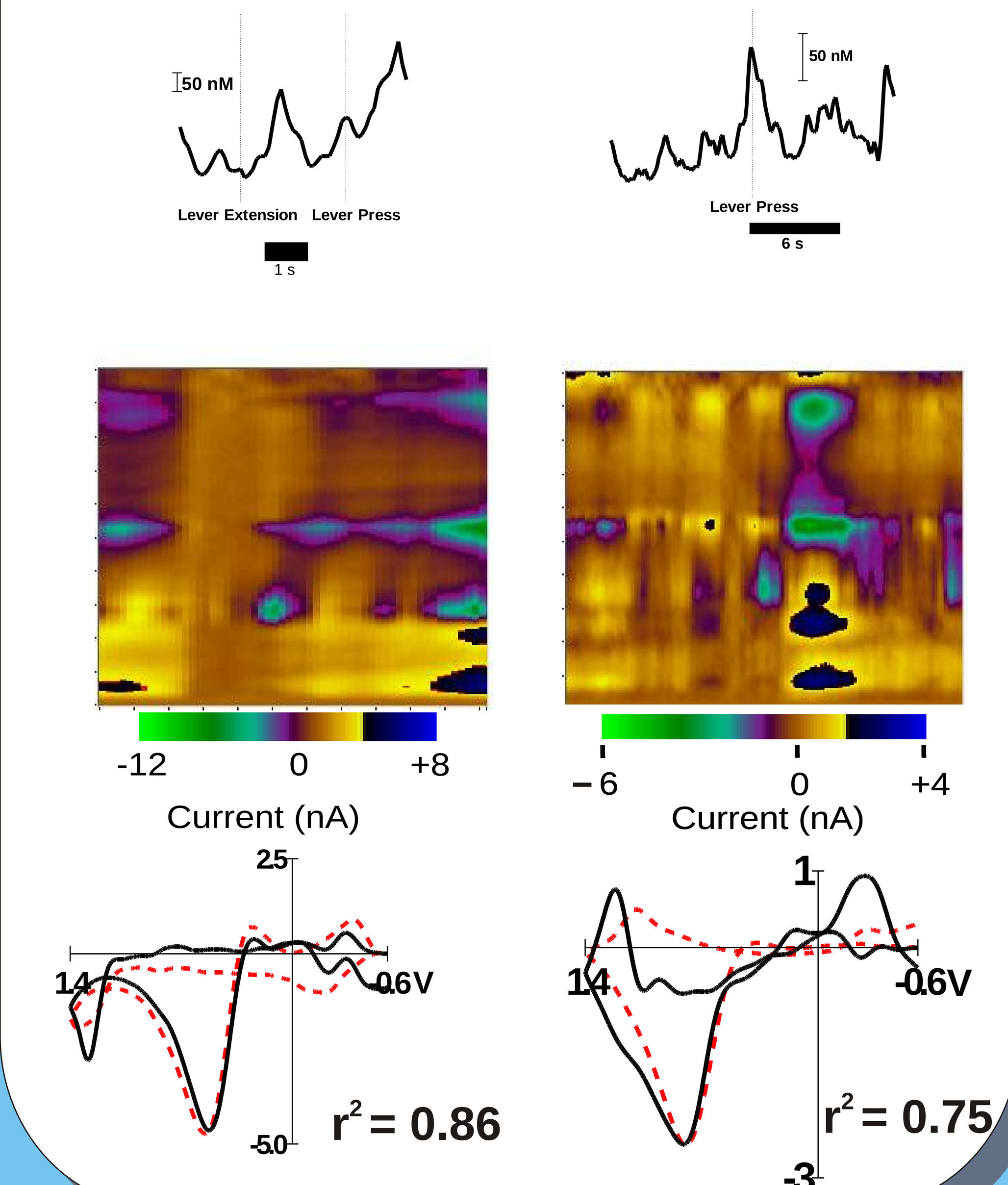
Comparison of *in vivo*, evoked DA release with *in vitro* calibration.

Chemical

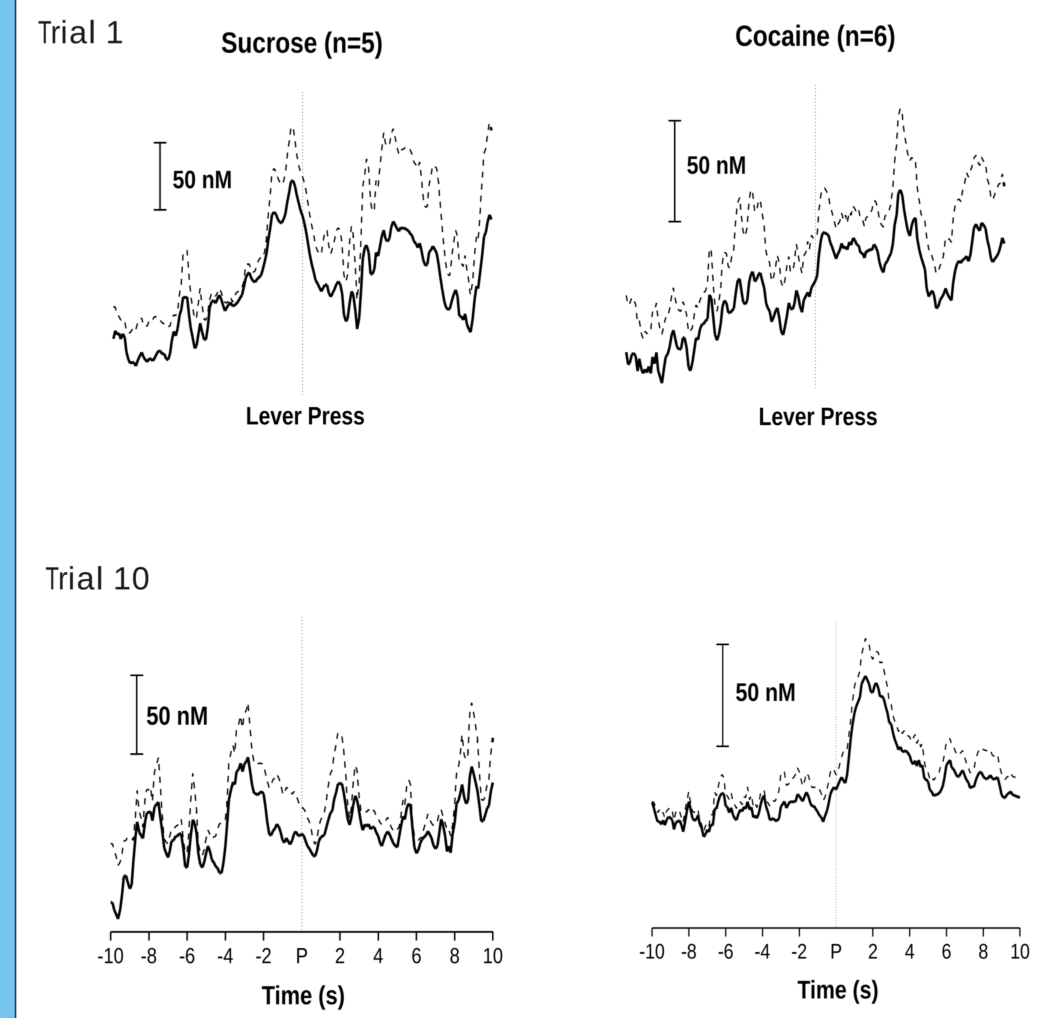
Evoked DA release

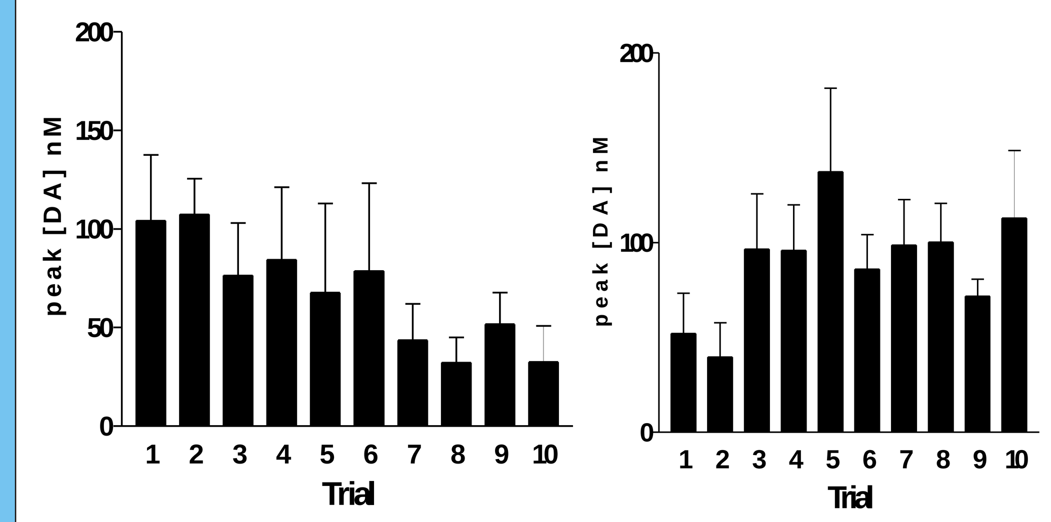


Dopamine release is linked to key aspects of the behavioral paradigm



Phasic DA release during operant responding for sucrose or cocaine



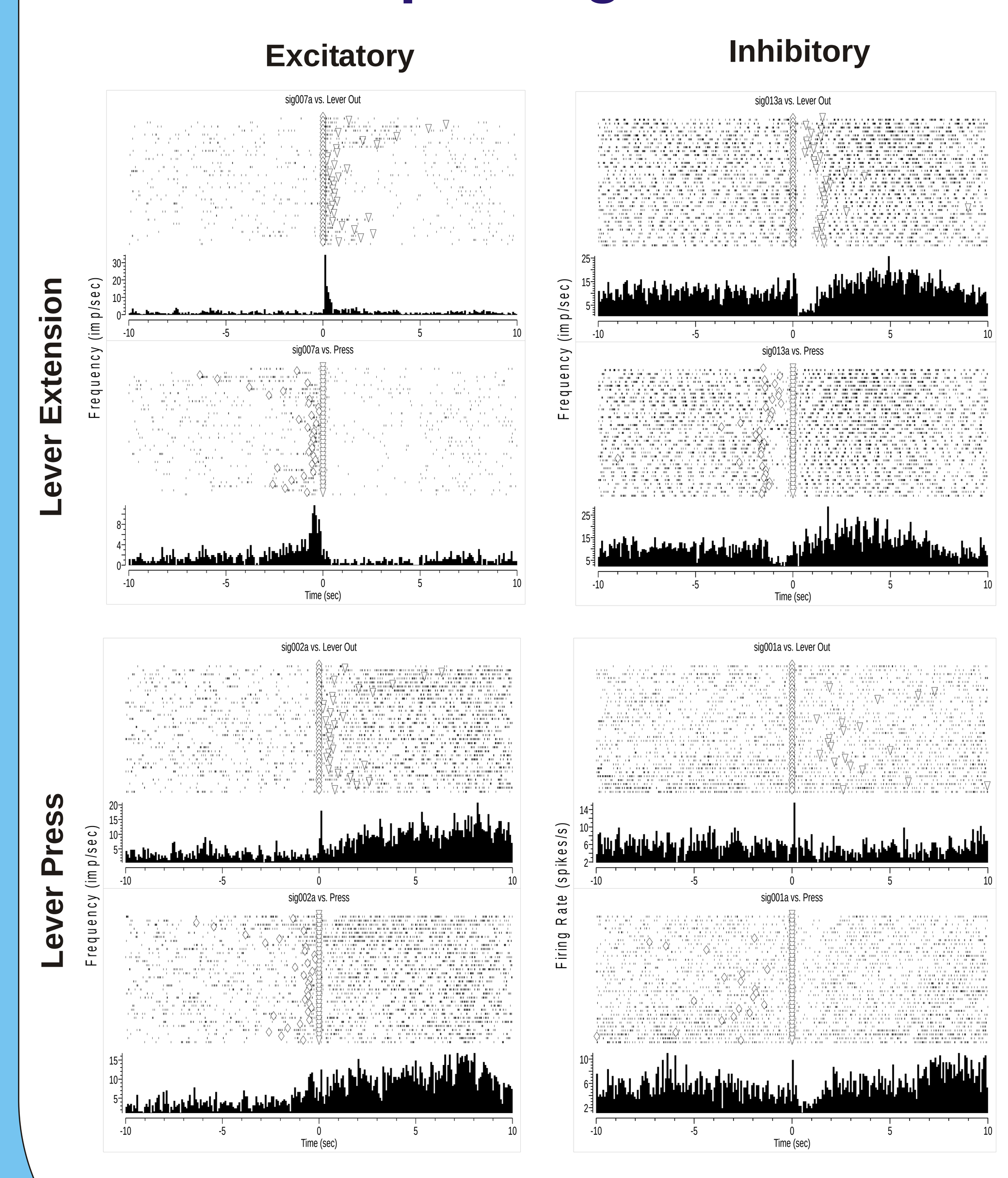


Phasic DA signaling time-locked to operant responding attenuates when the goal is sucrose but not when it is cocaine.

Do Acb neurons exhibit patterned phasic responses to the same behavioral events as phasic DA?

A separate group of rats (n=3) were trained in the same manner as before but implanted with microelectrode arrays aimed at the core and shell fo the Acb. One week after electrode implantation, rats were tested on the same behavioral paradigm.

Phasic changes in Acb firing rate are time-locked to key aspects fo the behavioral paradigm



Conclusions

Phasic increases in DA are time-locked to goal-directed behavior for natural reinforcement but attenuate over the course of the behavioral session

This attenuation is in stark contrast to results obtained in rats lever pressing for cocaine suggesting an alteration in phasic DA signaling in animals responding for cocaine.

Phasic changes in Acb firing rate occur to the same events as phasic DA

Response of Acb neurons do not attenuate over the sucrose session

DA may be necessary to organize neural response initially but not necessary to maintain the neural response over the course of the behavioral session.

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